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Beilstein Journal of Organic Chemistry

Gold catalysis for organic synthesis

F. Dean Toste

Editorial

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Address:
Department of Chemistry, University of California, Berkeley, CA, United States

Email:
F. Dean Toste - fdtoste@berkeley.edu

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Guest Editor: F. D. Toste

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The past decade has witnessed a remarkable growth in the number of organic reactions that are catalyzed by homogeneous gold complexes. Many of the early reported reactions took advantage of the propensity of gold complexes to serve as excellent catalysts for reactions that proceed through π-activation of carbon–carbon multiple bonds. Subsequently, the reactivity paradigms available for gold complexes have proven to be almost limitless. The contributions from over 25 research groups from 13 countries underscore the growing importance of homogenous gold catalysis. More importantly, the papers in this Thematic Series highlight the remarkable breath of reactivity that can be accessed using homogenous gold complexes as catalysts; from catalysis of sigmatropic rearrangement, cycloaddition and cycloisomerization reactions, to applications in enantioselective catalysis, oxidative coupling and the total synthesis of natural products, and transformations of alkynes, allenes, alkenes and even C–H bonds. A true treasure chest of reactivity!



F. Dean Toste

I am grateful to all of the authors that have contributed to this Thematic Series. I hope you enjoy reading of their achievements as much as I have.

F. Dean Toste

Berkeley, April 2011

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Beilstein Journal of Organic Chemistry

Synthesis of chiral mono(N-heterocyclic carbene) palladium and gold complexes with a 1,1'-biphenyl scaffold and their applications in catalysis

Lian-jun Liu[1], Feijun Wang[1], Wenfeng Wang[1], Mei-xin Zhao[1] and Min Shi[*1,2]

Full Research Paper

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Address:
[1]Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 MeiLong Road, Shanghai 200237, People's Republic of China and [2]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China, Fax: 86-21-64166128

Email:
Min Shi[*] - Mshi@mail.sioc.ac.cn

* Corresponding author

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Abstract

Axially chiral mono(NHC)–Pd(II) and mono(NHC)–Au(I) complexes with one side shaped 1,1'-biphenyl backbone have been prepared from chiral 6,6'-dimethoxybiphenyl-2,2'-diamine. The complexes were characterized by X-ray crystal structure diffraction. The Pd(II) complex showed good catalytic activities in the Suzuki–Miyaura and Heck–Mizoroki coupling reactions, and the (*S*)-Au(I) complexes also showed good catalytic activities in the asymmetric intramolecular hydroamination reaction to give the corresponding product in moderate ee.

Introduction

N-heterocyclic carbene (NHC) ligands, which have intrinsic characteristics such as strong σ-donor but poor π-acceptor abilities, easy preparation, air and thermal stability of their metal complexes, and convenient introduction of chiral elements, have been widely used as promising ligands in metal-catalyzed transformations [1-13]. Numbers of novel chiral NHCs and NHC–metal-catalyzed asymmetric transformations have been developed in a dramatic expansion of this area of chemistry during the past decade; however, up to 2010 only a very few efficient chiral NHCs or NHCs metal catalysts have been described [14-18]. From the typical configuration of NHC metal complex **1** (Figure 1), NHCs are generally more or less cone-shaped with flat heterocyclic structures, and that R^1, R^2 and M can rotate flexibly around the R^1–N, R^2–N and C–M bonds, res-

pectively. Such internal rotations cause the active chiral space at the metal center to be relatively ill-defined, which is a key factor for their low enantioselectivity in asymmetric catalysis. As a result, many monodentate NHCs (Figure 1) with sterically hindered R^1, R^2 groups have been designed, and these have been shown to be good to excellent catalysts in chiral induction reactions [19-25].

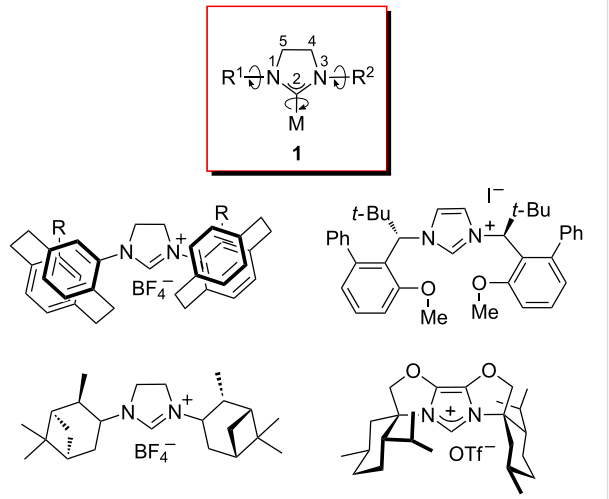


Figure 1: Monodentate NHCs with sterically hindered N-substituents.

The axially chiral biaryl framework, widely used in the design of chiral ligands such as BINAP [26,27], BINOL [28,29], and boxax [30], has proved to be very rigid, and was introduced in the development of NHC ligands by the Hoveyda group [31-36] and ours [37-44] (Figure 2). Several highly efficient asymmetric catalytic processes with these novel chiral NHCs-bonded metal catalysts have so far been reported. Encouraged by these results, we attempted to develop a new type of mono(NHC) metal complex **2** with a biaryl framework, in which one of biaryl groups bearing a substituent might provide steric hindrance to limit the rotation of the N–Ar bond. Herein we wish to report the synthesis of novel chiral [(NHC)Pd(allyl)I] and mono(NHC)–Au complexes bearing an axially chiral biphenyl framework, and their application in catalysis.

Results and Discussion

Synthesis of the NHC–Pd(II) and NHC–Au(I) complexes

The synthesis of the chiral benzimidazolium salt (*S*)-**5a** is shown in Scheme 1. Thus (*S*)-6,6'-dimethoxybiphenyl-2,2'-diamine was reacted with acetic anhydride in the presence of acetic acid at room temperature (25 °C) in DCM to afford the corresponding amide (*S*)-**1a** in 56% yield. The coupling reaction of (*S*)-**1a** with 2-bromonitrobenzene was achieved by the use of bis(2-diphenylphosphinophenyl)ether (DPEphos) as a ligand and $Pd_2(dba)_3$ as the catalyst in the presence of Cs_2CO_3 to give the desired compound (*S*)-**2a** in 98% yield. Reduction of (*S*)-**2a** by means of Pd-C/H_2 for 8 h gave (*S*)-**3a** in 98% yield. Subsequent cyclization with triethyl orthoformate catalyzed by *p*-toluenesulfonic acid at 100 °C for 5 h afforded (*S*)-**4a** in 83% yield. Quaternization of the benzimidazole ring of (*S*)-**4a** by heating with methyl iodide in acetonitrile provided the corresponding benzimidazolium salt (*S*)-**5a** in quantitative yield.

With the NHC precursor (*S*)-**5a** in hand, its coordination with Pd or Au metal salts was examined. Benzimidazolium salt (*S*)-**5a** was treated with $(\eta^3\text{-}C_3H_5PdCl)_2$ in tetrahydrofuran (THF) in the presence of *t*-BuOK at 50 °C to give [(NHC)Pd(allyl)I] complex (*S*)-**7** in 70% yield as a yellow solid after purification by silica gel column chromatography (Scheme 2) [45,46]. Due to the stereochemical orientation of π-allyl group relative to the unsymmetrical carbene ligand, this NHC–Pd complex exists as two stereoisomers in solution, (*S*)-**7a** and (*S*)-**7b**, which could be easily distinguished in its ^{1}H NMR spectrum recorded at 23 °C [47-50]. The ratio of (*S*)-**7a** and (*S*)-**7b** was found to be 1.2:1 on the basis of ^{1}H NMR spectroscopic data. It appears that (*S*)-**7a** is slightly more stable than (*S*)-**7b** presumably due to the steric repulsion between the π-allyl group and the acetylated amino group in another phenyl group. However, we were

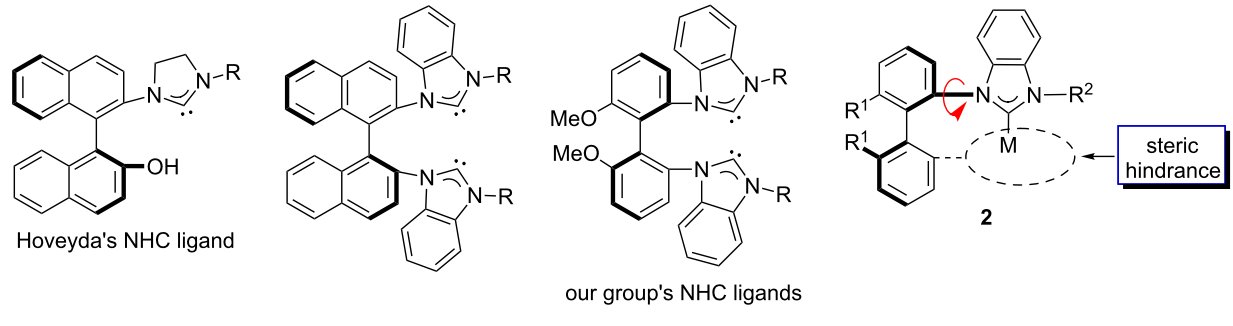
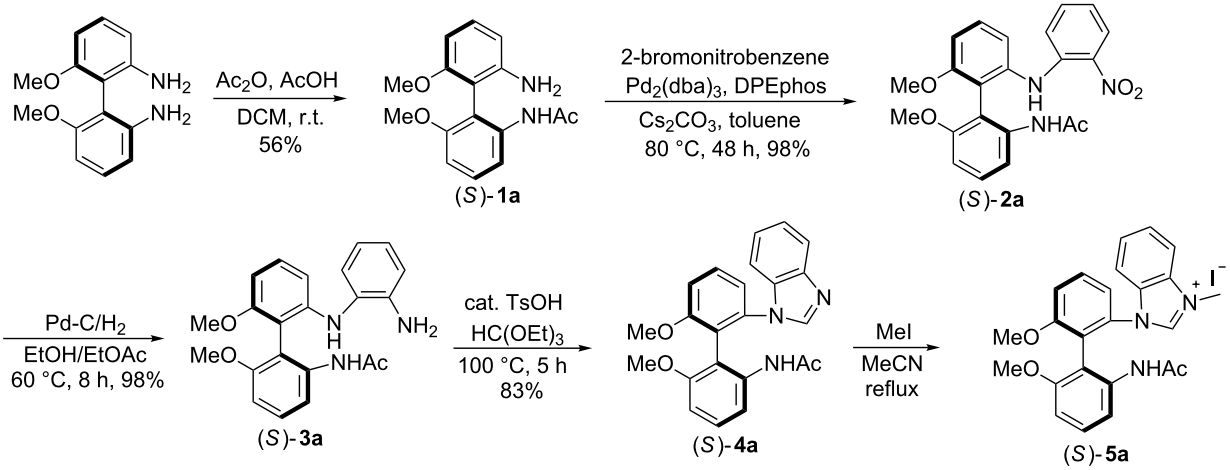
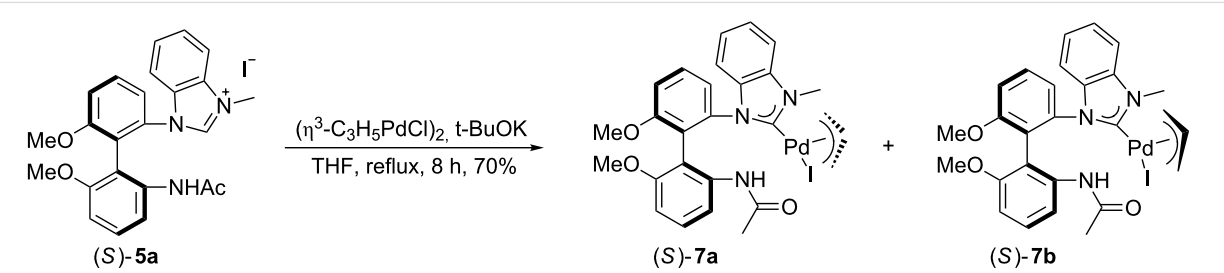


Figure 2: NHCs with axially chiral biaryl frameworks.



Scheme 1: Synthesis of N-heterocyclic carbene precursor.



Scheme 2: Synthesis of mono(NHC)–Pd(II) complex.

unable to isolate either stereoisomer in a pure form by silica gel column chromatography. After recrystallization from DCM and pentane (1:3), one of the two stereoisomers, [(NHC)Pd(allyl)I] (*S*)-**7a**, was obtained as a crystalline compound and its structure was confirmed by the X-ray single crystal diffraction (Figure 3) [51].

Benzimidazolium salt (*S*)-**5a** also complexed Au(I). According to the previously reported procedure [52-55], (*S*)-**5a** reacted with AuCl·S(Me) $_2$ on heating in THF for 8 h in the presence of KI and *t*-BuOK to give the expected chiral NHC–Au(I) complex (*S*)-**6a** in 65% yield (Scheme 3). Its structure was also confirmed by X-ray diffraction (Figure 4) [56]. It was found that the Au–carbene distance is 2.036 Å which is consistent with other reported NHC–Au complexes [57-59].

The NHC–metal complex [(NHC)Pd(allyl)I] complex **7** and NHC–Au(I) complex (*S*)-**6a**, are air and moisture stable both in the solid state and in solution, and can be used as catalysts. Therefore, the catalytic activities of these complexes were investigated in Pd-catalyzed coupling reactions and a Au-catalyzed asymmetric reaction, respectively.

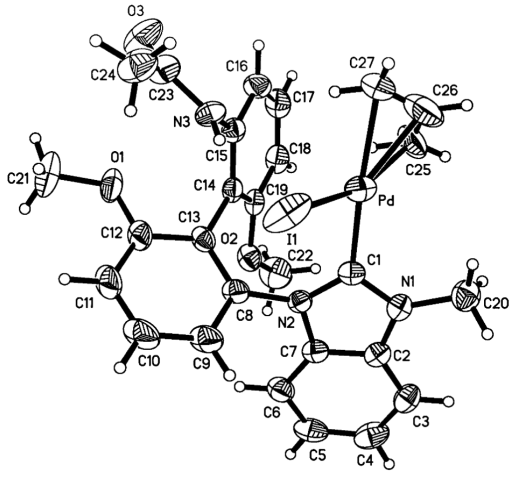
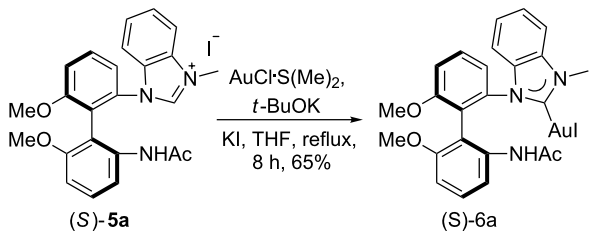


Figure 3: ORTEP drawing of NHC–Pd(II) complex (*S*)-**7a** with thermal ellipsoids at the 30% probability level. Selected bond distances (Å) and angles (deg): Pd–C1 = 2.050(5), Pd–C25 = 2.154(7), Pd–C26 = 2.128(9), Pd–C27 = 2.168(8), Pd–I1 = 2.6404(7), N1–C1–Pd = 125.6(4), N2–C1–Pd = 128.8(4), C1–Pd–I1 = 99.52(13), C1–Pd–C25 = 98.3(3), C1–Pd–C26 = 132.3(5), C1–Pd–C27 = 163.7(4), I1–Pd–C25 = 161.9(3), I1–Pd–C26 = 126.5(5), I1–Pd–C27 = 95.9(3), C25–Pd–C27 = 66.0(4), C25–Pd–C26 = 37.5(4), C26–Pd–C27 = 34.8(4).



Scheme 3: Synthesis of mono(NHC)–Au(I) complex.

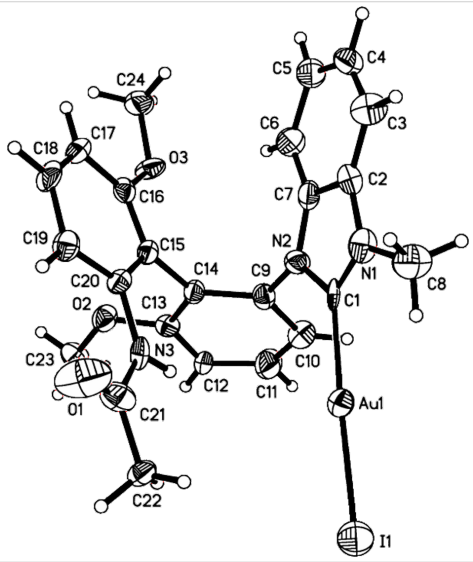
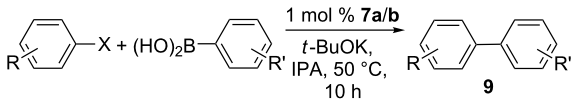


Figure 4: ORTEP drawing of NHC–Au(I) complex (*S*)-**6a** with thermal ellipsoids at the 30% probability level. Selected bond distances (Å) and angles (deg): Au1–C1 = 2.036(14), Au1–I1 = 2.5093(13), C1–Au1–I1 = 176.5(3), N1–C1–Au1 = 125.7(9), N2–C1–Au = 126.1(9).

Suzuki–Miyaura and Heck–Mizoroki coupling reactions catalyzed by NHC–Pd(II) complex

The Pd-catalyzed coupling reaction is one of the most powerful methods for the formation of carbon–carbon bonds in organic synthesis [60-66]. NHC–Allylpalladium complexes have been employed and showed good catalytic activities in carbon–carbon bond coupling reactions [67-70]. Stereoisomeric complex **7** was firstly applied as the catalyst in the catalyze Suzuki–Miyaura coupling reaction. On the basis of screening of the solvent and base in the reaction of phenylboronic acid with bromobenzene, it was found that using *t*-BuOK as the base in iPrOH at 50 °C for 10 h, the coupling product **9a** was obtained in the highest yield (81% yield) (Supporting Information File 1). Under the optimized conditions, the reactions of various aryl halides with arylboronic acids were carried out, and it was found that the electronic properties of the R groups and halide atoms significantly affected the reaction yield of the Suzuki–Miyaura reactions. The results have been summarized in Table 1.

Table 1: Suzuki–Miyaura reaction catalyzed by NHC–Pd(II) complex **7**[a].



Entry	R	R'	X	Product	Yield (%)[b]
1	4-Me	H	Br	**9a**	81
2	4-COMe	H	Br	**9b**	98
3	2-NO_2	H	Br	**9c**	96
4	2-MeO	H	Br	**9d**	89
5	2-Me	H	Br	**9e**	80
6	4-COMe	4-Me	Br	**9f**	97
7	4-MeO	4-Me	Br	**9g**	81
8	4-Me	2-Cl	Br	**9h**	74
9	H	4-Me	I	**9a**	>99
10	H	4-Me	Cl	**9a**	<5

[a]Reaction conditions: 1 mmol aryl halide, 1.3 mmol arylboronic acid, 1.3 mmol *t*-BuOK, 0.01 mmol NHC–Pd(II) complex, 2.0 mL IPA.
[b]Isolated yields.

The [(NHC)Pd(allyl)I] complex **7** was also examined in the Heck–Mizoroki coupling reaction. Under optimized conditions (Supporting Information File 1), the reactions of various aryl halides with *n*-butyl acrylate were carried out in the presence of Na_2CO_3 in *N*,*N*-dimethylacetamide (DMA) at 140 °C. [(NHC)Pd(allyl)I] complex **7** showed good catalytic activities in the reaction of arylbromides or iodobenzene with *n*-butyl acrylate to afford the coupling products **10** in up to 97% yield. The results have been summarized in Table 2.

Table 2: Heck–Mizoroki reaction catalyzed by NHC–Pd(II) complex **7**[a].



Entry	R	X	Time (h)	Product	Yield (%)[b]
1	H	Br	18	**10a**	82
2	4-Me	Br	18	**10b**	79
3	4-MeO	Br	18	**10c**	80
4	4-CHO	Br	18	**10d**	85
5	2-Me	Br	18	**10e**	76
6	H	I	18	**10a**	97
7	H	Cl	18	**10a**	<5

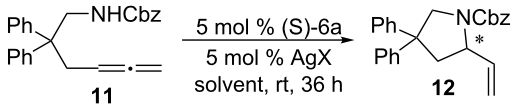
[a]Reaction conditions: **7** (1 mol % Pd), Na_2CO_3 (2.0 mmol), TBAB (0.1 mmol), aryl halide (1.0 mmol) and *n*-butyl acrylate (1.5 mmol) in DMA (3.0 mL) at 140 °C for 18 h.
[b]Isolated yield after silica gel column chromatography.

Intramolecular hydroamination reaction catalyzed by NHC–Au(I) complex (*S*)-6a

Since the first example of NHC–Au complex was reported in 1989 [71], a variety of neutral or cationic NHC–Au complexes has been synthesized and applied in many catalytic reactions [72,73]. For example, recently, NHC–Au showed good catalytic activity in the intramolecular [4 + 2] cycloadditions of 1,3-enynes or arylalkynes [74], rearrangement of allylic acetates [75,76], carbene-transfer reactions from ethyl diazoacetate [77], formation of conjugated enones and enals [78], regio- and stereoselective synthesis of fluoroalkenes [79], and so on [80-85]. However, reports on NHC–Au catalyzed asymmetric reactions are rare [86]. The NHC–Au(I) complex (*S*)-**6a** was consequently investigated as the catalyst in the asymmetric intramolecular hydroamination of allenes. This reaction has been achieved with high enantioselectivity by a chiral phosphine–Au(I) complex [87-93]. Treatment of allene **11** with (*S*)-**6a** and $AgSbF_6$ (5 mol %) in DCM at room temperature for 36 h afforded pyrrolidine derivative **12** in 53% yield with an ee of only 10%. When THF or toluene was used as solvent, only traces of compound **12** were formed. Further screening of AgX revealed that the combination of (*S*)-**6a** and $AgClO_4$ gave the best catalytic activity in this reaction (Table 3).

We assumed that the ill-defined chiral space at the Au center may be the cause of the low ee, and that a more sterically bulky group than an acetyl group in another phenyl framework may be required to improve the enantioselectivity. Accordingly, the original acetyl group was replaced by a more sterically bulky group such as *tert*-butoxycarbonyl group and adamantanecarbonyl group.

Table 3: NHC–Au complex (*S*)-**6a** catalyzed asymmetric intramolecular hydroamination.

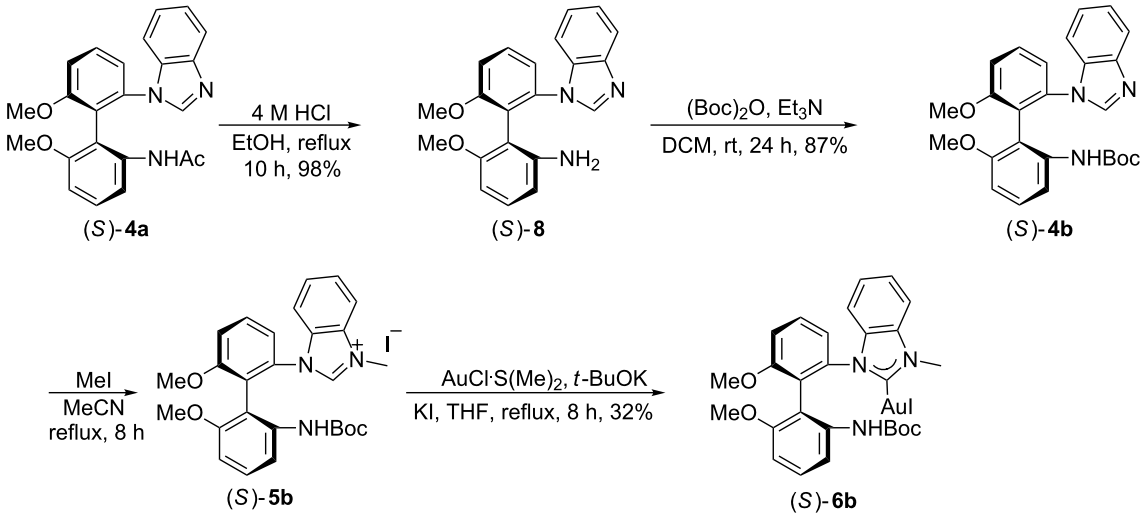


Entry	Solvent	AgX	Time (h)	Yield (%)[a]	ee (%)[b]
1	THF	$AgSbF_6$	36	trace	—[c]
2	Toluene	$AgSbF_6$	36	trace	—
3	DCM	$AgSbF_6$	36	53	10
4	DCE	$AgSbF_6$	36	43	7
5	DCM	$AgClO_4$	36	63	10
6	DCM	AgOTf	36	42	10
7	DCM	AgOTs	36	—[d]	—
8	DCM	$AgBF_4$	36	46	0

[a]Isolated yield.
[b]Determined by chiral HPLC.
[c]not determined.
[d]no reaction.

Synthesis of the NHC–Au(I) complexes (*S*)-6b and 6c

The synthesis of (*S*)-**6b** is shown in Scheme 4: Thus (*S*)-**4a** was heated under refux with 4 M HCl in EtOH to afford the corresponding amide (*S*)-**8** in 98% yield. Amine (*S*)-**8** was then treated with $(Boc)_2O$ in the presence of Et_3N at room temperature for 24 h to give the corresponding BOC derivative (*S*)-**4b** in 87% yield. Quaternization of the benzimidazole ring of (*S*)-**4b** with methyl iodide in acetonitrile gave the corresponding benzimidazolium salt (*S*)-**5b** in quantitative yield. Benzimida-

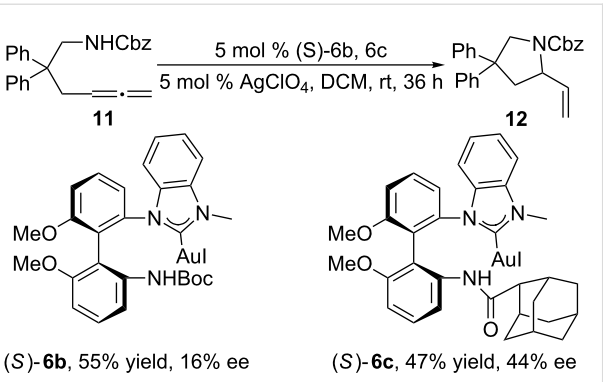


Scheme 4: Synthesis of mono(NHC)–Au(I) complex (*S*)-**6b**.

zolium salt (*S*)-**5b** was then complexed with Au (I) as described above for (*S*)-**6a** ($AuCl{\cdot}S(Me)_2$ in the presence of KI and *t*-BuOK in THF for 8 h) to produce the expected chiral NHC–Au(I) complex (*S*)-**6b** in 32% yield.

For the preparation of (*S*)-**6c**, (*S*)-6,6'-dimethoxybiphenyl-2,2'-diamine was treated with adamantane-2-carbonyl chloride in the presence of Et_3N at room temperature (25 °C) in DCM to afford the corresponding amide (*S*)-**1c** in 71% yield. According to the synthetic method for the synthesis of compound (*S*)-**6a**, NHC–Au complex (*S*)-**6c** was successfully prepared in 45% yield (Scheme 5).

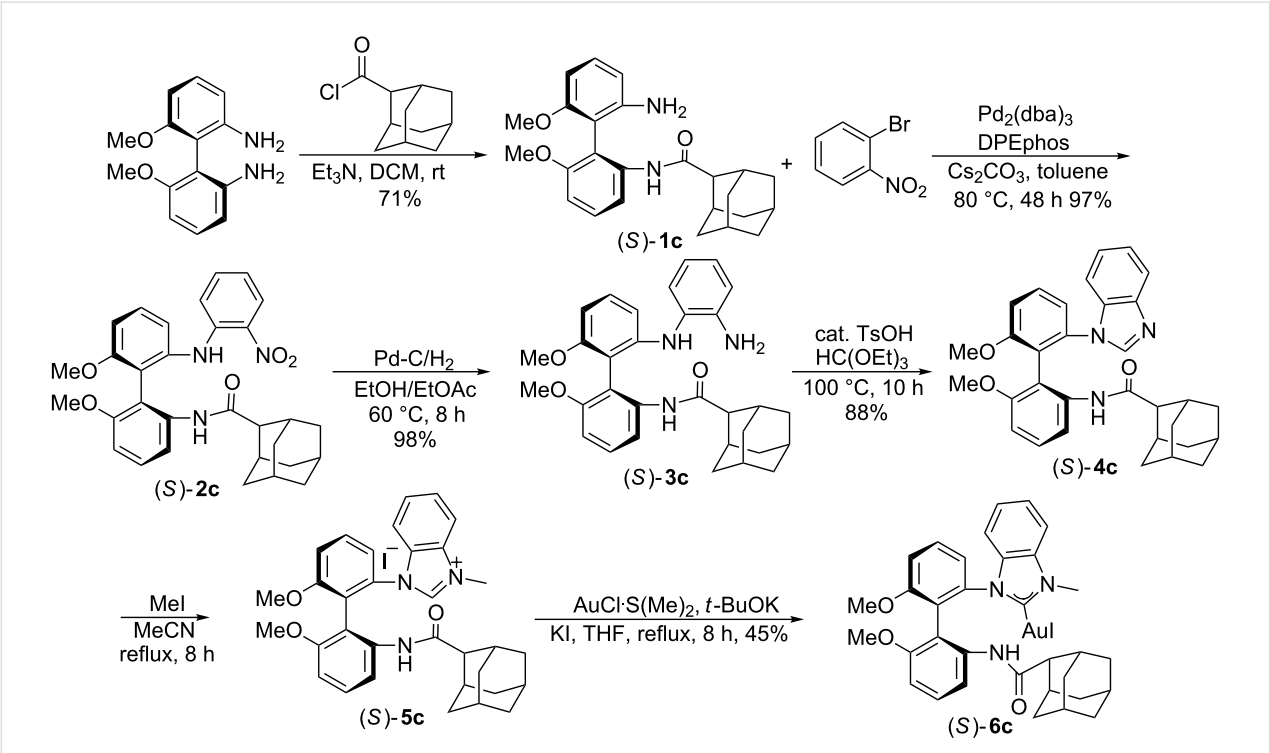
Under the optimized conditions, (*S*)-**6b** and (*S*)-**6c** were used as catalysts to examine their chiral induction abilities in the intramolecular hydroamination reaction (Scheme 6). As expected, the corresponding pyrrolidine derivative **12** was obtained in higher ee value but in lower isolated yield: With (*S*)-**6c** as catalyst, **12** was obtained in 47% yield with an ee of 44% whereas with (*S*)-**6b** as catalyst, **12** was obtained in 55% yield but the ee was only 16%.



Scheme 6: The application of catalysts (*S*)-**6b** and **6c** in the intramolecular hydroamination reaction.

Conclusion

Axially chiral mono(NHC)–Pd(II) and mono(NHC)–Au(I) complexes with one side shaped 1,1'-biphenyl backbone have been prepared from chiral 6,6'-dimethoxybiphenyl-2,2'-diamine. The Pd(II) complex showed good catalytic activity in the Suzuki–Miyaura and Heck–Mizoroki coupling reactions. The (*S*)-Au(I) complex also showed moderate catalytic activities along with moderate chiral inductions in the asymmetric intramolecular hydroamination reaction. Using chiral Au complex (*S*)-**6c**, having a sterically hindered 2-adamantanecarbonyl group, as the catalyst gave the corresponding intramolecular hydroamination product in higher enantioselectivity (44% ee). Efforts are underway to extend the scope and limitations of these chiral (NHC) Pd(II) and Au(I) complexes in other asymmetric catalytic reactions.



Scheme 5: Synthesis of mono(NHC)–Au(I) complex (*S*)-**6c**.

Experimental

Synthesis of NHC–Pd(II) complex 7

Compound **5a** (105.8 mg, 0.2 mmol) and $[PdCl(\eta^3\text{-allyl})]_2$ (109.1 mg, 0.3 mmol), *t*-BuOK (56 mg, 0.5 mmol) were heated under reflux in THF (10 mL) for 8 h. The volatiles were then removed under reduced pressure and the residue purified by a silica gel flash column chromatography (eluent: petroleum ether/ethyl acetate, 2:1–0:1) to give **7** as a mixture of two isomers (117.0 mg, 70%). A single crystal grown from racemic complex **7** in a saturated solution of DCM:pentane (1/3) was suitable for X-ray crystal structure analysis. (*S*)-**7**, light yellow solid; mp: 124.6–125.3 °C; $[\alpha]_D^{20}$ +13.0 (*c* 0.25, $CHCl_3$); IR (DCM) ν 3303, 3037, 2933, 2838, 1688, 1688, 1594, 1520, 1464, 1378, 1256, 1125, 1090, 1062, 1004, 976, 939, 733, 560, 530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ [2.07 (s, CH_3), 2.14 (s, CH_3), 1:1.2, 3H], [2.53 (d, *J* = 12.0 Hz, CH_2), 2.71 (d, *J* = 13.2 Hz, CH_2), 1:1.2, 1H], [2.84 (s, OCH_3), 2.88 (s, OCH_3), 1:1.2, 3H], [3.07 (d, *J* = 13.2. Hz, CH_2), 3.65 (d, *J* = 6.8 Hz, CH_2), 1.2:1, 1H], [3.76 (s, OCH_3), 3.79 (s, OCH_3), 1:1.2, 3H], [3.81 (s, CH_3), 3.92 (s, CH_3), 1:1.2, 3H], 4.23 (brs, 1H, CH_2), [4.86–4.95 (m, CH), 5.19–5.29 (m, CH), 1:1.2, 1H], [6.35 (d, *J* = 8.4 Hz, CH_2), 6.39 (d, *J* = 8.0. Hz, CH_2), 1:1.2, 1H], 7.09–7.23 (m, 3H, ArH), 7.29–7.36 (m, 4H, ArH), 7.43–7.69 (m, 3H, ArH), [8.10 (s, NH), 8.18 (s, NH), 1:1.2, 1H]; MS (ESI) *m/z* (%): 675 (M^+, 60.07), 402 (M^+−273, 100), 274 (M^+−401, 28.80); Anal. Calcd. for $C_{27}H_{28}IN_3O_3Pd$ requires: C, 47.98; H, 4.18; N, 6.22%. Found: $C_{27}H_{28}IN_3O_3Pd$, C 47.78, H 4.68, N 5.78%.

Synthesis of NHC–Au(I) complex (S)-6a

Compound (*S*)-**5a** (105.8 mg, 0.2 mmol) and $AuCl{\cdot}S(Me)_2$ (58.8 mg, 0.2 mmol), KI (49.8 mg, 0.3 mmol) *t*-BuOK (56 mg, 0.5 mmol) were heated under reflux in THF (10 mL) for 8 h. The volatiles were then removed under reduced pressure and the residue purified by a silica gel flash column chromatography (eluent: petroleum ether/ethyl acetate, 2:1–0:1) to give **8** as a white solid (94 mg, 65%). A single crystal grown from racemic complex **6a** in a saturated solution of DCM/pentane (1:3) was suitable for X-ray crystal structure analysis. (*S*)-**6a**: white solid; mp: 184.3–129.6 °C; $[\alpha]_D^{20}$ +5.0 (*c* 0.25, $CHCl_3$); IR (DCM) ν 3407, 2929, 2835, 1697, 1591, 1468, 1438, 1286, 1083, 1002, 852, 779, 747, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 2.19 (s, CH_3, 3H), 3.21 (s, OCH_3, 3H), 3.81 (s, OCH_3, 3H), 3.97 (s, CH_3, 3H), 6.36 (d, *J* = 8.4 Hz, Ar, 1H), 7.11–7.25 (m, Ar and NH, 5H), 7.32–7.37 (m, Ar, 4H), 7.47 (d, *J* = 8.0 Hz, Ar, 1H), 7.62 (t, *J* = 8.0 Hz, Ar, 1H); MS (ESI) *m/z* (%): 551 (M^+, 10.05), 598 (M^+−127, 100), 612 (M^+−113, 22.10); Anal. Calcd. for $C_{24}H_{23}IN_3O_3Au$ requires: C, 39.74; H, 3.20; N, 5.79%. Found: $C_{24}H_{23}IN_3O_3Au$ C 40.64, H 3.08, N 5.72%.

General procedure for the intramolecular hydroamination reaction catalyzed by NHC–Au(I) complex (*S*)-6a

A mixture of NHC–Au(I) (*S*)-**6a** (7.2 mg, 5 mol %) and AgX (5 mol %) in DCM (0.4 mL) was stirred at rt for 5 min. A solution of compound **11** (76.6 mg, 0.20 mmol) in DCM (0.6 mL) was added to the resulting solution and the mixture stirred at rt for 36 h. Column chromatography of the reaction mixture gave the desired product. The enantiomeric purity of the product was determined by chiral HPLC analysis.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data of compounds given in this article.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-64-S1.pdf]

Supporting Information File 2

Crystal structure data for NHC–Pd(II) complex **7a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-64-S2.pdf]

Supporting Information File 3

Crystal structure data for NHC–Au(I) complex **6a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-64-S3.pdf]

Supporting Information File 4

Crystal structure information file of compound **6a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-64-S4.cif]

Supporting Information File 5

Crystal structure information file of compound **7a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-64-S5.cif]

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Beilstein Journal of Organic Chemistry

One-pot gold-catalyzed synthesis of 3-silylethynyl indoles from unprotected *o*-alkynylanilines

Jonathan P. Brand, Clara Chevalley and Jérôme Waser*

Letter

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Address:
Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH4306, 1015 Lausanne, Switzerland

Email:
Jonathan P. Brand - jonathan.brand@epfl.ch; Jérôme Waser* - jerome.waser@epfl.ch

* Corresponding author

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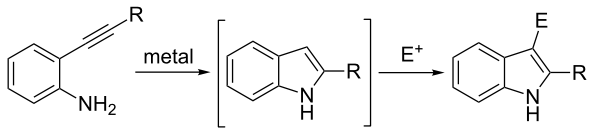
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Abstract

The Au(III)-catalyzed cyclization of 2-alkynylanilines was combined in a one-pot procedure with the Au(I)-catalyzed C3-selective direct alkynylation of indoles using the benziodoxolone reagent TIPS-EBX to give a mild, easy and straightforward entry to 2-substituted-3-alkynylindoles. The reaction can be applied to unprotected anilines, was tolerant to functional groups and easy to carry out (RT, and requires neither an inert atmosphere nor special solvents).

Introduction

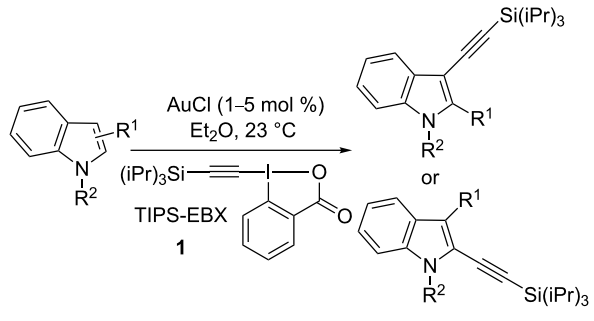
Indoles are widespread in both natural products and synthetic drugs [1,2] and as a result, their synthesis and functionalization have been extensively studied [3,4]. Among the numerous syntheses of indoles, the cyclization of 2-alkynylanilines has the advantage that the resulting products, 2-substituted indoles, are easily functionalized by electrophilic aromatic substitution at position 3. Traditionally, this transformation has been achieved in two separate steps, with isolation and purification of the 3-unsubstituted indole intermediate. Domino or one-pot processes constitute a more efficient access to organic molecules, as they avoid the use of time and resource consuming work-up, and purification procedures [5-7]. When considering the importance of multi-functionalized indoles, it is therefore not surprising that the aniline cyclization–electrophilic substitution sequence has been achieved by means of several metal-catalyzed domino processes (Scheme 1) [8-10].



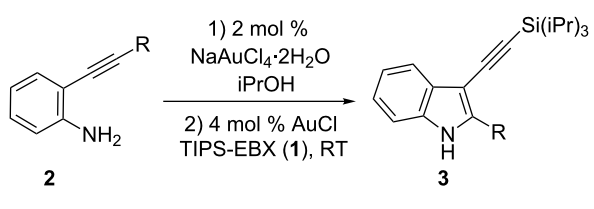
Scheme 1: Domino cyclization–substitution reactions of 2-alkynylanilines.

Among the different π-activating metals capable of promoting nucleophilic attack on acetylenes, gold has recently attracted interest from the synthetic chemistry community [11-14]. Gold catalysts have also been used in domino sequences starting from *o*-alkynylanilines. Arcadi and Marinelli reported that gold-catalyzed cyclization of 2-alkynylanilines can be followed by 1,4-addition to enones [15,16], iodination [17] or reaction with 1,3-dicarbonyl compounds [18]. Perumal recently demonstrated that aldehydes and nitroalkenes can be used as electrophilic partners [19,20]. Triple bonds can also serve as a second electrophile for the construction of tetrahydrofurans [21] and aryl-annulated[*a*]carbazoles [22]. Nakamura examined the cyclization of *N*-tosyl-*o*-alkynylanilines and observed an internal transfer of the sulfonyl group to the 3-position of the formed indoles [23,24]. Similar transformations were also achieved for the transfer of carbonyl groups, but using platinum catalysts [25-28].

To date, there are no gold- or platinum-catalyzed methods for the introduction of acetylenes as electrophiles. However, Cacchi developed a palladium-catalyzed domino sequence including cyclization of *o*-alkynyltrifluoroacetanilides and alkynylation with bromoacetylenes [29]. New methods are needed to expand the scope of this transformation and Au catalysis appears especially promising, due to its broad functional groups tolerance, which could allow the direct use of unprotected anilines.



Scheme 2: Gold-catalyzed direct alkynylation of indoles with TIPS-EBX (**1**).



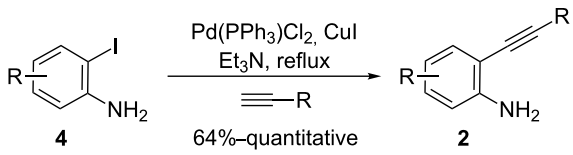
Scheme 3: One-pot alkynylaniline cyclization/direct alkynylation.

Recently, the direct alkynylation of preformed heterocycles has been intensively investigated [30-34]. Most of the developed methods involve the use of haloacetylenes. In contrast, our group has focused on the use of more reactive alkynyl hypervalent iodine reagents in order to expand the scope of direct alkynylation methods under milder conditions. We recently reported a mild procedure for the C3-selective alkynylation of indoles using AuCl and the commercially available benziodoxolone TIPS-EBX (1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**1**)) (Scheme 2) [35-40]. This methodology allowed the ethynylation of a wide range of indoles, including 2-substituted indoles.

In this letter we would like to report the one-pot combination of the cyclization of 2-alkynylanilines using $NaAuCl_4$ as catalyst [15] followed by C3-alkynylation with AuCl and TIPS-EBX (**1**) (Scheme 3). This method offers an operationally simple access to 3-silylalkynyl indoles. To the best of our knowledge, this is the first example of a one-pot process combining a Au(III) and a Au(I) catalyst.

Findings

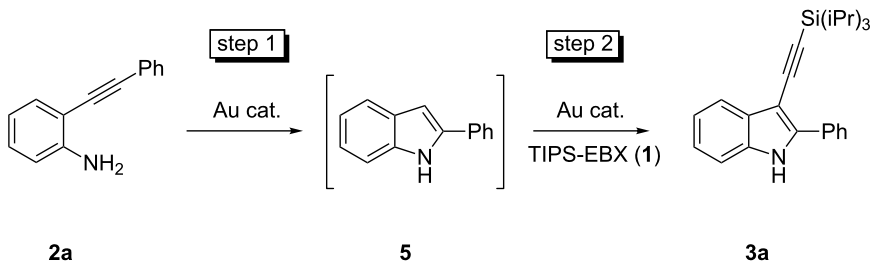
2-Alkynylanilines **2** can be efficiently prepared from 2-iodoanilines **4** and terminal alkynes via Sonogashira reaction with Et_3N as solvent (Scheme 4) [41,42]. The reaction was complete in less than 2 h and did not require aniline protection, solvent degassing or drying.



Scheme 4: Synthesis of 2-alkynylanilines **2**.

Our first investigations were focused on the cyclization of 2-(phenylethynyl)aniline (**2a**) into 2-phenylindole (**5**) with AuCl as the catalyst at room temperature (Scheme 5, step 1). Since AuCl has been shown to be the best catalyst for the alkynylation reaction [35], its use would allow a domino process with a single catalyst.

Despite the fact that the use of AuCl has been reported for step 1 [19,20], in our hands the reaction was not reproducible at room temperature in a variety of solvents (EtOH, CH_3CN, Et_2O). A black precipitate was observed after catalyst addition, which we postulate was due to the stochastically degradation of AuCl under these conditions. $NaAuCl_4$ has also been reported to be successful for the cyclization of 2-(phenylethynyl)aniline



2a 5 3a

Scheme 5: Domino cyclization–alkynylation of aniline **2a**.

(**2a**) [15]. This catalyst was next examined in different solvents in order to maximize the chance of finding conditions suitable for both steps of the process. Aniline **2a** was fully converted into 2-phenylindole (**5**) in EtOH, iPrOH and Et_2O after 3 h at room temperature using 2 mol % of $NaAuCl_4$ and there was no problem of reproducibility. Unfortunately, $NaAuCl_4$ was not an efficient catalyst for the direct alkynylation of indole, as no reaction was observed when TIPS-EBX (**1**) was added to the reaction mixture.

We then investigated the successive addition of $NaAuCl_4$ and AuCl in the same pot. Interestingly, one-pot sequential processes using both Au(I) and Au(III) have not yet been reported. AuCl and TIPS-EBX (**1**) were added when full conversion of the $NaAuCl_4$-catalyzed cyclization was observed. When 2 mol % of $NaAuCl_4$ and 2 mol % AuCl were added, the second step was unsuccessful. However, with 2 mol % of $NaAuCl_4$ and 4 mol % of AuCl, full conversion was observed after 30 h at room temperature in iPrOH (compared with 60% in EtOH and 40% in Et_2O). A basic work-up allowed the removal of the 2-iodobenzoic acid and column chromatography afforded the product in 96% yield (average of two reactions). Unfortunately, no reaction was observed when AuCl and TIPS-EBX (**1**) were added at the beginning of the reaction.

The scope of the reaction was then investigated (Scheme 6). Methyl- and fluoro groups were tolerated on the 2-aryl substituent to give products **3b** and **3c** in good yields. The low solubility of the indole intermediate in the synthesis of **3d** led to a low yield for the direct alkynylation step. The addition of CH_2Cl_2 overcame this problem. Chloro substitution in para-position of the aniline was also tolerated (**3e**, **3f**). Nevertheless, when the strongly electron-withdrawing cyano group was present, the cyclization step was too slow at room temperature. However, the use of 4 mol % of $NaAuCl_4$ and a reaction temperature of 80 °C led to the formation of the desired indole, which could then be alkynylated at room temperature to give **3g**. *o*-Hexynyl aniline (**2h**) was efficiently transformed into **3h** in 85% yield. In order to access 2-silyl indoles, the synthesis of the 2-trimethylsilylacetylene substituted compound **3i** was attempted. Unfortunately, only traces of the indole intermediate were observed in this case. The reaction with 2-ethynylaniline to give (**3j**) was also unsuccessful as previously reported [16].

These first results on the direct alkynylation reaction combined in a one-pot procedure with gold-catalyzed indole ring formation are promising, and analogous strategies combining palladium-catalyzed synthesis of indoles [3] and gold-catalyzed alkynylation could also be envisaged. The next step will be to attempt a one-pot 3-steps synthesis of alkynyl indoles starting directly from iodoaniline.

In conclusion, an efficient access to 2-substituted 3-silylalkynyl indoles is reported. 2-Alkynylanilines underwent a sequential one-pot Au(III)-catalyzed annulation and Au(I)-mediated direct alkynylation. Importantly, this transformation did not require prior aniline protection and proceeded under mild conditions. This methodology represents the first example of the sequential addition of Au(III) and Au(I) catalysts for a one-pot process.

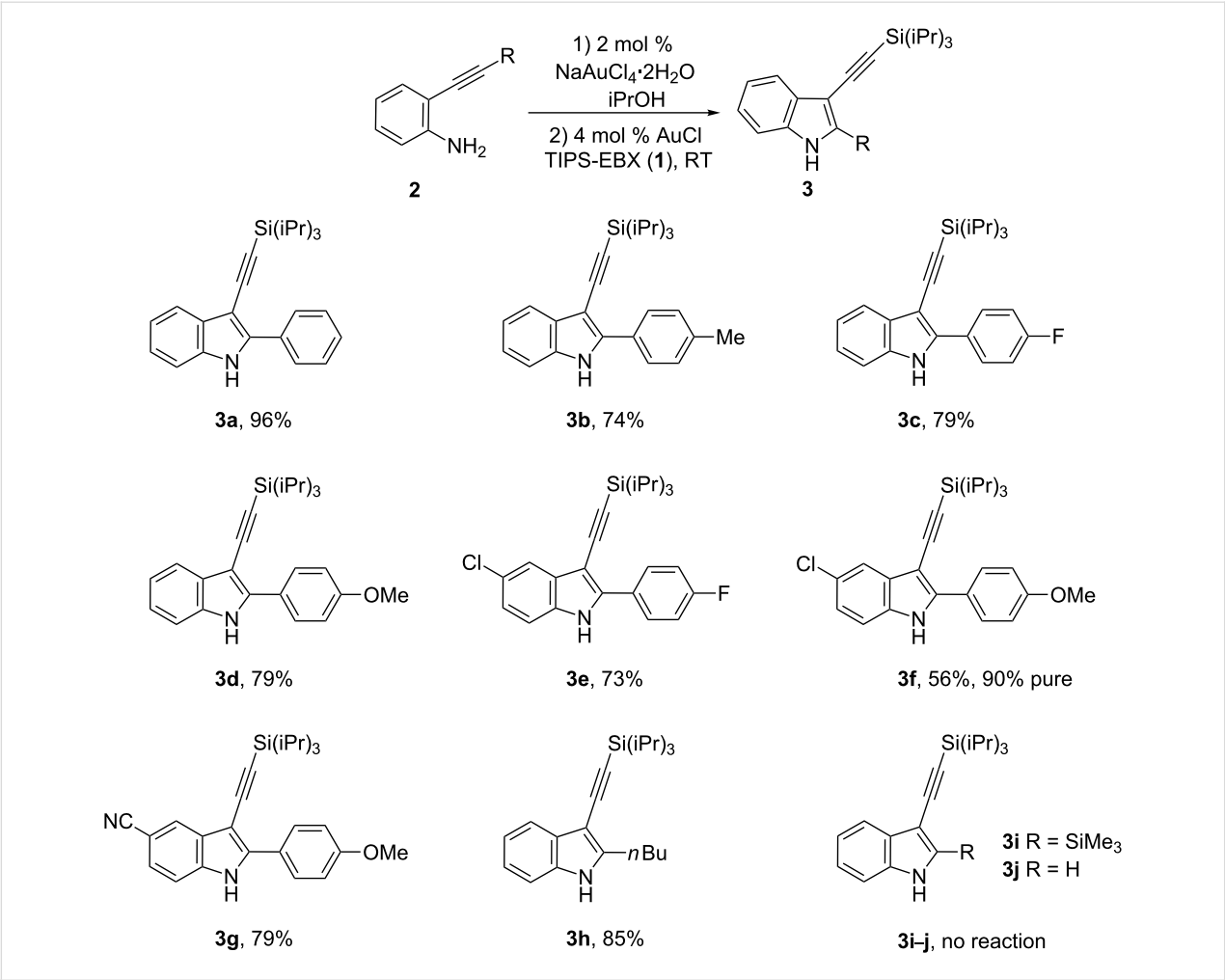
Experimental

General procedure for the synthesis of 2-alkynylanilines **2**

A solution of 2-iodoaniline (**4**) (1 equiv), terminal alkyne (1.2–1.3 equiv), $PdCl_2(PPh_3)_2$ (10 mol %) and CuI (10 mol %) was heated under reflux in Et_3N (15 mL) for 1.5–2 h under a nitrogen atmosphere. The resulting mixture was filtered through Celite®, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography.

General procedure for the synthesis of 2-substituted 3-alkynyl indoles **3**

$NaAuCl_4$ (2–4 mol %) was added to a stirred solution of 2-alkynylaniline **2** (0.40 mmol, 1 equiv) in iPrOH (3 mL) under an ambient atmosphere. The reaction was stirred at RT (80 °C for **3g**) until full conversion (3 h). TIPS-EBX (**1**) (1.2–2.4 equiv) and then AuCl (4–8 mol %) were added. The reaction was stirred until full conversion (4–30 h) and then concentrated



Scheme 6: Scope of the reaction.

under vacuum. Et_2O (20 mL) was added and the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed successively with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography.

Supporting Information

Supporting Information File 1

Experimental details and spectra of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-65-S1.pdf]

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A gold-catalyzed alkyne-diol cycloisomerization for the synthesis of oxygenated 5,5-spiroketals

Sami F. Tlais and Gregory B. Dudley*

Full Research Paper

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Address:
Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390 USA, Fax: (850) 644-8281

Email:
Gregory B. Dudley* - gdudley@chem.fsu.edu

* Corresponding author

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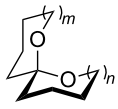
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Abstract

A highly efficient synthesis of oxygenated 5,5-spiroketals was performed towards the synthesis of the cephalosporolides. Gold(I) chloride in methanol induced the cycloisomerization of a protected alkyne triol with concomitant deprotection to give a strategically hydroxylated 5,5-spiroketal, despite the potential for regiochemical complications and elimination to furan. Other late transition metal Lewis acids were less effective. The use of methanol as solvent helped suppress the formation of the undesired furan by-product. This study provides yet another example of the advantages of gold catalysis in the activation of alkyne π-systems.

Introduction

Spiroketals, exemplified by structure shown in Figure 1, are prominent structural features of many biomedically relevant natural and non-natural target structures [1-4]. As such, the synthesis of spiroketals has received considerable attention, with most progress having been made on systems that include at least one six-membered ring [5]. 5,5-Spiroketals (*m*, *n* = 0, Figure 1), particularly oxygenated 5,5-spiroketals such as are found in the cephalosporolides (Figure 2), are the focus of this study.



m = 0, *n* = 0: 5,5-spiroketal
m = 0, *n* = 1: 5,6-spiroketal
m = 1, *n* = 1: 6,6-spiroketal

Figure 1: Common spiroketal motifs.

A variety of synthetic methods are available for the synthesis of 5,5-spiroketals, including cyclocondensation of ketone diols [6,7], the cycloisomerization of alkyne diols (Scheme 1) [8-16], oxidative spirocyclization of tetrahydrofuryl propanols [17-20], and others. Cyclocondensation of ketone diols is perhaps the most straighforward and the most used method, but the alter-

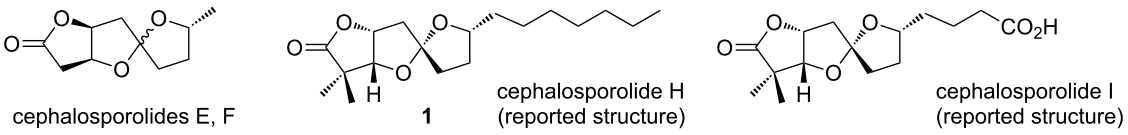
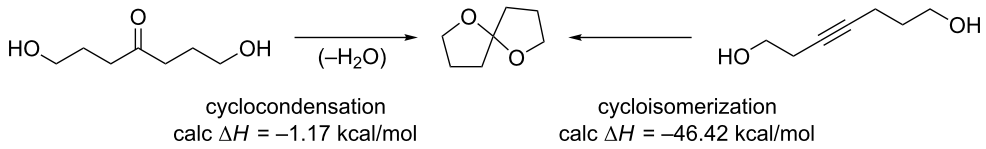


Figure 2: Spiroketal-containing cephalosporolide natural products.



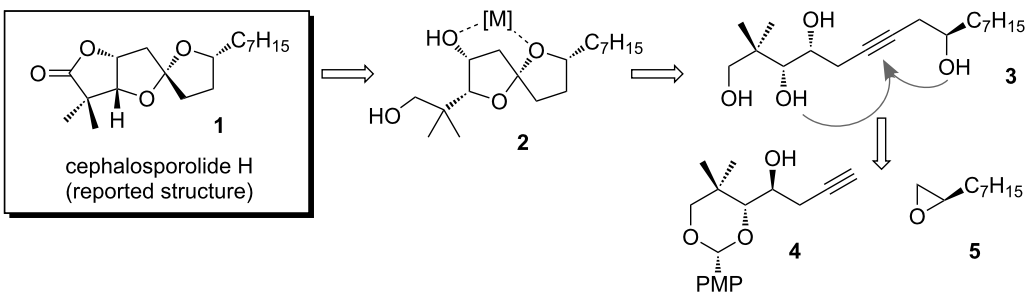
Scheme 1: Cyclocondensation vs. cycloisomerization for the synthesis of spiroketals.

native procedures offer specific advantages. For example, the cycloisomerization of alkyne diols is more exothermic (Scheme 1) [21] and atom economical [22], and non-polar alkyne π-bonds are more compatible than ketones (kinetically stable) towards a number of common reaction conditions. Conversely, the use of alkynes in the synthesis of spiroketals introduces regiochemistry concerns as to which of the two alkyne carbons becomes the spiroketal carbon, and the kinetic stability of alkynes must be overcome when alkyne reactivity is desired.

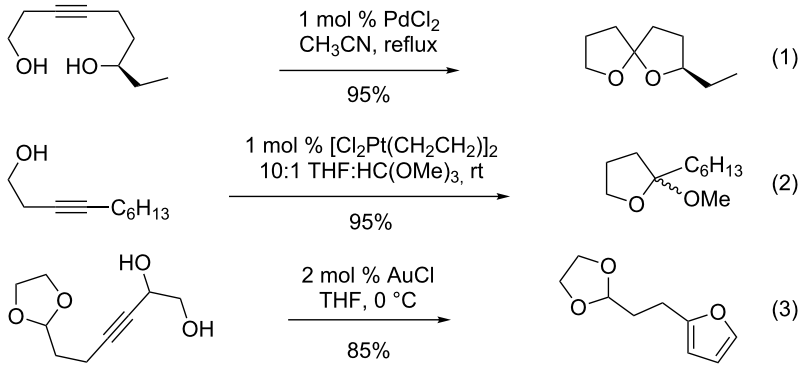
As an off-shoot of our program devoted to the synthesis of functionalized alkynes by fragmentation reactions [23-27], we became interested in the application of alkyne-diol cycloisomerization to the synthesis of the cephalosporolides and other oxygenated spiroketals. Our retrosynthetic analysis of the reported structure of cephalosporolide H (**1**) is outlined in Scheme 2. We recently demonstrated the use of inter-cycle chelation effects to control the spiroketal stereochemistry [28,29]. However, formation of the requisite oxygenated spiroketals (by cycloisomerization) posed significant challenges that required a focused study.

For this thematic issue on gold catalysis in organic synthesis, we detail here the challenges and considerations involved in the cycloisomerization of alkynes to oxygenated spiroketals and outline our screening of various late transition metal catalysts and conditions that ultimately resulted in the acquisition of our target structures [28]. Gold(I) chloride emerged as the best choice for the desired transformation.

The key precedents for the desired cycloisomerization are shown in Scheme 3, although many methods are available [30-34] and no consensus option has emerged. Utimoto studied the palladium-catalyzed cycloisomerization [8] and reported that a range of spiroketals are available in excellent yield (e.g., Scheme 3, Reaction 1). However, regiochemistry is sometimes difficult to control, and De Brabander later found variability in reaction selectivity using the Utimoto conditions to prepare 6,6-spiroketals. Therefore, he suggested the preferred use of Ziese's dimer, a platinum catalyst (Scheme 3, Reaction 2), for such cyclizations [9]. In an unrelated study that also bears on the current work, Aponick and co-workers described a gold-catalyzed cyclocondensation of alkyne diols to give substituted furans (Scheme 3, Reaction 3) [35].



Scheme 2: Retrosynthetic analysis of cephalosporolide H.



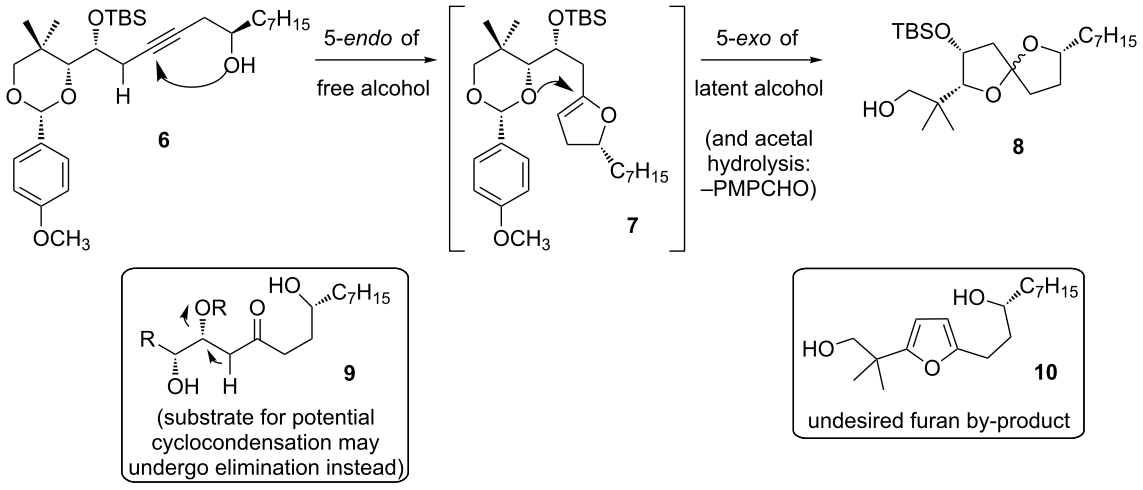
Scheme 3: Key precedents for the desired cycloisomerization.

Our objective, laid out in Scheme 4, was to initiate cycloisomerization with a 5-*endo*-dig cyclization of the homopropargyl alcohol **6**, followed by 5-*exo*-trig cyclization onto the resulting dihydrofuran, whilst avoiding dehydration to furan **10**. The use of alkyne-diol cycloisomerization instead of ketone-diol cyclocondensation is important for the potential success of this approach, since β-alkoxy ketone **9** (Scheme 4, inset) would be more prone to undesired elimination than homopropargyl ether **6**. We addressed regiochemistry by blocking one of the alcohols as an acetal (the alcohol that otherwise could undergo either 5-*exo* or 6-*endo* cyclization [9,13,36]), thus favoring the initial 5-*endo* cyclization of the other. In this way we aimed to ensure that the desired regioisomer could form, with the expectation of acetal hydrolysis during the course of the reaction. Indeed, attempts to induce spiroketalization after removal of the acetal resulted in complex product mixtures (not shown).

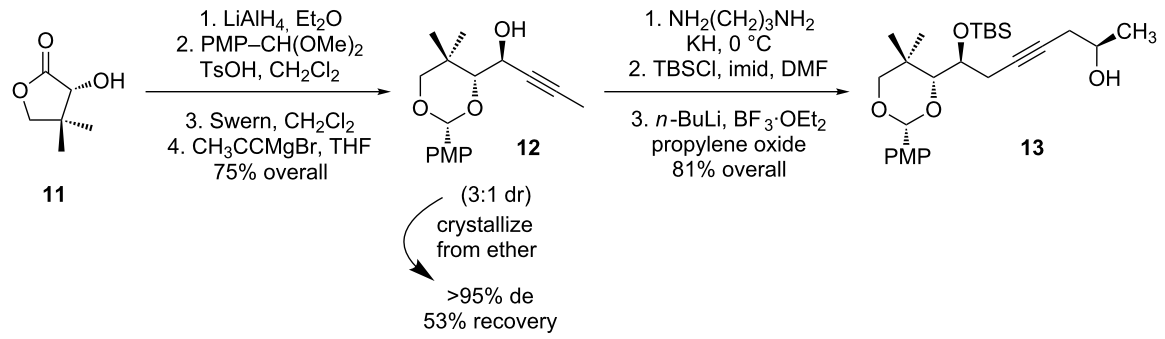
Results and Discussion

Initial studies on the cycloisomerization took advantage of chiral propargyl alcohol **12**, which is readily available from pantolactone (**11**, Scheme 5) [37]. An alkyne zipper reaction, protection, and coupling with propylene oxide gave homopropargyl **13**.

Cycloisomerization of **13** to the spiroketal (**14**) was investigated under a variety of conditions, some of which are featured in Table 1. Utimoto's general conditions as reported (Table 1, entry 1) resulted in decomposition of the substrate, but at room temperature the spiroketal was obtained in modest yield (Table 1, entry 2). Reactions involving Ziese's dimer were disappointing (Table 1, entry 3), but gold(I) chloride in methylene chloride (cf. Scheme 3, Reaction 3) gave more encouraging results. Other gold catalysts and solvents were screened,



Scheme 4: Proposed cycloisomerization with acetal hydrolysis.

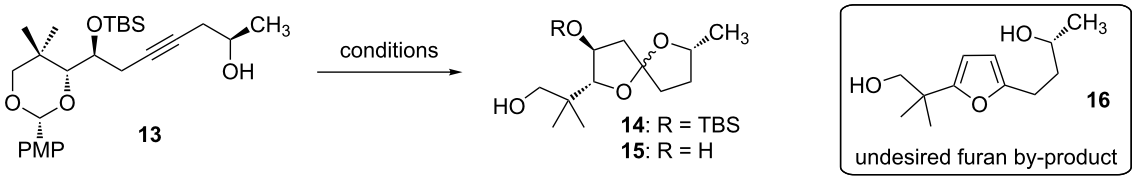


Scheme 5: Synthesis of model cyclization substrate **13**.

with the best results being achieved with a higher catalyst loading of gold(I) chloride in methanol (Table 1, entry 10). The need for higher catalyst loading is tentatively ascribed to some form of instability of the gold catalyst in methanol, as premixing the gold(I) chloride with methanol and aging this mixture prior to adding the substrate results in a less efficient reaction. This is not the first time that we have observed the importance of the order of addition in a gold-catalyzed reaction in a protic solvent [38], but nonetheless we were satisfied with these results for our current study. Furan **16**, which presumably arises by analogy to Aponick's cyclocondensation, was observed in varying amounts in many cases and was the major product in Table 1, entry 11: The use of methanol as a solvent seems to help suppress formation of the (undesired for our purposes) furan product.

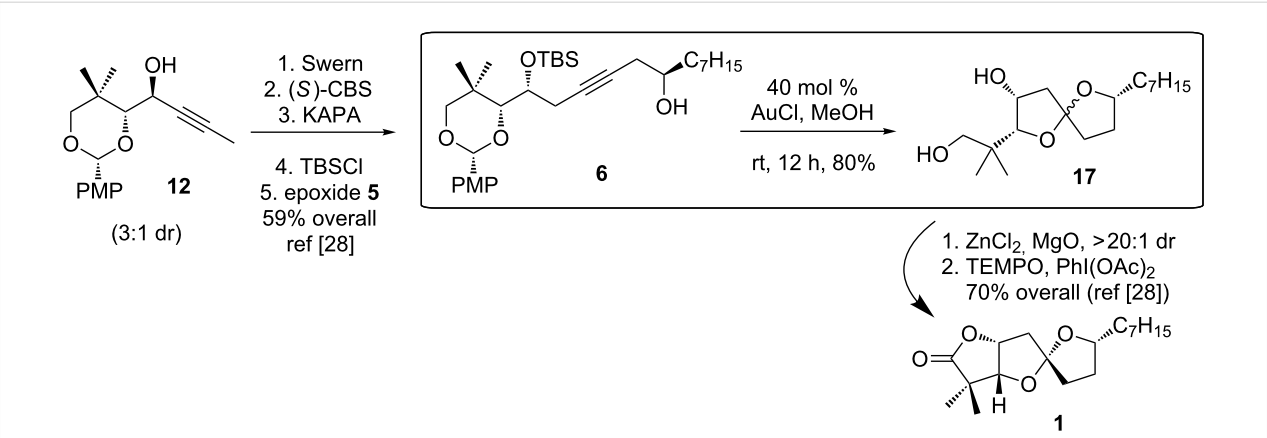
For the synthesis of cephalosporolide H, we prepared homopropargyl alcohol **6** by a two-step inversion of **12**, followed by an alkyne zipper reaction and coupling with nonene oxide (Scheme 6) [28]. Treatment of **6** with 40 mol % gold(I) chloride in methanol resulted in cycloisomerization with simultaneous hydrolysis of the PMP acetal. Meanwhile, cleavage of the silyl ether also occurred under the reaction conditions, and spiroketal diol **17** was isolated in 80% yield as a roughly 1:1 mixture of spiroketal epimers. This mixture of epimers led to a single diastereomer upon chelation with zinc chloride. TEMPO

Table 1: Spiroketalization using late transition metal salt complexes.



Entry	Conditions	Major Product	Yield
1	1% $PdCl_2$, CH_3CN, reflux, 1 h	—	—[a]
2	1% $PdCl_2$, CH_3CN, rt, 1.5 h	**14**	43%[b]
3	1% $[Cl_2Pt(CH_2{=}CH_2)]_2$, Et_2O, rt, then CSA	—	—[a]
4	5% AuCl, CH_2Cl_2, rt, 6 h	**14**	36%
5	5% AuCl, PPTS, CH_2Cl_2, rt, 14 h	**14**	37%
6	5% $AuCl(PPh_3)_3$, CH_2Cl_2, rt	—	—[a]
7	5% $AuCl(PPh_3)_3$, $AgSbF_6$, CH_2Cl_2, rt, 12 h	—	—[a]
8	5% $AuCl_3$, CH_2Cl_2, rt, 12 h	—	—[a]
9	5% AuCl, MeOH, rt, 12 h	**15**	35%
10[c]	25% + 25% AuCl, MeOH, rt, 12 h	**15**	68%
11	35% AuCl, MeCN, rt, 4 h	**16**	18%

[a]complex mixture of products was observed, [b]no increase in yield after a longer reaction time, [c]a second portion of AuCl (25 mol %) was added after 1 h to achieve full conversion.

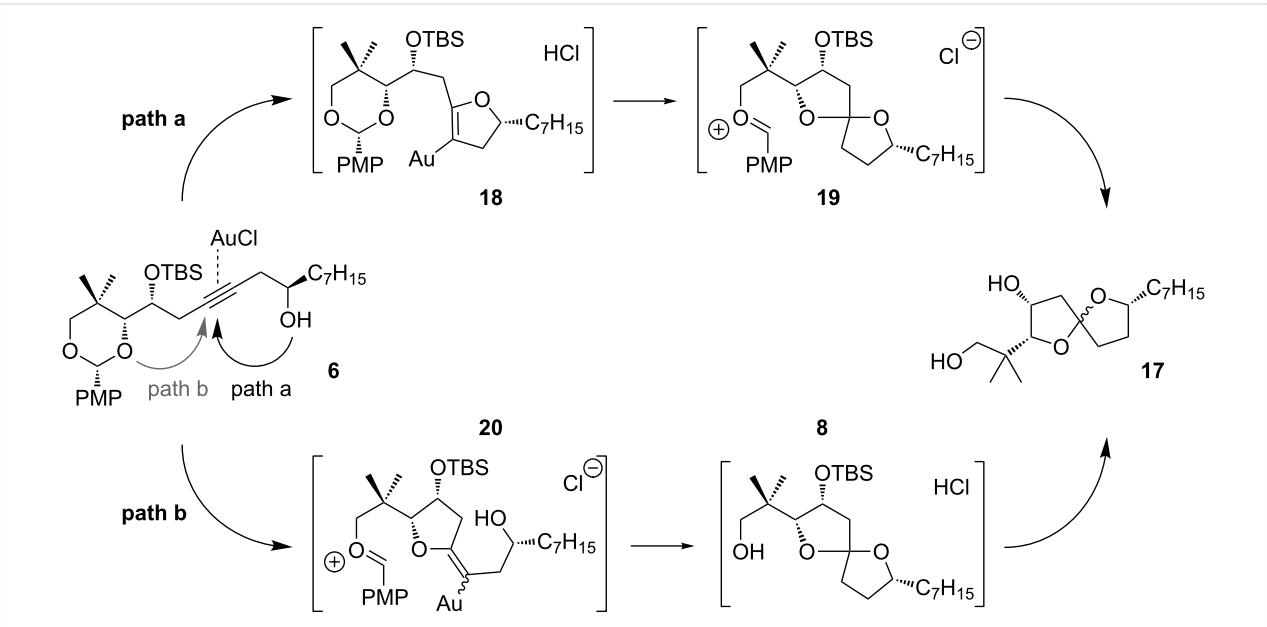


Scheme 6: Synthesis of reported structure of cephalosporolide H.

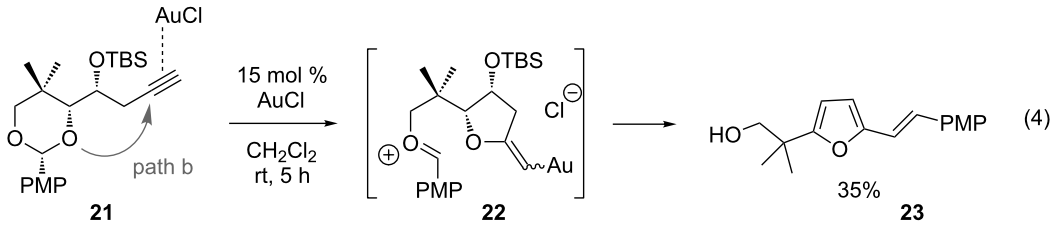
oxidation gave lactone **1**, which corresponds to the reported structure of cephalosporolide H. A more detailed discussion is found in our earlier report [28].

Two mechanistic alternatives (Scheme 7) are proposed for the conversion of **6** → **17** in methanol. Path a, which corresponds roughly to our original experimental designs, involves initial gold-catalyzed 5-*endo*-dig cyclization to dihydrofuran **18**. Once the regiochemistry is established, any number of condensation pathways would lead to spiroketal **17**. For example, protonation of the enol ether could assist in the opening of the acetal, with simultaneous formation of spiroketal **19**. Any carbenium intermediates could be intercepted reversibly by methanol. The acidity of the gold(I) chloride in methanol mixture is sufficient to hydrolyze the secondary silyl ether group in a separate event: The reaction time was intentionally extended to ensure complete desilylation.

A second mechanistic alternative, path b, cannot be ruled out at this time. Path b involves gold-activation of the alkyne followed by 5-*exo*-dig nucleophilic attack of the acetal oxygen. Methanolysis of the acetal and spirocyclization would quickly follow. Although this pathway seems unlikely to compete effectively with path a, a control experiment suggests that path b is feasible under certain conditions (Scheme 8, Reaction 4): We subjected terminal alkyne **21** to gold(I) chloride in methylene chloride and observed the formation of furan **23** in low yield, along with other products.



Scheme 7: Proposed mechanism.



Scheme 8: Control experiment for gold-activation of the alkyne.

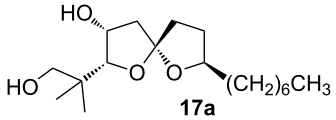
Conclusion

Gold(I) chloride effectively catalyzed the cycloisomerization of homopropargyl alcohol **6** to spiroketal **17** in good yield, despite the potential for regiochemical complications and elimination to give furan by-products. Other late transition metal Lewis acids were less effective. This study provides yet another example of the advantages of gold catalysis in the activation of alkyne π-systems.

Experimental

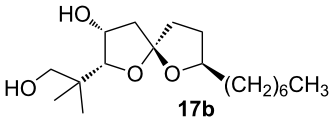
^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to the residual $CHCl_3$ peak (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) with TMS as internal standard. The coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a FT-IR spectrometer (100). Mass spectra were recorded either by electron ionization (EI) or fast-atom bombardment (FAB). Yields refer to isolated material judged to be ≥95% pure by ^{1}H NMR spectroscopy following silica gel chromatography. All solvents, solutions and liquid reagents were added via syringe. Methanol (MeOH), methylene chloride (CH_2Cl_2) and acetonitrile (CH_3CN) were used without any purification. All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. Purifications were performed by flash chromatography on silica gel F-254 (230–499 mesh particle size).

Typical procedure for gold-catalyzed spiroketalization: AuCl (8 mg, 0.036 mmol) was added to a solution of **6** (50 mg, 0.091 mmol) in MeOH (5 mL) at room temperature to give a black mixture. After 4 h, the reaction mixture was filtered, mixed with 100 mg of silica gel, and concentrated under reduced pressure. The silica gel admixed with the crude reaction mixture was transferred to a silica gel column and eluted with 15% EtOAc in hexane to afford pure product **17** (23 mg, 80%).



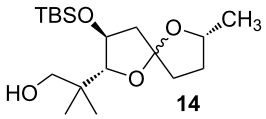
17a

Characterization data for **17a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.26 (m, 1H), 3.98 (ddd, *J* = 13.1, 9.4, 6.1 Hz, 1H), 3.59 (d, *J* = 3.1 Hz, 1H), 3.51 (d, *J* = 10.9 Hz, 1H), 3.46 (d, *J* = 10.9 Hz, 1H), 2.15 (dd, *J* = 13.4, 4.3 Hz, 1H), 2.10–1.91 (m, 4H), 1.75–1.66 (m, 2H), 1.55–1.47 (m, 1H), 1.40–1.20 (m, 13H), 1.09 (s, 3H), 1.02 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 114.1, 91.0, 81.3, 73.3, 71.1, 43.9, 38.0, 37.3, 36.1, 31.8, 30.6, 29.5, 29.2, 26.3, 23.4, 22.6, 20.9, 14.1; IR (Neat): 3280, 2926, 2857, 1461, 1334, 1108; HRMS (ESI$^+$): calcd. for $C_{18}H_{34}O_4Na$ 337.2354, found: 337.2354.



17b

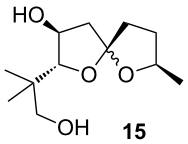
Characterization data for **17b** (obtained as a mixture with **17a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39–4.33 (m, 1H), 4.07–3.97 (m, 1H), 3.67 (d, *J* = 10.7 Hz, 1H), 3.65 (d, *J* = 2.9 Hz, 1H), 2.44 (dd, *J* = 14.3, 5.5 Hz, 1H), 2.21–1.98 (m, 5H), 1.54–1.46 (m, 1H), 1.36–1.23 (m, 12H), 1.07 (s, 3H), 1.05 (s, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 87.9, 78.3, 72.6, 69.7, 69.0, 46.4, 37.5, 36.9, 35.6, 31.8, 30.2, 29.7, 29.3, 25.8, 24.2, 22.7, 21.8, 14.1. IR (Neat): 3280, 2926, 2857, 1461, 1334, 1108; HRMS (ESI$^+$): calcd. for $C_{18}H_{34}O_4Na$ 337.2354, found: 337.2354.



14

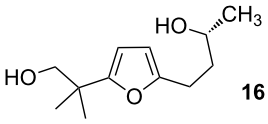
Characterization data for **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (m, 1H) [Major], 4.18 (m, 1H) [Minor], 3.76 (d, *J* = 6.9 Hz, 1H) [Minor], 3.60 (d, *J* = 6.5 Hz, 1H) [Major], 3.49 (m, 1H), 3.39–3.30 (m, 2H), 3.31–2.20 (m, 1H), 2.15–1.86 (m, 4H), 1.68 (m, 1H), 1.43 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 3H) [Major], 1.21 (d, *J* = 6.2 Hz, 3H) [Minor], 0.87 (s, 9H) [Minor], 0.86 (s, 9H) [Major], 0.071 (d, *J* = 1.8 Hz, 6H) [Minor], 0.07(d, *J* = 7.4 Hz, 6H) [Major]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 113.28, 112.79, 92.23, 89.87, 76.85, 74.43, 72.49, 71.61, 71.49, 71.43, 45.43, 45.15, 37.54, 37.18, 36.75, 36.70, 32.34, 31.77, 25.73,

25.70, 22.68, 22.39, 21.20, 21.04, 20.46, 19.73, 17.78, 17.70, −3.95, −4.01, −4.86, −4.95. HRMS (CI^+): calcd. for $C_{18}H_{37}O_4Si$ 345.2455, found: 345.2455.



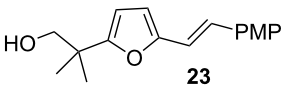
15

Characterization data for **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (dd, *J* = 16.2, 7.1 Hz, 1H), 4.24 (dq, *J* = 6.2, 12.6 Hz, 1H), 4.17–4.06 (m, 2H), 3.86 (d, *J* = 2.6 Hz, 1H), 3.55–3.32 (m, 5H), 3.08 (br s, 1H), 2.95 (br d, *J* = 9.3 Hz, 1H), 2.65 (br s, 1H), 2.57 (br s, 1H), 2.31 (dd, *J* = 12.5, 7.0 Hz, 1H), 2.19–1.88 (m, 9H), 1.76–1.57 (m, 4H), 1.53–1.40 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.6, 113.0, 94.5, 91.7, 76.8, 74.8, 72.9, 72.1, 70.9, 70.8, 44.3, 44.1, 37.5, 37.3, 36.9, 34.0, 32.3, 31.6, 22.5, 21.5, 21.3, 20.99, 20.84, 18.8; IR (Neat): 3389, 3005, 2969, 2873, 1461, 1350; HRMS (ESI^+): calcd. for $C_{12}H_{22}O_4SiNa$ 253.1416, found: 253.1413.



16

Characterization data for **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J* = 3.1 Hz, 1H), 5.90 (d, *J* = 3.0 Hz, 1H), 3.83 (m, 2H), 3.56 (s, 2H), 2.76–2.62 (m, 2H), 1.77 (m, 2H), 1.23 (d, *J* = 12.8 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 114.32, 91.01, 77.14, 73.25, 70.84, 43.98, 38.01, 36.43, 32.16, 23.77, 22.66, 21.01. HRMS (ESI^+): calcd. for $C_{12}H_{20}O_3Na$ 235.1310, found: 235.1315.



23

Characterization data for **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 16.24 Hz, 1H), 6.88 (d, *J* = 8.68 Hz, 2H), 6.71 (d, *J* = 16.24 Hz, 1H), 6.21 (d, *J* = 3.24 Hz, 1H), 6.12 (d, *J* = 3.24 Hz, 1H), 3.82 (s, 3H), 3.64 (d, *J* = 6.56 Hz, 2H), 1.62 (t, *J* = 6.60 Hz, 1H) 1.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.1, 152.4, 129.9, 127.4, 125.8, 114.7, 114.1, 108.4, 106.9, 71.0, 55.2, 38.5, 23.4. HRMS (CI^+): calcd. for $C_{17}H_{20}O_3$ 272.1412, found: 272.1421.

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Construction of cyclic enones via gold-catalyzed oxygen transfer reactions

Leping Liu*, Bo Xu and Gerald B. Hammond*

Review

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Address:
Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, KY 40292, USA

Email:
Leping Liu* - leping.liu@louisville.edu; Gerald B. Hammond* - gb.hammond@louisville.edu

* Corresponding author

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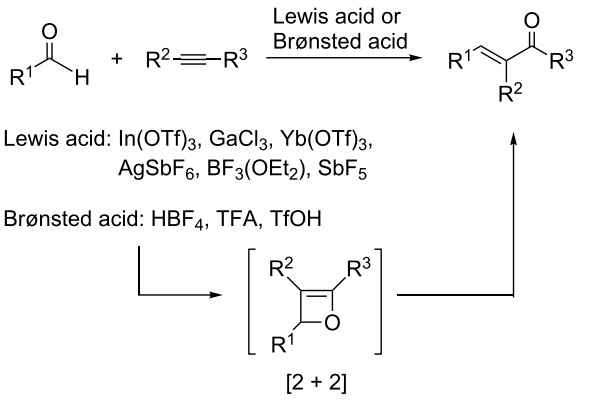
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Abstract

During the last decade, gold-catalyzed reactions have become a tour de force in organic synthesis. Recently, the gold-, Brønsted acid- or Lewis acid-catalyzed oxygen transfer from carbonyl to carbon–carbon triple bond, the so-called alkyne–carbonyl metathesis, has attracted much attention because this atom economical transformation generates α,β-unsaturated carbonyl derivatives which are of great interest in synthetic organic chemistry. This mini-review focuses on the most recent achievements on gold-catalyzed oxygen transfer reactions of tethered alkynones, diynes or alkynyl epoxides to cyclic enones. The corresponding mechanisms for the transformations are also discussed.

Review

α,β-Unsaturated carbonyl derivatives are not only important building blocks in synthetic organic chemistry, but are also a significant motif in natural products and biologically active compounds [1-8]. The construction of the conjugated enone substructure has attracted the interest of synthetic chemists for decades. Among numerous methodologies, aldol condensations and Wittig-type reactions have been widely utilized [9-18]. Recently, it was found that conjugated enones could be generated from the oxygen transfer from a carbonyl group to a carbon–carbon triple bond, the so-called alkyne–carbonyl metathesis. This methodology has sparked the attention of the synthetic community, because it could serve as an efficient and atom-economic alternative to the Wittig reaction by the formation of a new carbon–carbon double bond and the simultaneous installation of a carbonyl group. In this regard, several Lewis or Brønsted acid-catalyzed intermolecular or intramolecular alkyne–carbonyl metatheses have been extensively studied (Scheme 1) [19-27].



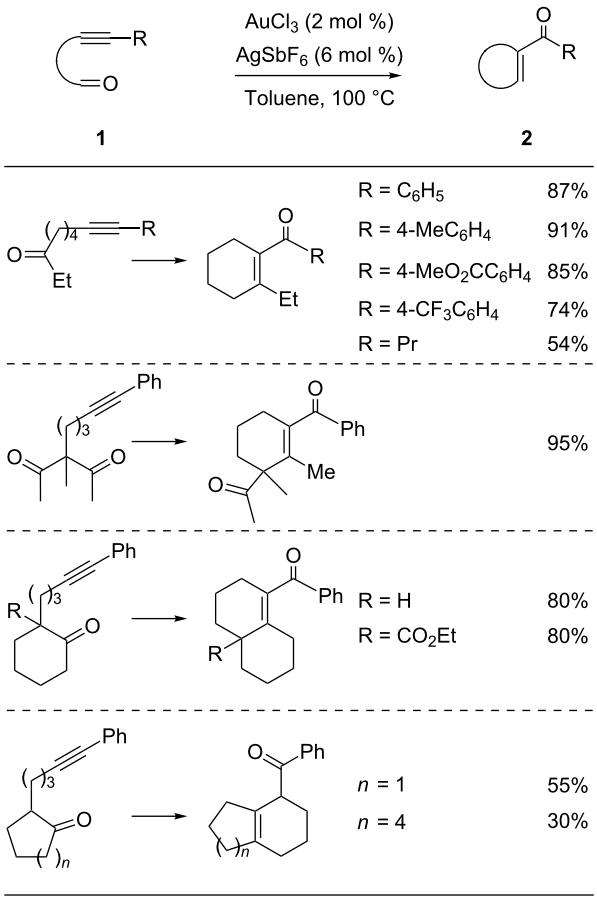
Scheme 1: Lewis acid or Brønsted acid-catalyzed alkyne–carbonyl metathesis and a proposed [2 + 2] intermediate.

During the early years of this century, organic chemists became aware that gold salts or complexes were highly active catalysts in homogeneous catalysis because of the strong π- and σ-electrophilicity of gold [28-33]. Since then, the number of new gold-catalyzed reactions reported in the literature has increased substantially and gold catalysis has become one of the hottest research fields in synthetic organic chemistry [34-42]. Due to their unique alkynophilicity, gold catalysts are especially suited to the activation of carbon–carbon triple bonds.

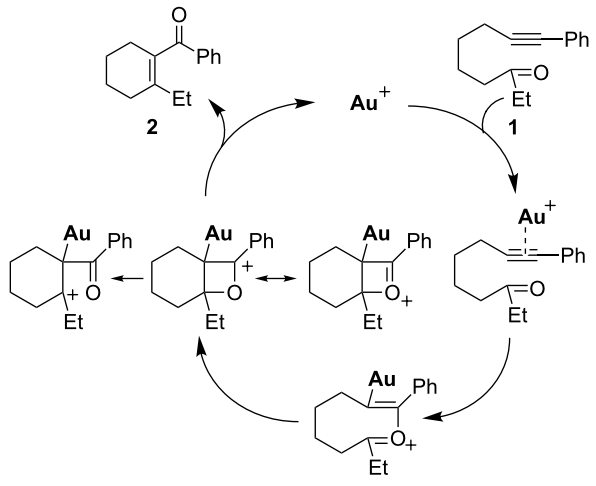
Gold-catalyzed formation of cyclic enones from alkynyl ketones

Yamamoto and co-workers were the first to report the gold-catalyzed formation of conjugated cyclic enones under mild conditions using tethered alkynyl ketones as substrates (Scheme 2) [43]. Both, aromatic and aliphatic groups substituted on alkynyl ketones **1** were investigated in this reaction, and the corresponding enone products **2** were isolated in good yields. They employed the alkyne–carbonyl metathesis in the preparation of fused ring systems and obtained two six-membered bicyclic products. However, if the original ring was five- or eight-membered, the reaction produced β,γ-unsaturated bicyclic enones rather than their α,β-unsaturated counterparts.

Yamamoto and co-workers proposed a [2 + 2] mechanism for their gold-catalyzed cyclization of alkynyl ketones (Scheme 3). In their mechanism, the carbonyl group attacks the gold activated triple bond to form an oxonium intermediate, which then generates an oxetenium intermediate. After several electron transfer steps, the cyclic enone product is formed. A similar [2 + 2] pathway has also been invoked for the Brønsted acid- or Lewis acid-mediated intramolecular and intermolecular alkyne–aldehyde metatheses.

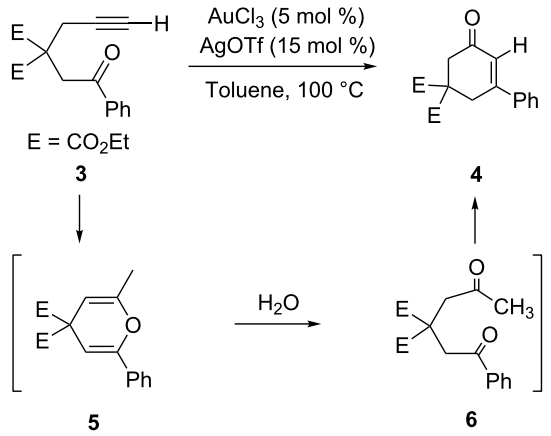


Scheme 2: Gold-catalyzed cyclization of internal alkynyl ketones.



Scheme 3: Proposed [2 + 2] mechanism for the cyclization of alkynyl ketones.

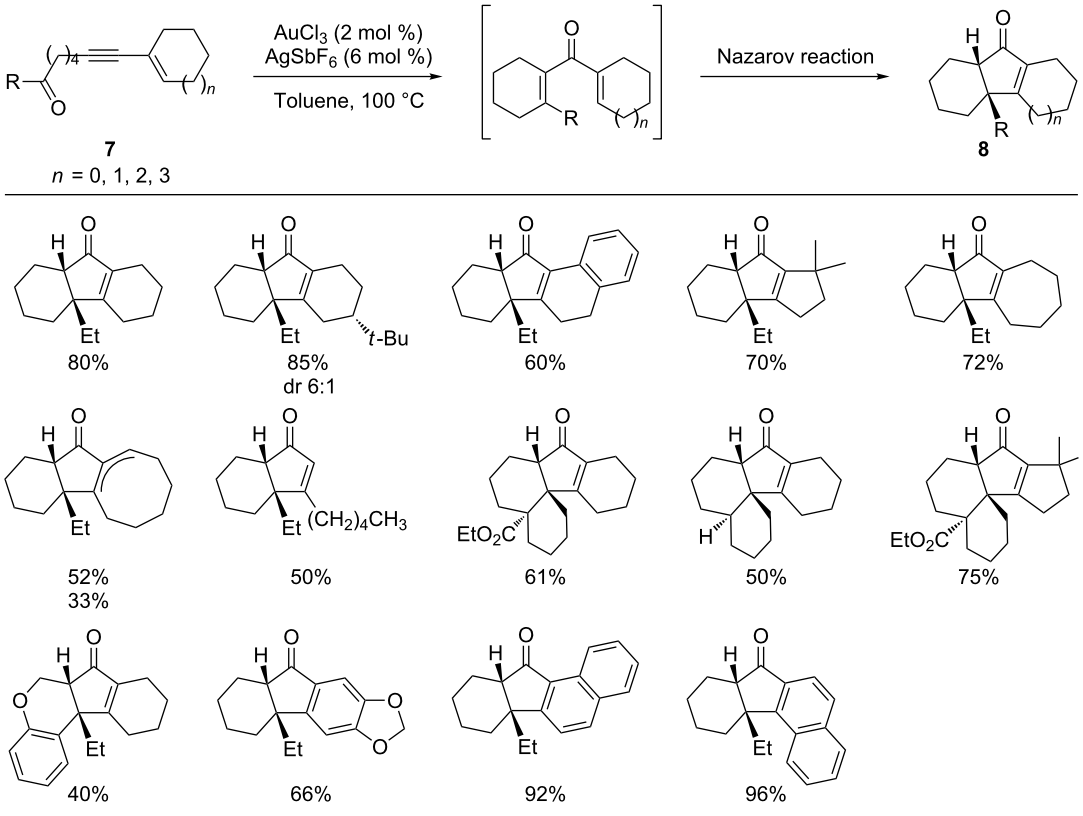
If terminal alkynyl ketone **3** is employed as the substrate, the reaction still furnishes α,β-unsaturated cyclic enone **4**, but it necessitates a larger catalyst load (Scheme 4). By carefully monitoring of the reaction, it was found that intermediate **5** was formed together with a mixture of a hydrolyzed derivative of **6** and the final product **4**. The isolated intermediate **5** could be transformed into a mixture of **6** and **4** under the reaction conditions, finally yielding **4** via intramolecular aldol condensation.



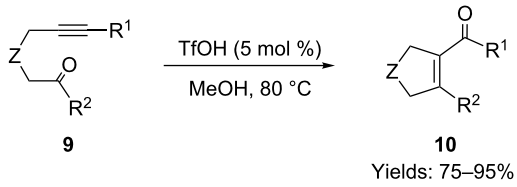
Scheme 4: Gold-catalyzed cyclization of terminal alkynyl ketones.

This gold-catalyzed cyclization of alkynyl ketones to enones was successfully utilized in a cascade reaction by the same authors (Scheme 5) [44]. Using enynones **7** as the substrate, the gold-catalyzed tandem alkyne–carbonyl metathesis/Nazarov reaction generated a number of intriguing fused bicyclic, tricyclic and tetracyclic derivatives of **8** in moderate to good yields and excellent diastereoselectivity. In this case, the gold catalyst exhibited a dual role, namely the activation of alkyne and carbonyl moieties.

Yamamoto and co-workers attempted to utilize their protocol to build five-membered cyclic enones, however, when they employed alkynyl ketone **9** as the substrate, the gold catalyst did not show good activity, and less than 30% of the desired product **10** was formed [45]. After optimizing the reaction conditions, the authors found that TfOH was the best catalyst for this oxygen transfer reaction in methanol (Scheme 6). This TfOH-mediated cyclization was applied to the synthesis of various fused tricyclic and tetracyclic derivatives of **10**.



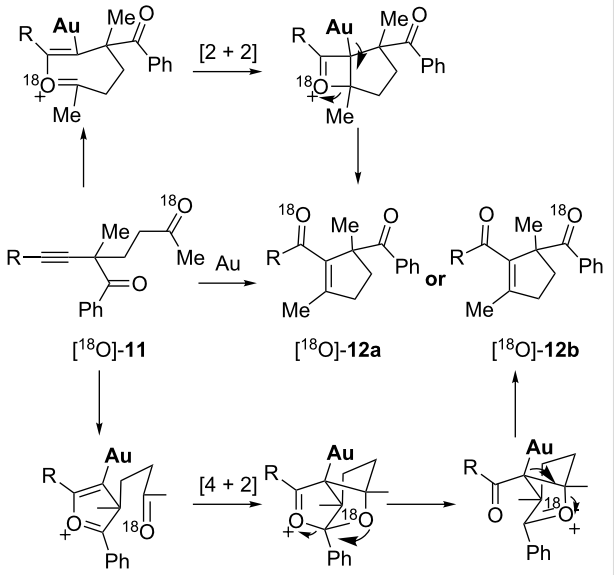
Scheme 5: Gold-catalyzed tandem oxygen transfer/Nazarov cyclizations.



Scheme 6: TfOH-mediated cyclization of alkynyl ketones.

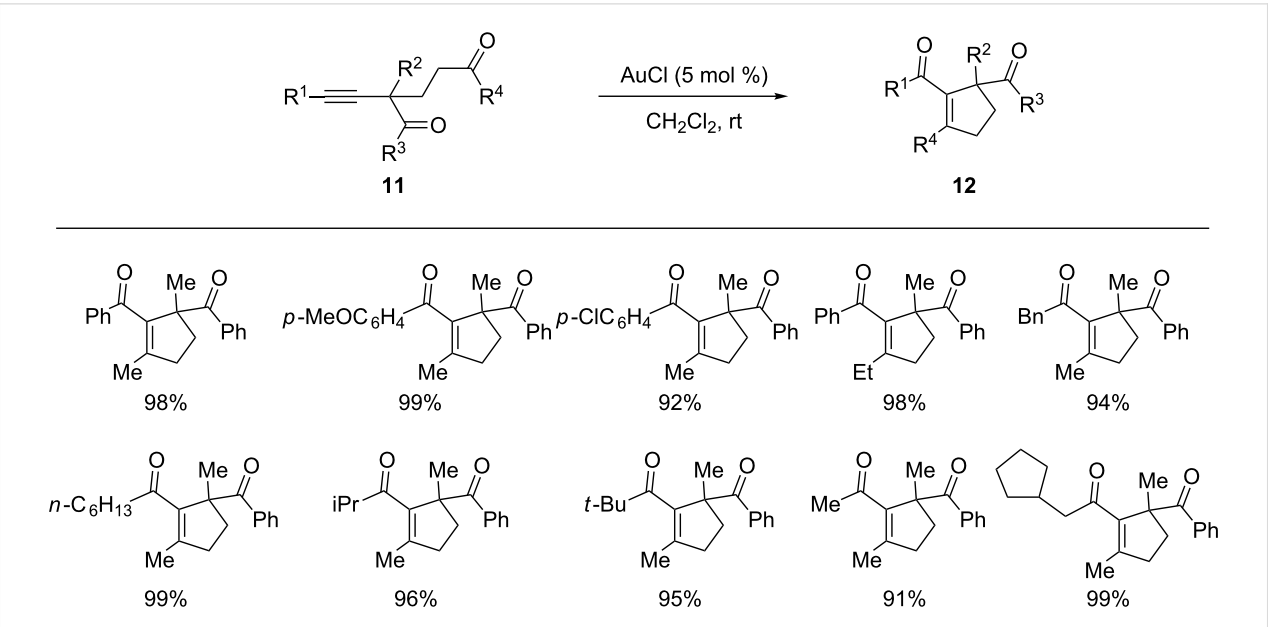
Hammond and co-workers found that the gold-catalyzed oxygen transfer reaction proceeded very smoothly when using alkynyldiketone **11** as the substrate (Scheme 7) [46]. Indeed, this reaction was complete in 5 minutes at room temperature to give the five-membered cyclic enones **12** cleanly and in excellent yields. The large reactivity difference between substrates **9** and **11** prompted the authors to propose an alternative [4 + 2] mechanism for this transformation, rather than the previously proposed and well-accepted [2 + 2] pathway for oxygen transfer reactions.

An isotopic labeling experiment was designed to elucidate the pathway responsible for the gold-catalyzed intramolecular oxygen transfer of 2-alkynyl-1,5-diketones (Scheme 8). By introducing an ^{18}O atom into one of the carbonyls of the substrate, and using the ^{13}C NMR spectra of the substrate and product to locate the ^{18}O atom, the authors hoped to elucidate the more favorable mechanistic pathway. The alkynyldiketone [^{18}O]-**11** was chosen as a model substrate. If the reaction follows a [2 + 2] route then ^{18}O would end up on the left carbonyl group in [^{18}O]-**12a** (Scheme 8, top), whereas it would be incorporated on the benzoyl group in [^{18}O]-**12b** if the reaction follows a [4 + 2] pathway (Scheme 8, bottom).



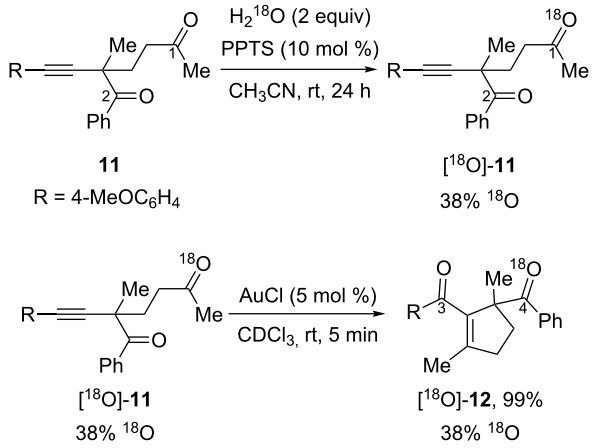
Scheme 8: Designed isotopic labeling experiment for mechanistic studies.

The result of this isotopic experiment is outlined in Scheme 9. Substrate [^{18}O]-**11** was synthesized from the ^{18}O exchange of compound **11** with $H_2{}^{18}O$ under acidic conditions, and its



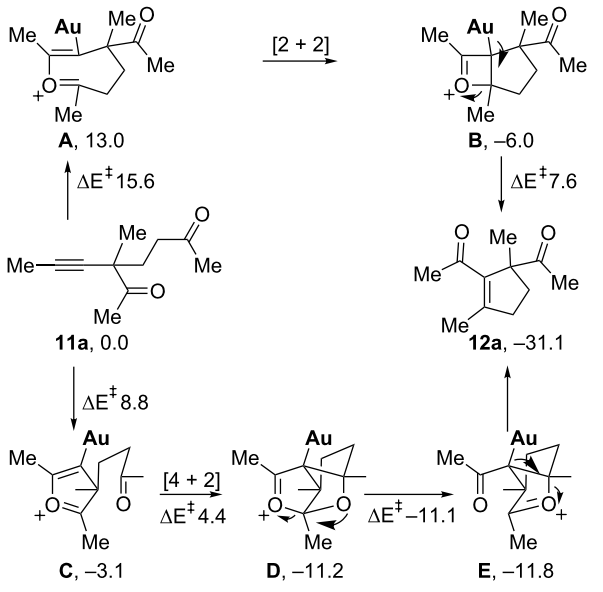
Scheme 7: Gold-catalyzed cyclizations of 2-alkynyl-1,5-diketones.

^{13}C NMR spectrum showed that the ^{18}O exchange happened only at the methyl carbonyl group (carbon 1). This substrate was subjected to the gold-catalyzed oxygen transfer reaction conditions and the product [^{18}O]-**12** was obtained in quantitative yield without any ^{18}O loss. It was later found that the ^{18}O was only incorporated into the benzoyl group (carbon 4) in product [^{18}O]-**12**, as determined from its ^{13}C NMR spectrum. The absence of any detectable ^{18}O incorporation at carbon 3 demonstrates that the [2 + 2] pathway is disfavored, and instead it is the [4 + 2] pathway that is the favored mechanism in the gold-catalyzed intramolecular oxygen transfer of 2-alkynyl-1,5-diketones.



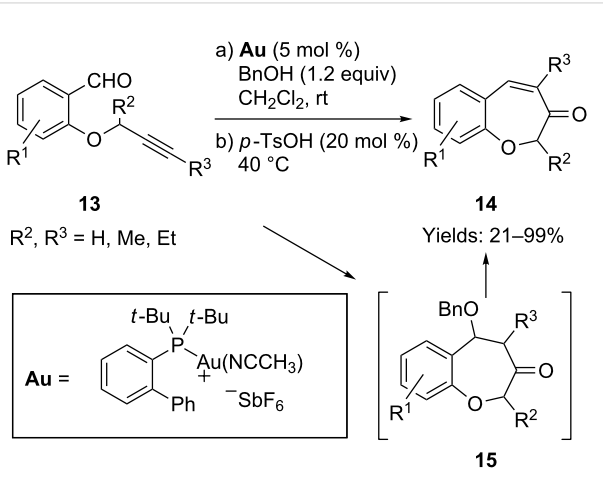
Scheme 9: ^{18}O isotopic experiments.

The discovery of a [4 + 2] cycloaddition of a furanium intermediate to a carbonyl group was further verified by quantum chemical calculations. The competing [2 + 2] and [4 + 2] reaction coordinates were computed for the simplified substrate **11a**, shown in Scheme 10. In accordance with the experimental findings, the [4 + 2] pathway is found to be the more favorable. The rate-limiting step in each pathway is the intramolecular nucleophilic addition to the Au-coordinated alkyne – the barrier for this step is computed to be 6.8 kcal/mol lower for the formation of the five-membered ring oxonium intermediate **C** than for the seven-membered ring oxonium **A**. This energetic preference is also observed in the stabilities of the oxoniums themselves, with **C** considerably more stable by 16.1 kcal/mol. The subsequent transformations are all computed to be feasible, with the barrier to [4 + 2] cyclization lying only 4.4 kcal/mol above the starting complex. Further calculations on the barrier for transition states were also consistent with the rapid conversion that was observed in the experiments. Overall, the large energetic preference of the intermediates and transition states for the [4 + 2] pathway over the [2 + 2] pathway supports the postulate that the [4 + 2] pathway is dominant in the gold-catalyzed oxygen transfer of 2-alkynyl-1,5-diketones, which is exactly in accordance with the ^{18}O isotopic experiments.



Scheme 10: B2PLYP/6-311+G(d,p)//B2PLYP/6-31G(d) computed reaction profile, relative energies in kcal/mol.

Chan and co-workers developed a gold-catalyzed tandem intramolecular rearrangement of alkynyl arylaldehydes **13** to benzoxepinones **14** with good regioselectivity (Scheme 11) [47]. This transformation was effectively promoted by the addition of benzyl alcohol and the sequential addition of *p*-toluenesulfonic acid. However, in the absence of *p*-toluenesulfonic acid, benzyl ether **15** was isolated as the major product. The

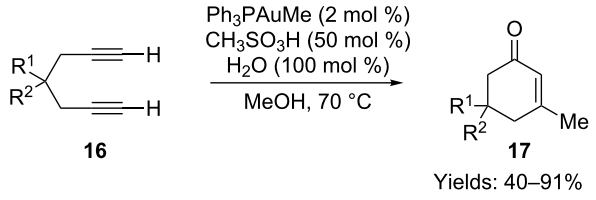


Scheme 11: Gold-catalyzed cyclization of tethered alkynyl arylaldehydes.

latter was considered to be an intermediate in the reaction and moreover, the isolated compound **15** could be transformed into the final product **14** under the mediation of *p*-toluenesulfonic acid.

Gold-catalyzed formation of cyclic enones from diynes

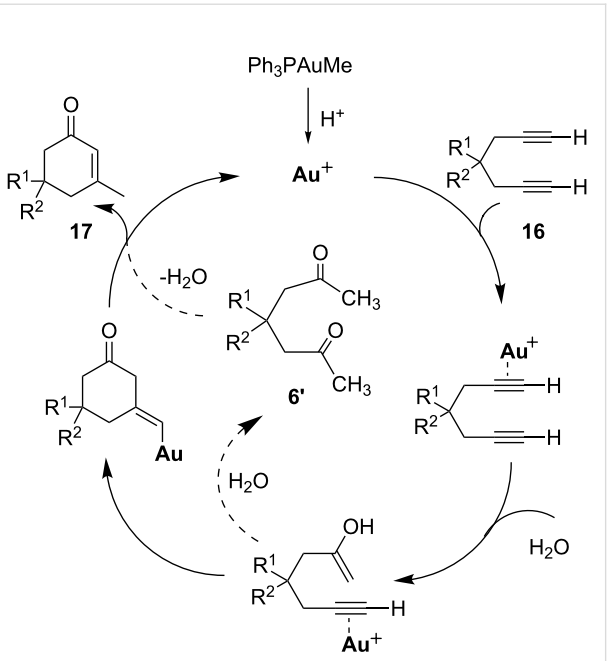
Zhang and co-workers reported gold-catalyzed cyclizations to cyclohexenones **17**, employing terminal 1,6-diynes **16** as substrates in the presence of a Brønsted acid and 1 equiv of water (Scheme 12) [48]. None of the desired products were obtained in the absence of the gold catalyst, the Brønsted acid or water. Interestingly, when the diacid 1,6-diyne ($R^1 = R^2 =$ COOH) was employed in the reaction, only the esterified product ($R^1 = R^2 =$ COOMe) was isolated, albeit in low yield. The authors also carried out this gold-catalyzed transformation in an ionic liquid [49]. This modification enabled the separation of the gold catalyst from the organic mixture and the recovered gold catalyst in the ionic liquid was re-used as many as five times without loss of activity.



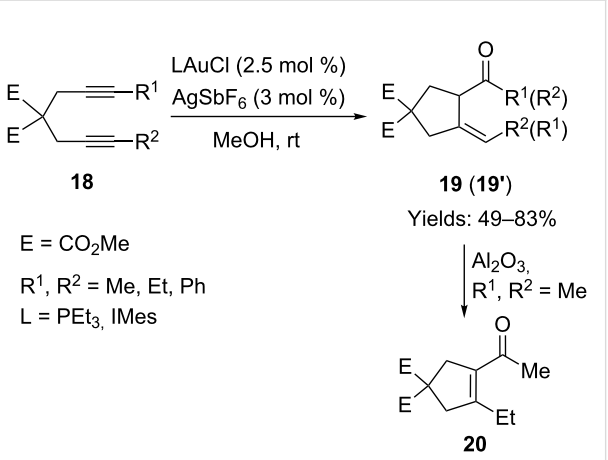
Scheme 12: Gold-catalyzed cyclization of terminal diynes.

A hydrolysis/cyclization mechanism was proposed for the transformation (Scheme 13). Although this mechanism is plausible, another option for the cyclization step might exist. One of the key intermediates in the catalytic cycle is the hydrolyzed product – the alkynyl ketone from hydrolysis of one triple bond – which is the same as the substrate that was employed by Yamamoto and co-workers. Thus, a similar diketone intermediate **6'** could also have been formed before being transformed into the final product via intramolecular aldol condensation.

Fiksdahl and co-workers investigated a similar gold-catalyzed transformation of internal 1,6-diynes **18** in methanol at room temperature (Scheme 14) [50,51]. Interestingly, a non-conjugated five-membered cyclic enone **19** was isolated as the product, instead of the conjugated cyclohexenone that was obtained from terminal 1,6-diynes. However, the scope of this transformation was limited to just a few substituent variations on the alkynes. When both R^1 and R^2 were ethyl groups, this cyclization was dramatically retarded and only traces of the desired product were obtained. Under the mediation of aluminium oxide, this non-conjugated cyclopentylidene ketone product isomerized to the conjugated cyclopentenyl ketone **20**.



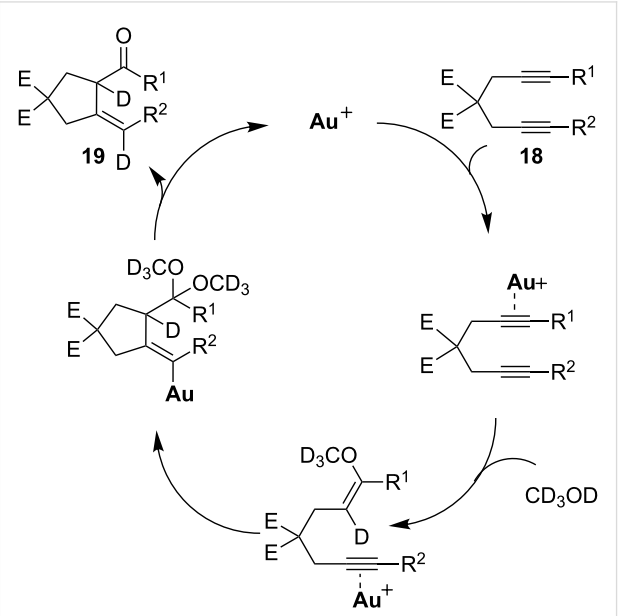
Scheme 13: Proposed hydrolysis/cyclization mechanism.



Scheme 14: Gold-catalyzed cyclization of internal diynes.

The authors proposed a solvolysis/cyclization mechanism for this gold-catalyzed cyclization, which was supported by a deuterium isotopic experiment (Scheme 15). Two molecules of methanol were involved in the transformation and a dimethoxyketal intermediate was formed: The final product was derived from the hydrolysis of this ketal intermediate. When

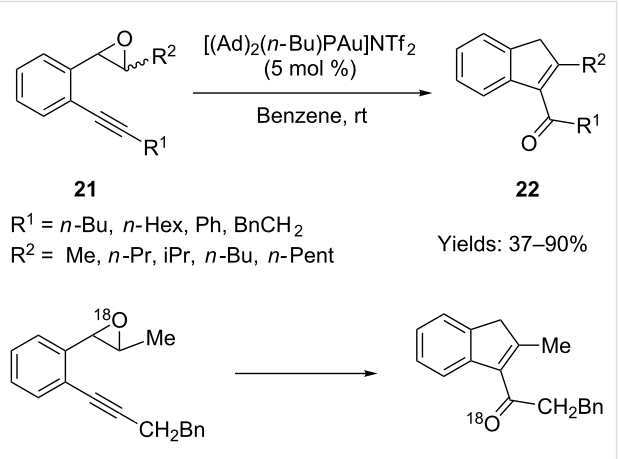
d_4-methanol was used as the solvent, a highly deuterated product was isolated, which provided strong support for the proposed mechanism.



Scheme 15: Proposed solvolysis/cyclization mechanism.

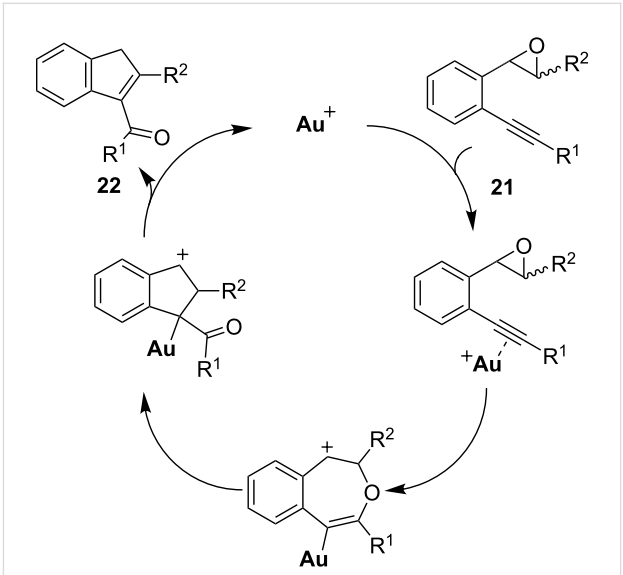
Gold-catalyzed formation of cyclic enones from alkynyl epoxides

Hashmi and co-workers synthesized a number of 2-alkynyl aryl epoxides **21** intended to be used as substrates for a gold-catalyzed rearrangement to naphthols. Surprisingly, acylindene **22** turned out to be the product of this reaction, rather than the expected naphthol (Scheme 16) [52]. However, when a bulky group was substituted on the triple bond, this gold-catalyzed transformation was completely suppressed. Moreover, none of the desired product could be obtained when a terminal alkyne, a TMS-substituted alkyne, or even an ester-substituted epoxide was used as the starting material.



Scheme 16: Gold-catalyzed cyclization of alkynyl epoxides and the ^{18}O isotopic labeling experiment.

An ^{18}O isotopic experiment helped the authors to propose an intramolecular oxygen transfer mechanism for the above transformation (Scheme 17). When employing the ^{18}O incorporated substrate in the reaction, the authors found that the isolated product still contained the isotopic atom which excludes the involvement of external water in the reaction. A cross-over experiment with a mixture of two substrates (one with ^{18}O, the other without) was also conducted, and no ^{18}O scramble was found in the products, which clearly supported the intramolecular nature of the oxygen transfer.

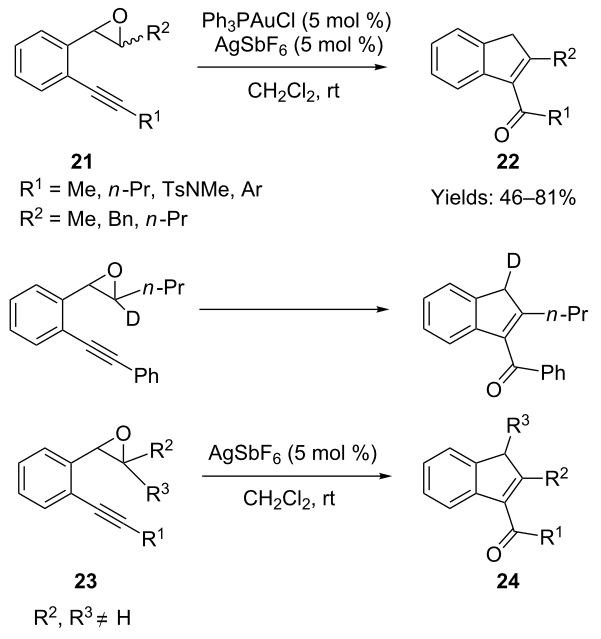


Scheme 17: Proposed oxygen transfer mechanism.

Liu and co-workers independently reported a very similar gold-catalyzed cyclization of 2-alkynyl aryl epoxide **21** to acylindene **22** (Scheme 18) [53]. A deuterium isotopic experiment was conducted to support the intramolecular oxygen transfer mechanism. However, when a trisubstituted epoxide **23** was employed in the reaction, the gold catalyst did not promote the transformation. By contrast, when $AgSbF_6$ was used as the catalyst, the 1,2-alkyl shifted product **24** was obtained.

Conclusion

This short review compiles recently reported gold-catalyzed oxygen transfer reactions used to build cyclic enones from tethered alkynyl ketones, 1,6-diynes or 2-alkynyl aryl epoxides. Most of these reactions take place under mild conditions and the corresponding products were isolated in good yields. The mechanisms for these transformations were also comparatively



Scheme 18: Gold or silver-catalyzed cyclization of alkynyl epoxides and the corresponding deuterium labeling experiment.

discussed. Similar Brønsted acid or other metal mediated transformations and their applications to cascade cyclizations were additionally described. Given gold's strong π-electrophilicity, it is expected that novel applications of gold catalysts in reactions of alkynes, allenes, and even alkenes, will continue to attract the attention of synthetic chemists.

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Gold-catalyzed heterocyclizations in alkynyl- and allenyl-β-lactams

Benito Alcaide*[1] and Pedro Almendros*[2]

Review

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Address:
[1]Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain and [2]Instituto de Química Orgánica General (IQOG), Consejo Superior de Investigaciones Científicas (CSIC), Juan de la Cierva 3, 28006-Madrid, Spain

Email:
Benito Alcaide* - alcaideb@quim.ucm.es; Pedro Almendros* - Palmendros@iqog.csic.es

* Corresponding author

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Abstract

New gold-catalyzed methods using the β-lactam scaffold have been recently developed for the synthesis of different sized heterocycles. This overview focuses on heterocyclization reactions of allenic and alkynic β-lactams which rely on the activation of the allene and alkyne component. The mechanism as well as the regio- and stereoselectivity of the cyclizations are also discussed.

Introduction

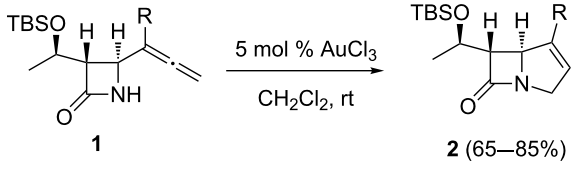
The chemistry of alkynes and allenes has been extensively studied and many reviews on their preparation and reactivity have been published [1-9]. These compounds show interesting reactivity and selectivity and can lead to complex structures in only a few steps. The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acidic nature [10-16]. In particular, gold-catalyzed intramolecular addition of oxygen and nitrogen nucleophiles across an allene or a carbon–carbon triple bond is intriguing from the point of view of regioselectivity (*endo* versus *exo* cyclizations) as well as it being one of the most rapid and convenient methods for the preparation of heterocycles. On the other hand, in addition to the key role that β-lactams play in medicinal chemistry, namely, their action against pathogenic bacteria, enzyme inhibition, or gene activation [17-23], the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established [24-28]. Moreover, the cyclic 2-azetidinone skeleton has been extensively used as a template on which to build carbo(hetero)cyclic structures joined to the four-membered ring, using the chirality and functionalization of the β-lactam ring as a stereo-controlling element [29,30]. This overview focuses on gold-catalyzed heterocyclization reactions of allenic and alkynic β-lactams which rely on the activation of the allene and alkyne component. The mechanism as well as the regio- and stereoselectivity of the cyclizations are also discussed.

Review

Gold-catalyzed heterocyclizations in allenyl-β-lactams

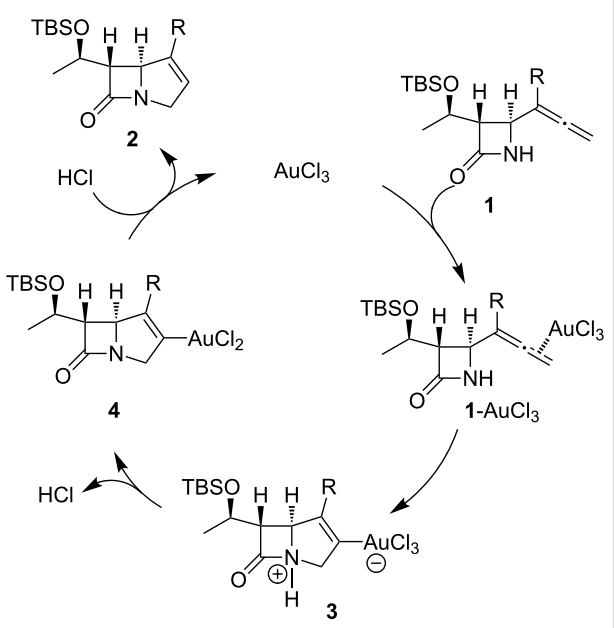
Aminocyclizations

The $AuCl_3$-catalyzed cyclization of 4-allenyl-2-azetidinones affords bicyclic β-lactams [31]. The former were prepared by the selective introduction of the allenyl group at the C4-position of 2-azetidinones with the help of organo–indium reagents. The best results, among the several reaction conditions examined for the incorporation of the allene moiety in the four-membered ring, were obtained when the organo–indium reagent was generated in situ from the reaction of 2.0 equivalents of indium with 3.0 equivalents of substituted propargyl bromide in the presence of 3.0 equivalents of KI. The best solvent from those that were screened (DMF, THF, C_6H_6, and $C_6H_5CH_3$) was found to be DMF. Because further functionalization of the allene group could potentially lead to the construction of a bicyclic nucleus, an especially intriguing and fundamental problem in the field of carbapenem synthesis, considerable efforts were devoted to the aminocyclization of 4-(1'-methylallenyl)-2-azetidinone derivatives with a variety of catalysts. Although many palladium-based catalysts such as $Pd(OAc)_2$, $PdCl_2$, $[Pd(PPh_3)_4]$, and $[Pd_2(dba)_3]\cdot CHCl_3$ failed to give the desired cyclized products, exposure of allenyl-β-lactams **1** to 5 mol % $AuCl_3$ in CH_2Cl_2 produced the bicyclic β-lactam products, i.e., the Δ^1-carbapenems **2** (Scheme 1). The desired products were produced in good yields for 2-azetidinones with *n*-butyl, $THPOCH_2$, phenyl, and 2-naphthyl substituents. It should be mentioned that the cyclization of allenyl-β-lactams **1** is an application of the gold-catalyzed cycloisomerization of α-aminoallenes which was discovered earlier [32,33].



Scheme 1: Gold-catalyzed cyclization of 4-allenyl-2-azetidinones for the preparation of bicyclic β-lactams.

Although the mechanism of the cyclization reaction has not been fully established, a possible reaction pathway has been proposed (Scheme 2) in which $AuCl_3$ activates the allene group of 4-allenyl-2-azetidinones **1** to give **1**-$AuCl_3$. Subsequent cyclization affords **3**, which then gives a transient vinyl–gold intermediate **4** [34-37]. Protonation of **4** produces bicyclic β-lactams **2** and regenerates $AuCl_3$ to continue the catalytic cycle.

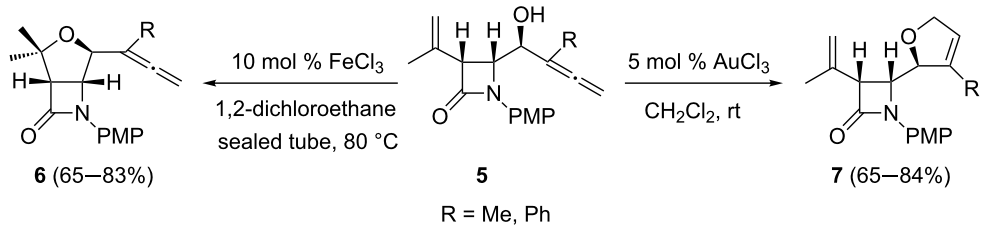


Scheme 2: Possible catalytic cycle for the gold-catalyzed cyclization of 4-allenyl-2-azetidinones.

Oxycyclizations

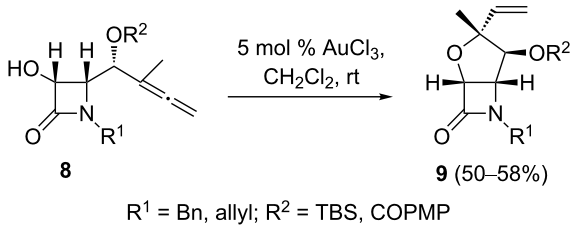
Furan, tetrahydrofuran, dihydropyran, and oxepane ether rings are ubiquitous structural units that are extensively encountered in a number of biologically active natural products and functional molecules, and therefore, their stereocontrolled synthesis remains an important research area. On the other hand, the recent resplendent age of gold has been accompanied by the emergence of iron salts as powerful alternatives in view of their inexpensiveness and environmental friendliness [38-40]. The chemodivergent metal-catalyzed heterocyclization of alcohols bearing both an allene and an alkene center has been reported [41]. Starting from 2-azetidinone-tethered ene-allenols **5**, $FeCl_3$ was able to catalyze the cyclization chemospecifically in favour of the alkene component to afford exclusively β-lactam–tetrahydrofuran hybrids **6** in good isolated yields (Scheme 3). Besides total chemocontrol, the reaction was regiospecific and only the five-membered ring ether was formed: The isomeric six-membered ring product was not observed. By contrast, when the cyclization of olefinic α-allenols **5** was catalyzed by gold salts ($AuCl_3$), allene cycloisomerization adducts **7** were obtained as the sole isomers (Scheme 3). The cyclization of allenyl-β-lactams **5** is an application of the previously reported gold-catalyzed cycloisomerization of α-hydroxyallenes [42-44].

Similarly to the transition metal-catalyzed reactions of α-allenols which afford heterocyclization products, intramolecular cyclizations of γ-allenols have also attracted a great deal of interest [45-47]. A study of the regioselectivity control during the gold-catalyzed O–C functionalization of 2-azetidinone-



Scheme 3: Gold- and iron-catalyzed chemodivergent cyclization of ene-allenols for the preparation of oxacyclic β-lactam derivatives.

tethered γ-allenol derivatives has been published [48,49]. The general reactivity of 2-azetidinone-tethered γ-allenols toward the regioselective hydroalkoxylation reaction was investigated with substrate **8a** (R^1 = Bn, R^2 = TBS) using $[PtCl_2(CH_2{=}CH_2)]_2$, $AgNO_3$, AuCl and $AuCl_3$ as catalysts. $[PtCl_2(CH_2{=}CH_2)]_2$ and $AgNO_3$ afforded rather low yields or disappointing diastereomeric mixtures of the bicyclic compound **9a**. Although $AgNO_3$ was less diastereoselective than $[PtCl_2(CH_2{=}CH_2)]_2$ (60:40 vs 100:0), it was, nevertheless, a more efficient catalyst and gave adduct **9a** in reasonable yield. Gratifyingly, it was found that Au salts were effective as selective 5-*exo* hydroalkoxylation catalysts. $AuCl_3$ was found to be the catalyst of choice because of its superior performance and produced the fused 2-azetidinones **9** in moderate yields (Scheme 4). No regioisomeric products were detected: The reaction gave exclusively the fused five-membered oxacycle.



Scheme 4: Gold-catalyzed cyclization of hydroxyallenes for the preparation of five-membered oxacyclic β-lactams; COPMP = O=C-C_6H_4-OCH_3.

A computational study (using density functional theory, DFT) of the above heterocyclization has been carried out [50]. The Au(III)-catalyzed cyclization of γ-allenol **I** (Figure 1) takes place regio- and stereoselectively through a 5-*exo* hydroalkoxy-

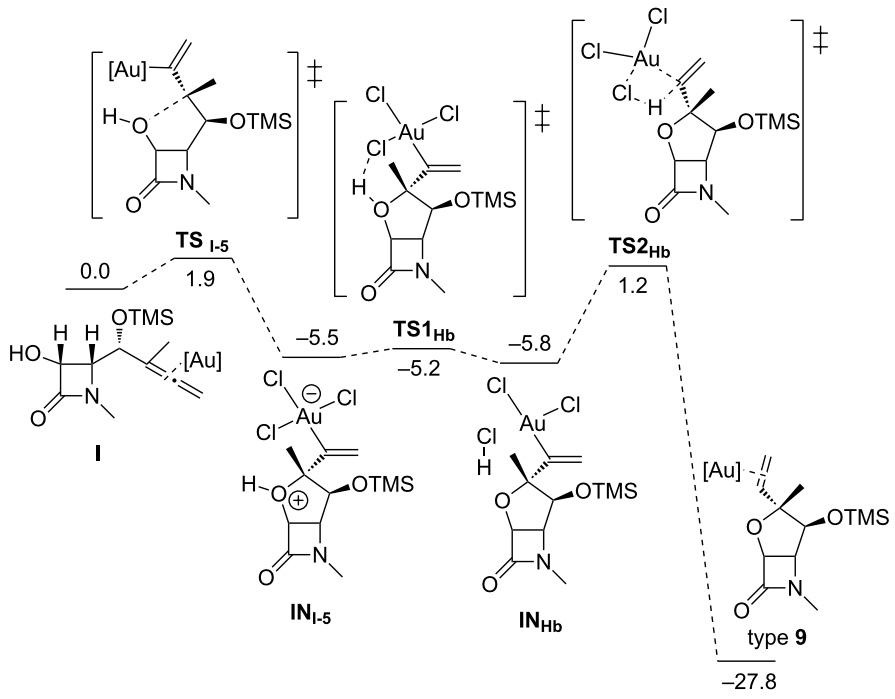
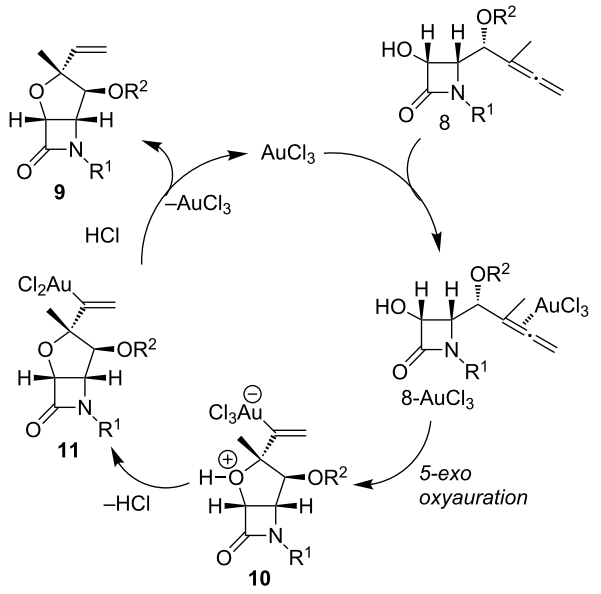


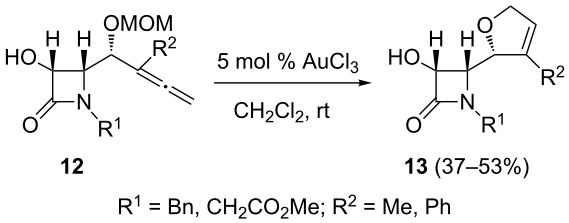
Figure 1: Free energy profile [kcal mol^{-1}] for the transformation of γ-allenol **I** into the tetrahydrofuran type **9**.

lation because of a kinetic preference governed by electronic and steric factors. A possible pathway for the formation of bicyclic compounds **9** from γ-allenols **8** may initially involve the formation of a complex **8**-$AuCl_3$ via coordination of the gold trichloride to the proximal allenic double bond which undergoes regioselective 5-*exo* oxyauration to form the zwitterionic species **10**. Loss of HCl followed by protonolysis of the carbon–gold bond of **11** affords products **9** and regenerates the gold catalyst (Scheme 5).

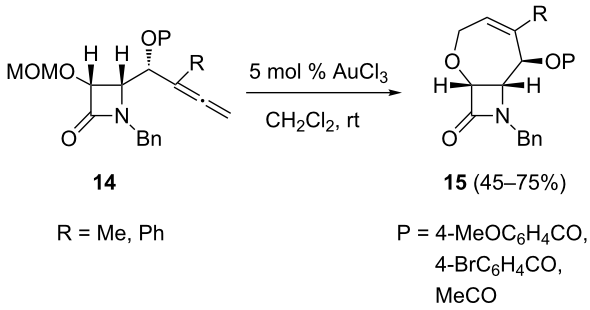


Scheme 5: Possible catalytic cycle for the gold-catalyzed cyclization of hydroxyallenes.

Having found a solution for the 5-*exo* selective hydroalkoxylation, attention was turned to the more intricate heterocyclization problem associated with the tuning of the regioselectivities of γ-allenol derivatives. It should be mentioned that one of the challenges for modern synthesis is to create distinct types of complex molecules from identical starting materials based solely on catalyst selection. As the stability of the benzoate and TBS-protective groups under the gold-catalyzed conditions had been demonstrated, it was decided to see if (methoxymethyl)oxy substitution has a beneficial impact on the cyclization reactions. In the event, when γ-allenols **12** were treated with $AuCl_3$ the 2,5-dihydrofurans **13** were the sole products (Scheme 6). These transformations may involve a chemoselective (5-*endo-trig* versus 7-*endo-trig*) allenol oxycyclization with concomitant MOM ether deprotection. Taking into account the above results, it was decided to see whether the metal-catalyzed preparation of bicycles **9** can be directly accomplished from the MOM protected γ-allenol derivatives **14**. However, when the allenic MOM ethers **14** were treated with $AuCl_3$, the 5-*exo* mode was completely suppressed and 7-*endo* cyclization occurred instead to afford bicyclic derivatives **15** in fair yields (Scheme 7). It seems that the reactivity in this type of Au(III)-catalyzed reaction is determined by the presence or absence of a methoxymethyl protecting group at the γ-allenol oxygen atom, thus allenols **8** gave 5-*exo* hydroalkoxylation whilst γ-allenol derivatives **14** exclusively underwent a 7-*endo* oxycyclization. Thus, it has been demonstrated that regioselectivity control in the metal-catalyzed O–C functionalization of γ-allenols can be achieved through the nature of the γ-allenol (free versus protected).

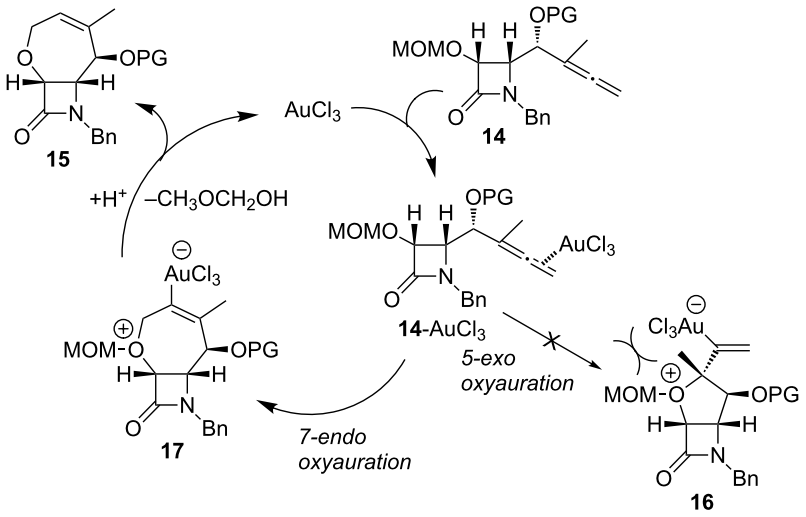


Scheme 6: Gold-catalyzed cyclization of MOM-protected α-hydroxyallenes for the preparation of five-membered oxacyclic β-lactams.



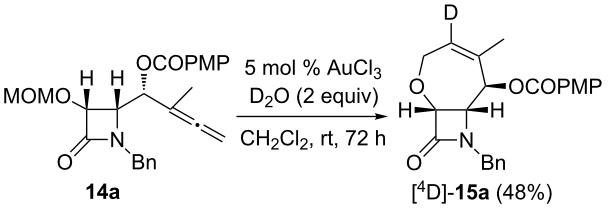
Scheme 7: Gold-catalyzed cyclization of MOM-protected γ-hydroxyallenes for the preparation of seven-membered oxacyclic β-lactams.

The pathway proposed in Scheme 8 appears valid for the formation of products **15** from MOM protected γ-allenol derivatives **14**. It is presumed that the initially formed allene–gold complex **14**-$AuCl_3$ undergoes an intramolecular attack (7-*endo* versus 5-*exo* oxyauration) by the (methoxymethyl)oxy group, giving rise not to species **16** but instead to the tetrahydrooxepine intermediate **17**. Protonolysis of the carbon–gold bond and elimination of methoxymethanol would then liberate the compound **15** with concomitant regeneration of the Au(III) species. Probably, the proton in the last step of the catalytic cycle arises from trace amounts of water present in the solvent or the catalyst. In the presence of the MOM group, 5-*exo* cyclization falters. As calculations reveal, 5-*exo* oxyauration via **16** is restricted by the steric hindrance between the (methoxymethyl)oxy group and the substituents at the quaternary stereocenter.



Scheme 8: Possible catalytic cycle for the gold-catalyzed cyclization of MOM protected γ-allenol derivatives. PG = Protecting group.

With the aim of trapping the organo–gold intermediate to confirm the mechanism of this reaction, deuterium labeling studies with deuterium oxide were performed. Under the same conditions but with the addition of two equivalents of D_2O, heterocyclization reaction of MOM protected γ-allenol **14a** catalyzed by $AuCl_3$ in dichloromethane afforded [^{4}D]-**15a** in 48% yield, indicating that a deuterium atom was incorporated at the alkenyl carbon (Scheme 9). In the ^{1}H NMR spectrum of [^{4}D]-**15a**, the peak for proton H4 at 6.35 ppm was absent which suggests that deuterolysis of the carbon–gold bond in species **17** has occurred. Along with the clarification of the reaction mechanism, it should be pointed out that, although metal-catalyzed oxycyclization reactions of allenes are well-known in hydroxyallenes, the heterocyclization of alkoxyallenes is not an easy task and still remains a significant challenge.

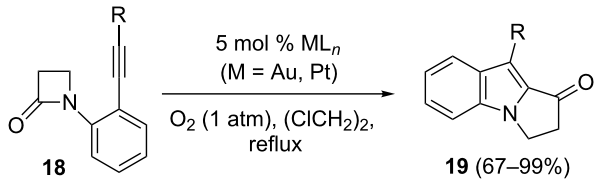


Scheme 9: Au(III)-catalyzed heterocyclization reaction of MOM protected γ-allenol derivative **14a**.

Gold-catalyzed heterocyclizations in alkynyl-β-lactams

Aminocyclizations

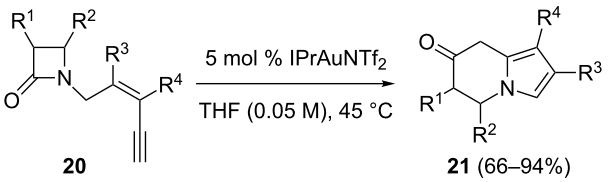
The precious metal-catalyzed formation of benzo-fused pyrrolizinones **19** from *N*-(2-alkynylphenyl)-β-lactams **18** has been accomplished (Scheme 10). Platinum was the metal of choice, gold salts being less effective [51]. This cycloisomerization can be viewed as a net intramolecular insertion of one end of the alkyne into the lactam amide bond with concurrent migration of the substituent at the alkyne terminus. An initial *5-endo-dig* cyclization of the lactam nitrogen to the metal-activated alkyne was proposed, followed by the fragmentation of the lactam amide bond and the formation of an acyl cation.



Scheme 10: Precious metal-catalyzed formation of benzo-fused pyrrolizinones from *N*-(2-alkynylphenyl)-β-lactams.

The above chemistry was extended to non-aromatic substrates, providing a new approach to other *N*-heterocycles [52]. Thus, the benzene ring was substituted by a *cis*-alkene, and a gold-catalyzed synthesis of 5,6-dihydro-8*H*-indolizin-7-ones **21** from *N*-(pent-2-en-4-ynyl)-β-lactams **20** was developed (Scheme 11). Pt(II) and Pt(IV) also catalyzed this reaction, albeit less efficiently. In this reaction, a *5-exo-dig* cyclization of the β-lactam nitrogen to the Au-activated C–C triple bond is followed by heterolytic fragmentation of the amide bond to form a reactive acyl cation. While substrates with substituents at the alkyne terminus did not undergo this catalytic reaction, various substituents at the C–C double bond were tolerated, including

benzyloxyethyl and cyclohexyl (geminal to the ethynyl group) as well as hexyl and phenyl (vicinal to the lactam), and gave dihydroindolizinones with different substituents at their 1- and 2-positions. Substrates with the C–C double bond embedded in medium-sized rings also reacted well to yield interesting seven- or eight-membered ring fused dihydroindolizinones in good yields. Surprisingly, the corresponding cyclopentene or cyclohexene substrates did not afford the corresponding five- or six-membered ring-fused dihydroindolizinones. After 10 h, the starting materials were mostly unreacted in the case of cyclohexene substrates and partly decomposed in the case of cyclopentene substrates. This method allows an expedient formal synthesis of indolizidine 167B.



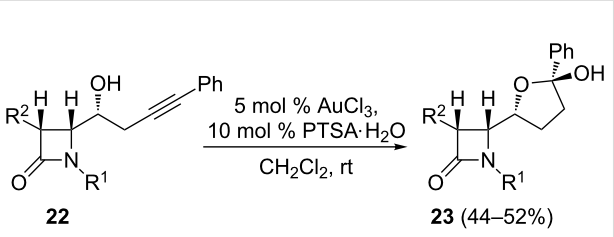
Scheme 11: Gold-catalyzed formation of 5,6-dihydro-8*H*-indolizin-7-ones from *N*-(pent-2-en-4-ynyl)-β-lactams.

Oxycyclizations

Transition metal-assisted intramolecular addition of oxygen nucleophiles across a carbon–carbon triple bond is intriguing from the point of view of regioselectivity as well as it being one of the most rapid and convenient methods for the preparation of oxacycles [53-64]. Recently, the gold-catalyzed cycloisomerization and tandem oxycyclization/hydroxylation of 2-azetidinone-tethered alkynols for the synthesis of non-fused, spiro, and fused oxabicyclic β-lactams has been reported [65].

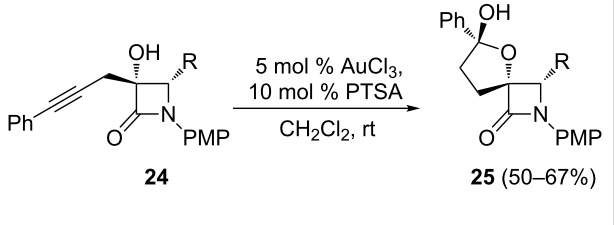
Attempts at a cyclization reaction of terminal alkynols using gold catalysts failed. However, under the appropriate reaction conditions was found that $AuCl_3$ could be a good catalyst for the cycloetherification reaction of non-terminal alkynols **22**. Scheme 12 shows that tetrahydrofuryl hemiacetals **23** are accessible as single isomers in fair yields via the gold-catalyzed tandem oxycyclization/hydroxylation reaction of 2-azetidinone-tethered homopropargylic alcohols. In the conversion from alkynols **22** to tetrahydrofuryl hemiacetals **23**, water is required, which is probably provided by trace amounts of water present in the solvent or the catalyst. Additionally, it should be noted that PTSA contains water since the monohydrate is actually employed.

In order to determine whether the conclusions drawn from the homopropargylic alcohols **22** could be extrapolated to other



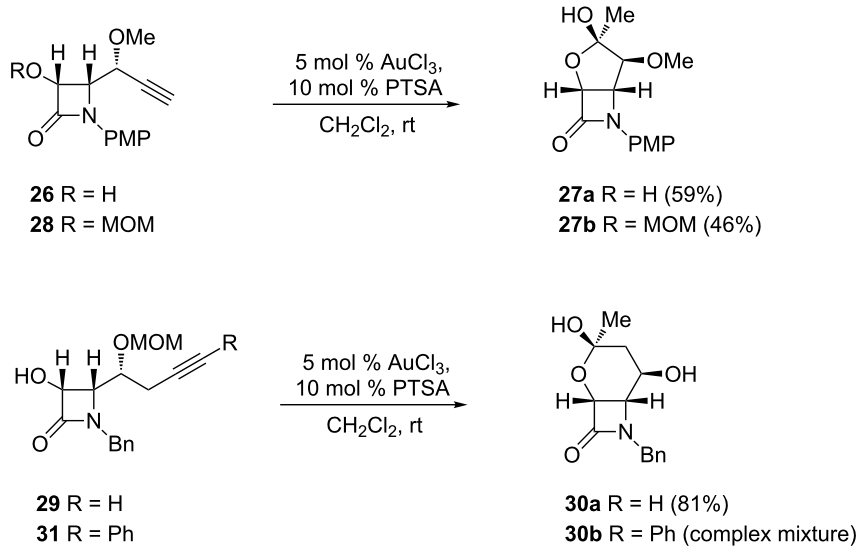
Scheme 12: Gold-catalyzed formation of non-fused tetrahydrofuryl-β-lactam hemiacetals from 2-azetidinone-tethered homopropargylic alcohols.

alkynols, tertiary carbinols **24** were examined. Under similar gold-catalyzed conditions, spiro β-lactams **25** were obtained as single isomers in good yields (Scheme 13). To further probe the scope of these transformations, gold-catalyzed heterocyclization reactions of alkynols to the fused bicyclic systems was also examined. Indeed, treatment of 2-azetidinone-tethered bishomopropargylic alcohol **26** with $AuCl_3$ provided the desired cycloetherification/hydroxylation product **27a** in good yield (Scheme 14). Interestingly, the gold-catalyzed reaction of **28,** with a (methoxymethyl)oxy moiety instead of the free hydroxy group, also proceeded smoothly to give the cyclization product **27b,** albeit in lower yield (Scheme 14). Notably, the observed regioselectivity (5-*exo* cyclization) was unaffected by the presence of a protective group at the hydroxy moiety. These gold-catalyzed oxycyclizations were successfully extended to trishomopropargylic alcohol **29**, which afforded the oxycyclization/hydroxylation adduct **30a** with concomitant MOM cleavage (Scheme 14). In contrast, the presence of a phenyl substituent at the terminal alkyne carbon showed a substantial effect on the reactivity, as illustrated by the fact that phenyl alkynol **31** gave a complex mixture of products.

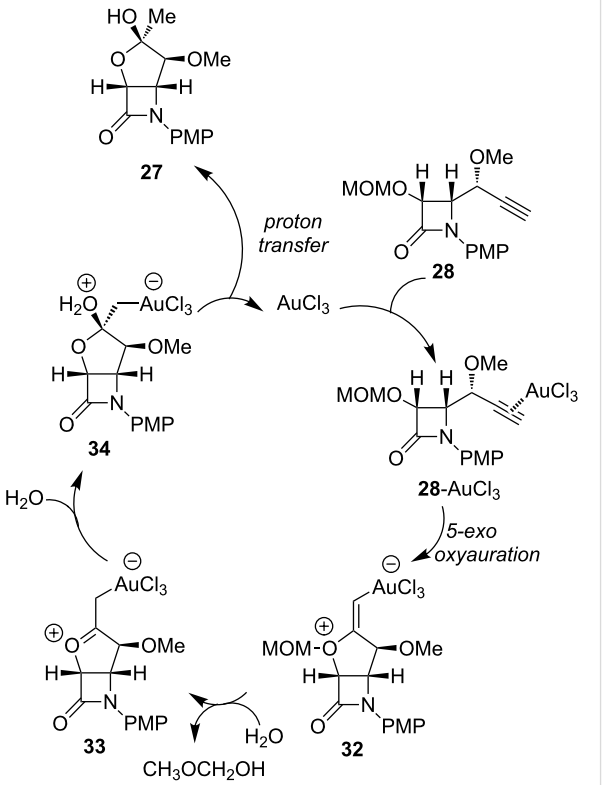


Scheme 13: Gold-catalyzed formation of spiro tetrahydrofuryl-β-lactam hemiacetals from 2-azetidinone-tethered homopropargylic alcohols.

A conceivable mechanism for the formation of bicyclic tetrahydrofuran **27** from the methoxymethyl ether **28** may initially involve the formation of a π-complex **28**-$AuCl_3$ through coordination of the gold trichloride to the alkyne moiety. The initially formed alkyne–gold complex **28**-$AuCl_3$ could undergo a regioselective intramolecular attack (5-*exo* versus 6-*endo* oxyaura-



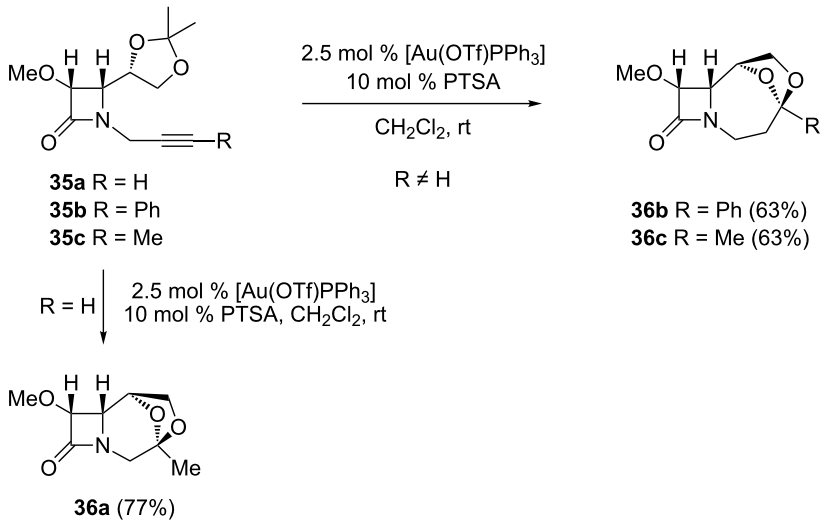
Scheme 14: Gold-catalyzed formation of fused tetrahydrofuryl-β-lactam hemiacetals from 2-azetidinone-tethered bis- and tris-homopropargylic alcohols.



Scheme 15: Possible catalytic cycle for the gold-catalyzed cyclization of MOM protected alkynol derivatives.

tion) by the (methoxymethyl)oxy group to yield the vinyl–gold intermediate **32**. The elimination of methoxymethanol followed by isomerization would lead to the metallaoxocarbenium species **33**. Subsequent nucleophilic attack by water, from trace amounts present in the solvent or the catalyst, from the less hindered face of intermediate **33** would form the ate complex **34**. Deauration and proton transfer leads to adduct **27** with concomitant regeneration of the Au(III) species (Scheme 15).

Regiocontrolled gold/Brønsted acid co-catalyzed direct bis-heterocyclization of alkynyl-β-lactams allows the efficient synthesis of optically pure tricyclic bridged acetals bearing a 2-azetidinone nucleus [66,67]. Treatment of the terminal alkyne **35a** with the catalytic system $AuCl_3$/PTSA gave the desired ketal **36a**. Appreciable amounts of a polar ketone arising from alkyne hydration were also produced. Fortunately, the [AuClPPh$_3$]/AgOTf/PTSA system demonstrated better activity. Interestingly, in contrast to the precious metal/acid co-catalyzed reaction of terminal alkynyl dioxolane **35a**, which leads to the 6,8-dioxabicyclo[3.2.1]octane derivative **36a** (proximal adduct), the reaction of alkynyl dioxolanes **35b** and **35c**, substituted at the terminal end gave under identical conditions the 7,9-dioxabicyclo[4.2.1]nonane derivatives **36b** and **36c** (distal adducts) as the sole products (Scheme 16), through an exclusive 7-*endo*/5-*exo* bis-oxycyclization by initial attack of the oxygen atom on the external alkyne carbon. Competition between the initial 6-*exo* and 7-*endo* oxycyclizations appears to favor the latter, despite that fact that a priori this should be energetically more demanding.



Scheme 16: Gold/Brønsted acid co-catalyzed formation of bridged β-lactam acetals from 2-azetidinone-tethered alkynyl dioxolanes.

Conclusion

In summary, regiocontrolled gold-catalyzed heterocyclization reactions of 2-azetidinone-tethered allenes and alkynes which lead to a variety of oxa- and azacycles have been developed. Density functional theory (DFT) calculations were performed to obtain insight on various aspects of this reactivity and indicated the selective activation of the allene and alkyne component.

Acknowledgements

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Sequential Au(I)-catalyzed reaction of water with *o*-acetylenyl-substituted phenyldiazoacetates

Lei Zhou, Yizhou Liu, Yan Zhang and Jianbo Wang*

Full Research Paper

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Address:
Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

Email:
Jianbo Wang* - wangjb@pku.edu.cn

* Corresponding author

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Abstract

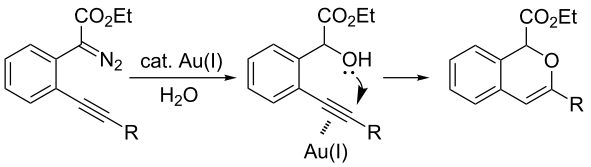
The gold(I)-catalyzed reaction of water with *o*-acetylenyl-substituted phenyldiazoacetates provides 1*H*-isochromene derivatives in good yields. The reaction follows a catalytic sequence of gold carbene formation/water O–H insertion/alcohol-alkyne cyclization. The gold(I) complex is the only catalyst in each of these steps.

Introduction

Transition metal carbene complexes are versatile intermediates and can undergo diverse transformations, including X–H (X = C, O, S, N, etc.) insertions, cyclopropanations, ylide formation, and 1,2-migrations [1-5]. Among the various methods to generate metal carbene complexes, transition metal-catalyzed decomposition of diazo compounds is the most straightforward and is highly reliable. Various transition metals have been found to decompose diazo compounds and then transfer a carbene unit to saturated or unsaturated organic substrates [3]. However, compared to the other group 11 metals, i.e., copper and silver, there are only a few reports on gold-catalyzed carbene transfer reactions of diazo compounds [6-20]. In 2005, Díaz-Requejo, Nolan, Pérez and co-workers reported the first example of carbene transfer from ethyl diazoacetate (EDA) using (IPr)AuCl. The subsequent generation of a gold carbene was followed by insertion into a phenyl C–H bond, an O–H bond, or an N–H bond [6]. Similar reactions were also reported by Dias and co-workers with a gold(I) ethylene complex [7]. Although the scope of those studies was limited to ethyl diazoacetate, the examples therein demonstrated that gold complexes can be used as efficient catalysts in carbene transfer reactions with diazo compounds.

On the other hand, the development of reaction systems in which a single catalyst mediates two or more different reactions in a selective manner has become an emerging area of

research [21-28]. This type of sequential or concurrent catalysis is particularly appealing in view of the requirements of green chemical processes in the fine chemical industry. In this context, we have previously reported the copper(I)-catalyzed reaction of amines with *o*-acetylenyl-substituted phenyldiazoacetates, which leads to a Cu(I)-catalyzed tandem N–H insertion/hydroamination of an alkyne [29]. Subsequently, we have tried to extend this reaction by replacing the amine component with water, and we expected that similar tandem reaction would occur. Copper is a good catalyst for the decomposition of diazo compounds and the subsequent insertion of water. However, we have found that it is not a suitable catalyst for the alcohol–alkyne cyclization. Since gold complexes are well-known for their efficacy in activating alkynes, we reasoned that a concurrent catalysis based on gold-catalyzed reaction of diazo compounds and alkynes might be possible [30]. Herein we report such a catalytic system, namely a gold(I)-catalyzed insertion/cyclization cascade by reacting water with *o*-acetylenyl-substituted phenyldiazoacetates. The reaction affords 1*H*-isochromene derivatives in good yields (Scheme 1) [31].

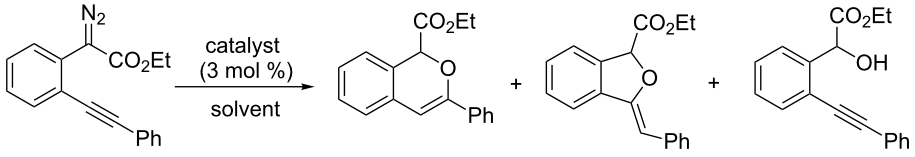


Scheme 1: Gold(I)-catalyzed insertion/cyclization of *o*-acetylenyl-substituted phenyldiazoacetates providing 1*H*-isochromene derivatives.

Results and Discussion

At the onset of this investigation, *o*-acetylenyl-substituted phenyldiazoacetate **1a** was selected as the model substrate. In a preliminary experiment, **1a** was treated with CuI catalyst in a mixture of CH_3CN and H_2O (v:v = 1:1) (Table 1). As expected, only the water insertion product **4a** was obtained as the major product and in high yield (91%) (Table 1, entry 1). Since previous reports have shown that silver [32-34] and gold [35-38] complexes are efficient catalysts for alcohol–alkyne cyclization, we then proceeded to examine other catalysts viz. AgOTf,

Table 1: Optimization of reaction conditions with phenyldiazoacetate **1a**[a].



1a **2a** **3a** **4a**

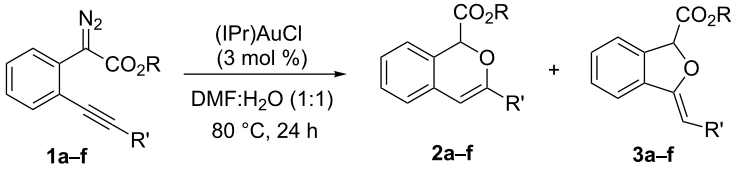
Entry	Catalyst	Solvent	*T*/°C	Yield (**2a** + **3a**)[b]	**2a**:**3a**	**4a**, Yield
1	CuI	H_2O:CH_3CN (1:1)	80	0%	—	91%
2	AgOTf	H_2O:CH_3CN (1:1)	80	0%	—	<10%
3	AgF/PCy_3	H_2O:CH_3CN (1:1)	80	trace	—	trace
4	$NaAuCl_4$	H_2O:CH_3CN (1:1)	80	0%	—	trace
5	AuCl	H_2O:CH_3CN (1:1)	80	0%	—	trace
6	(PPh_3)AuCl	H_2O:CH_3CN (1:1)	80	8%	—	80%
7	(PMe_3)AuCl	H_2O:CH_3CN (1:1)	80	10%	—	15%
8	(IPr)AuCl	H_2O:CH_3CN (1:1)	80	95%	1:1	0%
9	(IPr)AuCl	H_2O:CH_3CN (1:3)	80	25%	2:3	61%
10	(IPr)AuCl	H_2O:CH_3CN (3:1)	80	57%	1:1.3	11%
11	(IPr)AuCl	H_2O	80	54%	1:2	0%
12[c]	(IPr)AuCl	CH_3CN	80	0%	0	41%
13	(IPr)AuCl	H_2O:DMF (1:1)	80	90%	4:1	0%
14	(IPr)AuCl	H_2O:NMP (1:1)	80	0%	—	trace
15	(IPr)AuCl	H_2O:toluene (1:1)	80	19%	1:1	0%
16	(IPr)AuCl	H_2O:DMF (1:1)	100	57%	3:1	0%
17	(IPr)AuCl	H_2O:DMF (1:1)	60	66%	5:1	0%
18	(IPr)AuCl	H_2O:DMF (1:1)	40	48%	5:1	0%

[a]All the reactions were carried out using 0.2 mmol phenyldiazoacetate **1a** with 3 mol % of catalyst in 1 mL solvent for 24 h. [b]Yield and ratio of **2a** and **3a** were measured by ^{1}H NMR. [c]1 mmol of water was added.

AgF/PCy_3, $NaAuCl_4$ and AuCl (Table 1, entries 2–5). However, these metal complexes were not efficient catalysts for the decomposition of diazo compounds, and a large amount of starting materials remained. However, when **1a** was treated with $(PPh_3)AuCl$ in a mixture of CH_3CN and H_2O, product **4a** was obtained in 80% yield, along with the minor cyclization product **2a** (8%) (Table 1, entry 6). Encouraged by this result, electron-rich ligand coordinated gold complexes $(PMe_3)AuCl$ and (IPr)AuCl were examined (Table 1, entries 7 and 8). It was found that (IPr)AuCl was an efficient catalyst for both carbene transfer and cyclization. Product **2a** from 6-*endo*-*dig* cyclization and product **3a** from 5-*exo*-*dig* cyclization were both obtained in nearly equal amounts in combined yield of 95%. Next, we examined the effect of the ratio of CH_3CN and H_2O with (IPr)AuCl as catalyst: A ratio of 1:1 (v:v) afforded the best results (Table 1, entries 9–12). It is worth noting that the reaction also occurred in pure water to afford the cyclization products, **2a** and **3a**, in moderate yield (Table 1, entry 11). Next, the effect of different co-solvents, such as DMF, NMP (*N*-methylpyrrolidone) and toluene, was investigated (Table 1, entries 13–15). Interestingly, when a mixture of H_2O and DMF (v:v = 1:1) was used as the solvent, the ratio of **2a**:**3a** increased to 4:1, with slightly diminished overall yield. The reaction with NMP or toluene as the co-solvent gave poor yields of desired products (Table 1, entries 14,15). Finally, the effect of temperature was evaluated: The reaction gave diminished yields when carried out at a temperature higher or lower than 80 °C (Table 1, entries 16–18).

With the optimized reaction conditions in hand, a series of substituted diazo compounds **1a**–**f** were prepared, and their reactions with water in the presence of (IPr)AuCl in aqueous DMF were investigated. As shown in Table 2, all the reactions gave isochromene derivatives as the major products. In the reaction of diazo compounds **1e** and **1f** with water, only 6-*endo*-*dig* cyclization products **2e** and **2f** were isolated as the sole product in yields of 69% and 75%, respectively. Functional groups such as bromo and hydroxy groups were tolerated under the present catalytic systems. When diazo compound **1g** (R' = H) was employed as the substrate, none of the cyclization product was detected and the water insertion product **4g** was obtained in 81% yield.

Table 2: Gold(I)-catalyzed cascade insertion/cyclization of water with various substituted phenyldiazoacetates[a].



1a–f **2a–f** **3a–f**

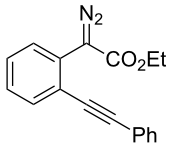
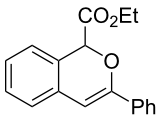
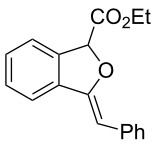
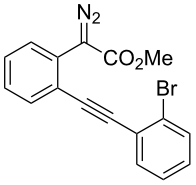
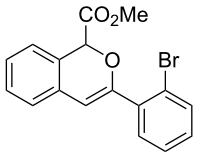
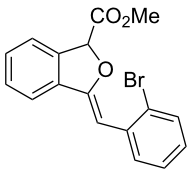
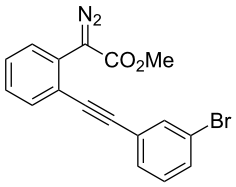
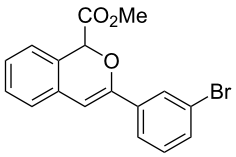
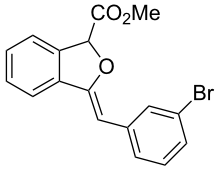
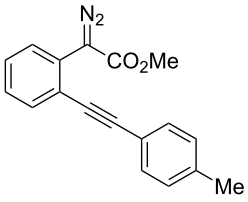
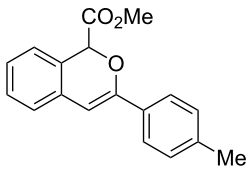
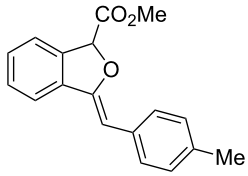
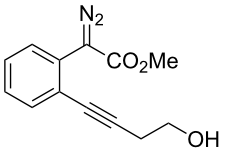
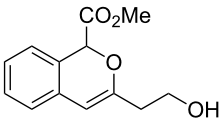
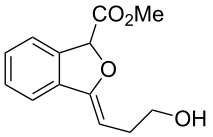
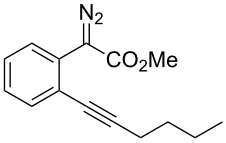
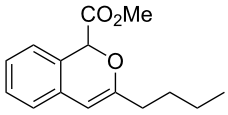
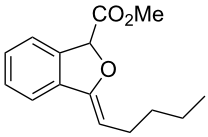
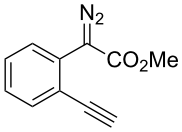
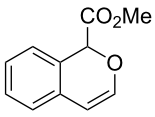
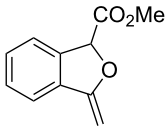
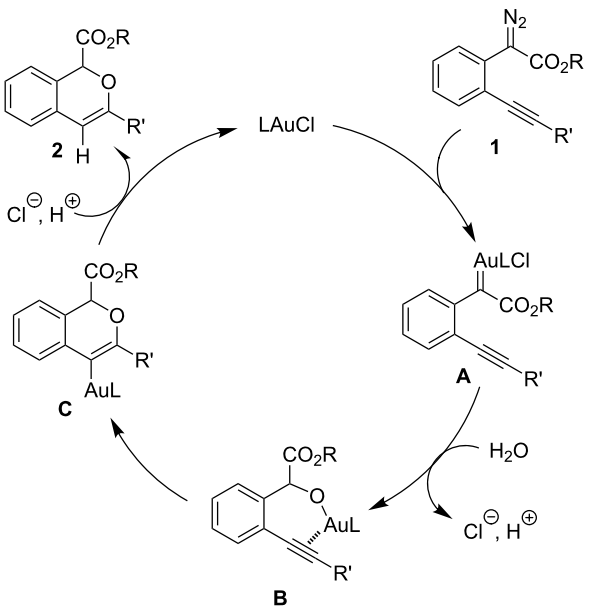
Entry	Substrate	Yield of **2**[b]	Yield of **3**[b]
1	 **1a**	 **2a**, 70%	 **3a**, 15%
2	 **1b**	 **2b**, 64%	 **3b**, 31%
3	 **1c**	 **2c**, 67%	 **3c**, 22%

Table 2: Gold(I)-catalyzed cascade insertion/cyclization of water with various substituted phenyldiazoacetates[a]. (continued)

4	 **1d**	 **2d**, 82%	 **3d**, <10%
5	 **1e**	 **2e**, 69%	 **3e**, Trace
6	 **1f**	 **2f**, 75%	 **3f**, Trace
7[c]	 **1g**	 **2g**, 0%	 **3g**, 0%

[a]All the reactions were carried out using 0.5 mmol phenyldiazoacetate **1** with 3 mol % of (IPr)AuCl catalyst in 2 mL solvent for 24 h. [b]Isolated yield. [c]Only the water insertion product methyl 2-(2-ethynylphenyl)-2-hydroxyacetate (**4g**) was isolated as the major product in a yield of 81%.

A tentative mechanism for this gold(I)-catalyzed cascade insertion/cyclization is proposed in Scheme 2. Decomposition of diazo compound **1** by (IPr)AuCl generates gold carbene species **A**, which inserts into the O–H bond of H_2O to form the chelating intermediate **B**. Subsequently, 6-*endo*-*dig* attack of the Au(I)-activated triple bond affords the vinylgold intermediate **C**, which is protonated to give the final product **2** with regeneration of the catalyst. This mechanism is supported by the fact that when **4a** was subjected to the gold(I)-catalyzed reaction under identical conditions **2a** and **3a** were obtained in similar yields.



Scheme 2: Tentative mechanism.

Conclusion

In summary, we have developed a cascade insertion/cyclization of water with *o*-acetylenyl-substituted phenyldiazoacetates catalyzed by a single Au(I) catalyst. This tandem process provides a novel and straightforward method to synthesize isochromene derivatives. Isochromene and its derivatives frequently occur as structural units in natural products and exhibit interesting biological activities such as antibiotic properties [39-51]. Moreover, this study further demonstrates the possibility to incorporate gold-catalyzed reaction of diazo com-

pounds with various other gold-catalyzed transformations. Further studies to broaden the scope of these reactions are currently underway.

Experimental

General. For chromatography, 200–300 mesh silica gel (Qingdao, China) was employed. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or Bruker ARX 400 spectrometer in $CDCl_3$ solution and chemical shifts are reported in parts per million (δ) relative to internal standard TMS (0 ppm). Mass spectra were obtained on a VG ZAB-HS mass spectrometer. Diazo compounds were prepared according to our previous reported procedures. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for the gold(I)-catalyzed cascade insertion/cyclization reaction. Distilled water (0.5 mL) was added to a solution of complex **1** (0.5 mmol) and (IPr)AuCl (3 mol %, 9.3 mg) in DMF (1.5 mL) at room temperature under a N_2 atmosphere. The reaction mixture was stirred for 24 h at 80 °C. After the mixture cooled to room temperature, it was diluted with ether and water. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were washed with brine (1 × 10 mL), dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel afforded products **2** and **3**.

Ethyl 3-phenyl-1*H*-isochromene-1-carboxylate (2a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 6.8 Hz, 2H), 7.41–7.35 (m, 3H), 7.28–7.20 (m, 3H), 7.09 (d, J = 7.6 Hz, 1H), 6.36 (s, 1H), 5.83 (s, 1H), 4.15 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 153.0, 134.2, 130.6, 129.18, 129.16, 128.4, 126.7, 126.2, 126.0, 125.8, 124.1, 100.5, 76.6, 61.7, 14.2; MS (70 eV) *m*/*z* (%): 280 (29) [M^+], 207 (100), 178 (47), 152 (8); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{18}H_{17}O_3$, 281.1172; found, 281.1168.

Ethyl 3-benzylidene-1,3-dihydroisobenzofuran-1-carboxylate (3a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 2H), 7.75–7.55 (m, 1H), 7.53–7.51 (m, 1H), 7.41–7.32 (m, 4H), 7.18–7.17 (m, 1H), 6.03 (s, 1H), 6.00 (s, 1H), 4.33–4.23 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 154.8, 136.8, 135.8, 134.6, 129.4, 129.1, 128.5, 128.4, 125.9, 122.3, 120.1, 97.9, 82.6, 62.0, 14.3; MS (70 eV) *m*/*z* (%): 280 (11) [M^+], 264 (8), 207 (100), 191 (13), 178 (43); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{18}H_{17}O_3$, 281.1172; found, 281.1166.

Methyl 3-(2-bromophenyl)-1*H*-isochromene-1-carboxylate (2b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.86 (m, 1H), 7.64–7.62 (m, 1H), 7.39–7.35 (m, 1H), 7.30–7.19 (m, 4H), 7.11–7.09 (m, 1H), 6.27 (s, 1H), 5.87 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 151.5, 135.5, 133.5, 131.4, 130.1, 129.9, 129.1, 127.3, 127.2, 125.9, 125.5, 124.2, 106.0, 77.2, 52.5; MS (70 eV) *m*/*z* (%): 344 (41, ^{79}Br) [M^+], 285 (100), 206 (36), 178 (96), 151 (17); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{17}H_{14}BrO_3$, 345.0120; found, 345.0125.

Methyl 3-(2-bromobenzylidene)-1,3-dihydroisobenzofuran-1-carboxylate (3b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36–8.34 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.58–7.52 (m, 2H), 7.41–7.39 (m, 2H), 7.34–7.29 (m, 1H), 7.03–7.01 (m, 1H), 6.42 (s, 1H), 6.05 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 155.9, 136.6, 134.9, 134.2, 132.6, 130.0, 129.5, 129.4, 127.3, 127.0, 123.0, 122.1, 96.1, 82.6, 52.8; MS (70 eV) *m*/*z* (%): 344 (13, ^{79}Br) [M^+], 285 (100), 206 (32), 178 (67), 151 (14); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{17}H_{14}BrO_3$, 345.0120; found, 345.0127.

Methyl 3-(3-bromophenyl)-1*H*-isochromene-1-carboxylate (2c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.95 (m, 1H), 7.72–7.71 (m, 1H), 7.49–7.47 (m, 1H), 7.32–7.25 (m, 4H), 7.11–7.09 (m, 1H), 6.37 (s, 1H), 5.86 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 151.3, 136.1, 131.8, 129.8, 129.1, 128.6, 127.1, 126.2, 125.7, 124.2, 124.1, 122.6, 101.4, 76.2, 52.6; MS (70 eV) *m*/*z* (%): 344 (34, ^{79}Br) [M^+], 285 (100), 206 (35), 178 (82), 151 (14); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{17}H_{14}BrO_3$, 345.0120; found, 345.0117.

Methyl 3-(3-bromobenzylidene)-1,3-dihydroisobenzofuran-1-carboxylate (3c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.93 (m, 1H), 7.68–7.66 (m, 1H), 7.55–7.52 (m, 2H), 7.45–7.38 (m, 2H), 7.30–7.27 (m, 1H), 7.22–7.17 (m, 1H), 6.07 (s, 1H), 5.92 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 155.7, 137.8, 136.8, 134.0, 130.8, 129.8, 129.47, 129.44, 128.5, 126.7, 122.5, 122.2, 120.1, 96.4, 82.6, 52.8; MS (70 eV) *m*/*z* (%): 344 (28, ^{79}Br) [M^+], 285 (100), 206 (34), 178 (50), 151 (19); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{17}H_{14}BrO_3$, 345.0120; found, 345.0126.

Methyl 3-*p*-tolyl-1*H*-isochromene-1-carboxylate (2d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.25–7.17 (m, 5H), 7.05 (d, J = 6.8 Hz, 1H), 6.31 (s, 1H), 5.83 (s, 1H), 3.67 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 153.1, 139.2, 131.4, 130.7, 129.17, 129.15, 126.5, 126.2, 125.76, 125.71, 123.9, 99.7, 76.5, 52.5, 21.4; MS (70 eV) *m*/*z* (%): 280 (17) [M^+], 221 (100), 207 (7), 178 (27); HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{18}H_{17}O_3$, 287.1172; found, 281.1168.

Methyl 3-(2-hydroxyethyl)-1*H*-isochromene-1-carboxylate (2e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (m, 3H), 6.92 (d, *J* = 7.2 Hz, 1H), 5.74 (s, 1H), 5.70 (s, 1H), 4.09–4.07 (m, 1H), 3.78–3.64 (m, 2H), 3.69 (s, 3H), 2.51–2.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 154.0, 130.1, 129.3, 126.5, 126.4, 124.4, 123.2, 102.9, 76.1, 59.7, 52.9, 37.5; MS (70 eV) *m*/*z* (%): 234 (2) [M^+], 192 (8), 175 (100), 145 (28), 133 (77); HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{15}O_4$, 235.0964; found, 235.0960.

Methyl 3-butyl-1*H*-isochromene-1-carboxylate (2f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.11 (m, 3H), 6.89 (d, *J* = 7.6 Hz, 1H), 5.67 (s, 1H), 5.58 (s, 1H), 3.68 (s, 3H), 2.77 (t , *J* = 7.6 Hz, 2H), 1.65–1.58 (m , 2H), 1.42–1.36 (m , 2H), 0.94 (t , *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 157.3, 130.7, 129.0, 126.0, 124.7, 123.0, 99.9, 76.3, 52.4, 33.5, 28.6, 22.4, 14.0; MS (70 eV) *m*/*z* (%): 246 (12) [M^+], 187 (100), 115 (16); HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{19}O_3$, 247.1328; found, 247.1322.

Methyl 2-(2-ethynylphenyl)-2-hydroxyacetate (4g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 1H), 7.37–7.36 (m, 2H), 7.32–7.29 (m, 1H), 5.63 (d, *J* = 5.6 Hz, 1H), 3.75 (s, 3H), 3.59 (d, *J* = 5.2 Hz, 1H), 3.31 (s , 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 140.5, 133.4, 129.4, 128.5, 127.1, 121.5, 82.2, 81.3, 71.4, 53.2; MS (70 eV) *m*/*z* (%): 190 (100) [M^+], 159 (69), 132 (57), 103 (53); HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{11}H_{11}O_3$, 191.0702; found, 191.0699.

Supporting Information

Supporting Information File 1

^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-74-S1.pdf]

Acknowledgements

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Gold-catalyzed alkylation of silyl enol ethers with *ortho*-alkynylbenzoic acid esters

Haruo Aikawa[1,2], Tetsuro Kaneko[1], Naoki Asao*[1,3] and Yoshinori Yamamoto[1,3]

Letter

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Address:
[1]Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan, [2]International Advanced Research and Education Organization, Tohoku University, Sendai 980-8578, Japan and [3]WPI-Advanced Institute for Materials Research, Tohoku University, Sendai 980-8578, Japan

Email:
Naoki Asao* - asao@m.tohoku.ac.jp

* Corresponding author

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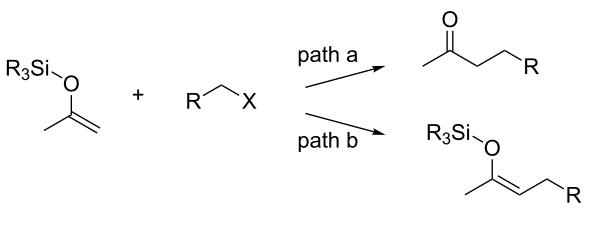
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Abstract

Unprecedented alkylation of silyl enol ethers has been developed by the use of *ortho*-alkynylbenzoic acid alkyl esters as alkylating agents in the presence of a gold catalyst. The reaction probably proceeds through the gold-induced in situ construction of leaving groups and subsequent nucleophilic attack on the silyl enol ethers. The generated leaving compound abstracts a proton to regenerate the silyl enol ether structure.

Findings

Silyl enol ethers have been widely used in organic synthesis as effective carbon nucleophiles for the construction of carbon frameworks [1-4]. Generally, they react with a variety of electrophiles to give carbonyl compounds as products due to cleavage of the silicon–oxygen bond. For example, the Lewis acid-catalyzed reaction of silyl enol ethers with alkyl halides is well known as one of the most efficient preparative methods for regio-defined α-alkylated ketones (path a in Scheme 1) [5-17]. In contrast, in this paper, we report a gold-catalyzed reaction of silyl enol ethers with *ortho*-alkynylbenzoic acid esters which leads to the formation of α-alkylated silyl enol ethers (path b).



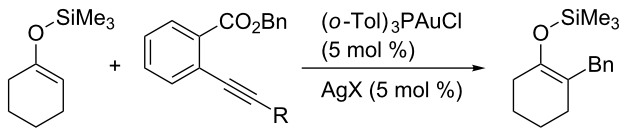
Scheme 1: Alkylation of silyl enol ethers.

We examined the reactions of silyl enol ether **1a** with *ortho*-alkynylbenzoic acid benzyl esters **2** in the presence of gold catalysts under several reaction conditions and the results are summarized in Table 1 [18-21]. With a cationic gold catalyst, derived from Ph_3PAuCl and $AgClO_4$, the reaction of **1a** with **2a** proceeded at 80 °C over 2 h and the benzylated silyl enol ether **3a** was obtained in 35% yield, along with the eliminated isocoumarin **4a** and recovered **2a** in 32% and 65% yields, respectively (entry 1). On the other hand, no products were obtained from the reaction of **1a** with benzyl benzoate (having no alkynyl group at the *ortho*-position) under similar reaction conditions. These results clearly show that the alkynyl moiety of ester **2a** is essential for the formation of **3a**. It is well known that concerted pericyclic ene-type reaction of silyl enol ethers with electrophiles, such as aldehydes or ketones, gives functionalized silyl enol ethers without desilylation [22-36]. To the best of our knowledge, however, this is the first example of the introduction of simple alkyl groups through a substitution-type reaction [37-40]. The chemical yield was increased to 55% by use of sterically hindered $(o\text{-Tol})_3PAuCl$ as the gold catalyst (entry 2). Besides benzene, $(CH_2Cl)_2$ and 1,4-dioxane were also suitable solvents (entries 3 and 4). The use of 5 equiv of **1a** improved the chemical yield and **3a** was obtained in 72% yield (entry 5). The catalyst derived from AgOTf gave a better yield, although a longer reaction time was required (entry 6). Analogously, the reaction with **2b**, with a butyl group at the alkynyl terminus, gave **3a** in 75% yield (entry 7). In the current catalyst system using AgOTf, TfOH might be produced during the reactions due to the decomposition of AgOTf with a trace amount of water, which could be present in the reaction medium. However, the alkylation of **1a** with **2a** did not proceed at all with 5 mol % of TfOH. This result clearly indicates that the gold complex functions as a catalyst in the current transformations.

We next examined the substrate generality with several types of silyl enol ethers **1** and esters **2** (Table 2). Treatment of five-membered silyl enol ether, cyclopentenyloxytrimethylsilane (**1b**), with **2b** in the presence of the gold catalyst gave the corresponding benzylated product **3b** in 61% yield (entry 1). It is worth mentioning that benzo-fused silyl enol ether **1c** is suitable for this transformation as shown in entries 2 and 3, whereas it cannot be used for ene-reaction due to the lack of a hydrogen atom at the α'-position. Not only cyclic silyl enol ethers but also an acyclic silyl enol ether underwent the reaction. Thus, **1d** reacted stereoselectively with **2a** to yield *E*-**3e**. Interestingly, the formation of the isomeric *Z*-**3e** was not detected at all (entry 4) [41]. The reaction of **1a** with allyl ester **2d** proceeded smoothly and the corresponding allylated product **3f** was obtained in 70% yield (entry 5) [42].

A plausible mechanism for the gold-catalyzed alkylation of silyl enol ethers is shown in Scheme 2. The gold catalyst enhances the electrophilicity of the alkynyl moiety of **2**, leading to the formation of a cationic intermediate **6** via the intramolecular nucleophilic attack of the carbonyl oxygen on the alkyne as shown in **5**. Due to the high leaving ability of the isocoumarin moiety of **6**, the silyl enol ether **1** attacks the R group to give the intermediate **7** together with the gold complex **8** as a leaving compound [43-46]. In the case of ordinary substitution reactions with alkyl halides (path a in Scheme 1), generated halide ions would attack the silyl group, due to their strong affinities

Table 1: Gold-catalyzed alkylation of silyl enol ether[a].

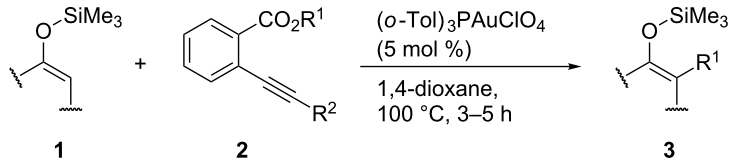


1a **2a:** R = Ph **2b:** R = Bu **3a**

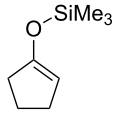
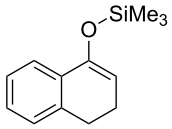
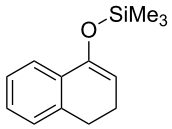
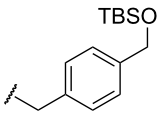
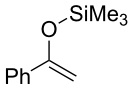
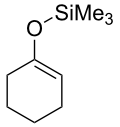
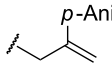
Entry	2	AgX	Solvent	Conditions	Yield (%)[b]
1[c]	**2a**	$AgClO_4$	benzene	80 °C, 2 h	35
2	**2a**	$AgClO_4$	benzene	80 °C, 2 h	55
3	**2a**	$AgClO_4$	$(CH_2Cl)_2$	80 °C, 2 h	44
4	**2a**	$AgClO_4$	dioxane	100 °C, 2 h	58
5[d]	**2a**	$AgClO_4$	dioxane	100 °C, 1 h	72
6[d]	**2a**	AgOTf	dioxane	100 °C, 10 h	80
7[d]	**2b**	AgOTf	dioxane	80 °C, 5 h	75

[a]Reaction conditions: 0.25 M solution of **2** was treated with **1a** (3 equiv) in the presence of the gold catalyst. [b]NMR yield using CH_2Br_2 as an internal standard. [c]Ph_3PAuCl was used instead of $(o\text{-Tol})_3PAuCl$. [d]5 equiv of **1a** was used.

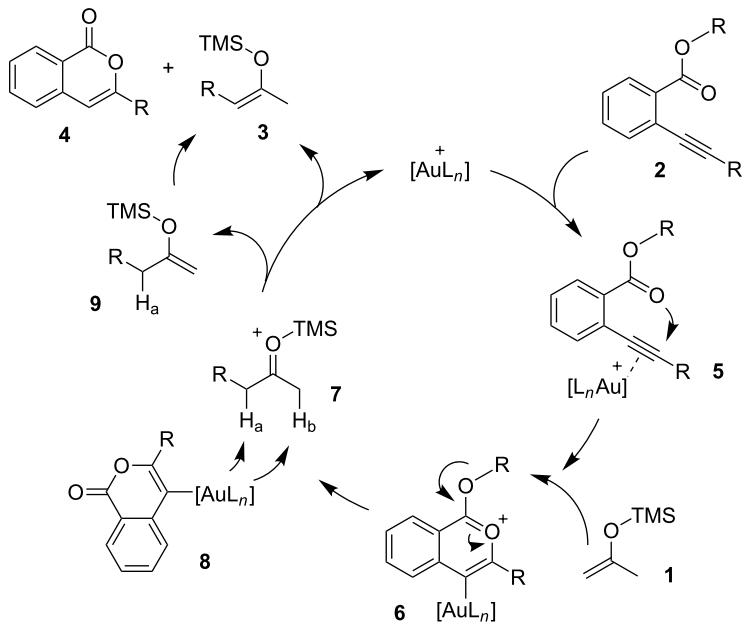
Table 2: Gold-catalyzed alkylation of silyl enol ether[a].



1 **2** **3**

Entry		**1**	**2**	R^1	R^2	**3**	Yield (%)[b]
1[c]	**1b**		**2b**	Bn	Bu	**3b**	61
2	**1c**		**2b**	Bn	Bu	**3c**	70
3[d]	**1c**		**2c**		Ph	**3d**	60[e]
4[c,f]	**1d**		**2a**	Bn	Ph	**3e**	61
5	**1a**		**2d**		Ph	**3f**	70

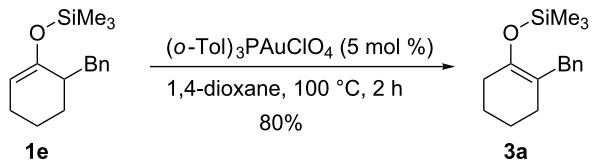
[a]Reaction conditions: 0.25 M solution of **2** was treated with **1** (5 equiv) in the presence of the gold catalyst. [b]NMR yield using CH_2Br_2 as an internal standard. [c]10 mol % of the catalyst was used. [d]3 equiv of **1** was used. [e]Yield of isolated product. [f]AgOTf was used instead of $AgClO_4$.



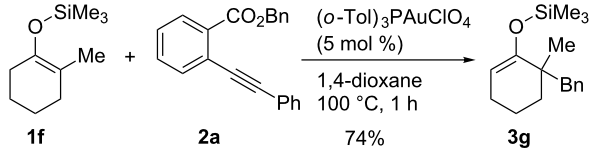
Scheme 2: Plausible mechanism for the alkylation of silyl enol ether.

with the silicon atom, and cleave the silicon–oxygen bond of **7**. However, in the present reaction system, intermediate **8** would prefer to act as a base and abstract a proton, H_a, from the α-position rather than attack the silyl group as a nucleophile, probably due to steric and electronic reasons. For these reasons, deprotonation of **7** occurs to give the product **3** together with **4** as a final leaving compound.

On the other hand, in the case of reactions with silyl enol ethers having a proton, H_b, at the α'-position, compound **9** might be produced through the deprotonation of H_b by **8**. However, such products were not obtained in any of the examples studied. These results imply that isomerism from **9** to **3** would occur during the reaction. Thus, compound **1e** was prepared according to a known procedure and treated with the gold catalyst at 100 °C for 2 h (Scheme 3). As expected, the isomerization of the double bond occurred and **3a** was obtained in 80% yield. This result shows that the indirect pathway from **7** to **3** via deprotonation of H_b is also possible. In addition, it was found that the reaction of **1f**, having no hydrogen at the α-position, proceeded smoothly and α,α-dialkyl silyl enol ether **3g** was obtained in good yield (Scheme 4). Obviously, this result supports the possibility of the indirect pathway.



Scheme 3: Gold-catalyzed isomerism of silyl enol ether.



Scheme 4: Gold-catalyzed alkylation of tetra-substituted silyl enol ether.

In conclusion, we have developed an unprecedented alkylation method for silyl enol ethers, using a gold catalyst and *ortho*-alkynylbenzoic acid esters as alkylating agents. The reaction probably proceeds through the gold-induced in situ construction of a leaving group and subsequent nucleophilic attack on the silyl enol ether. Unlike ordinary leaving groups, such as halide ions, the generated leaving compound **8** acts as a base and abstracts a proton to regenerate the silyl enol ether structure. The current protocol can also be used with substrates having no hydrogen at the α-position, such as **1f**. Further studies to elucidate the mechanism of this reaction and to extend the scope of synthetic utility are underway.

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Gold-catalyzed naphthalene functionalization

Pedro J. Pérez*, M. Mar Díaz-Requejo* and Iván Rivilla

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Address:
Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Centro de Investigación en Química Sostenible (CIQSO), Universidad de Huelva, Campus de El Carmen 21007-Huelva, Spain

Email:
Pedro J. Pérez* - perez@dqcm.uhu.es; M. Mar Díaz-Requejo* - mmdiaz@dqcm.uhu.es; Iván Rivilla - ivan.rivilla@dqcm.uhu.es

* Corresponding author

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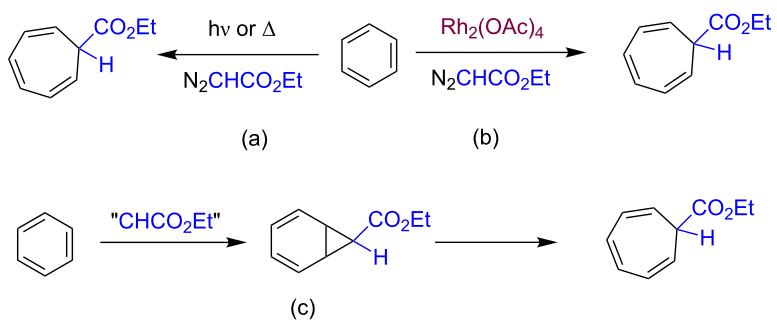
Abstract

The complexes IPrMCl (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, M = Cu, **1a**; M = Au, **1b**), in the presence of one equiv of $NaBAr'_4$ (Ar' = 3,5-bis(trifluoromethyl)phenyl), catalyze the transfer of carbene groups: $C(R)CO_2Et$ (R = H, Me) from $N_2C(R)CO_2Et$ to afford products that depend on the nature of the metal center. The copper-based catalyst yields exclusively a cycloheptatriene derivative from the Buchner reaction, whereas the gold analog affords a mixture of products derived either from the formal insertion of the carbene unit into the aromatic C–H bond or from its addition to a double bond. In addition, no byproducts derived from carbene coupling were observed.

Introduction

At the end of the nineteenth century, Buchner discovered [1] the thermal and photochemical route for the functionalization of benzene using diazo compounds to provide a carbene moiety. The first step of this transformation consists of the addition of such a unit to the aromatic double bond to give a norcaradiene intermediate that spontaneously undergoes ring opening to afford the more stable cycloheptatriene product (Scheme 1) [2]. Nearly one century later, Teyssié and co-workers discovered the potential of dirhodium tetraacetate and related $Rh_2(L\text{-}L)_4$ compounds as catalysts for the decomposition of diazo compounds and subsequent transfer of the carbene moiety to several saturated and unsaturated substrates, including aromatics [3]. Thus, the reaction of ethyl diazoacetate (EDA) with benzene in the presence of such catalysts at room temperature exclusively affords the cycloheptatriene product in quantitative yields. The reaction, always referred to the intermolecular version, was later observed with other metal-based catalysts [4-6].

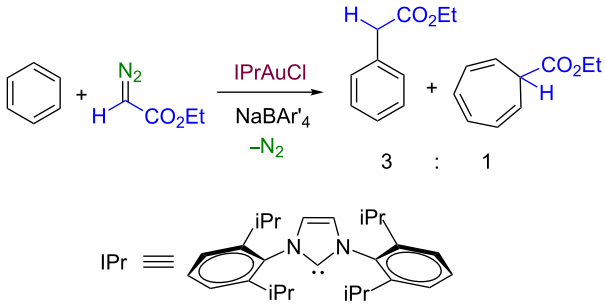
The above transformation with rhodium-based catalysts [7,8] has also been investigated with naphthalene as a substrate. In this case, Teyssié and co-workers showed that it could be converted, using *t*-butyl diazoacetate, into norcaradiene type



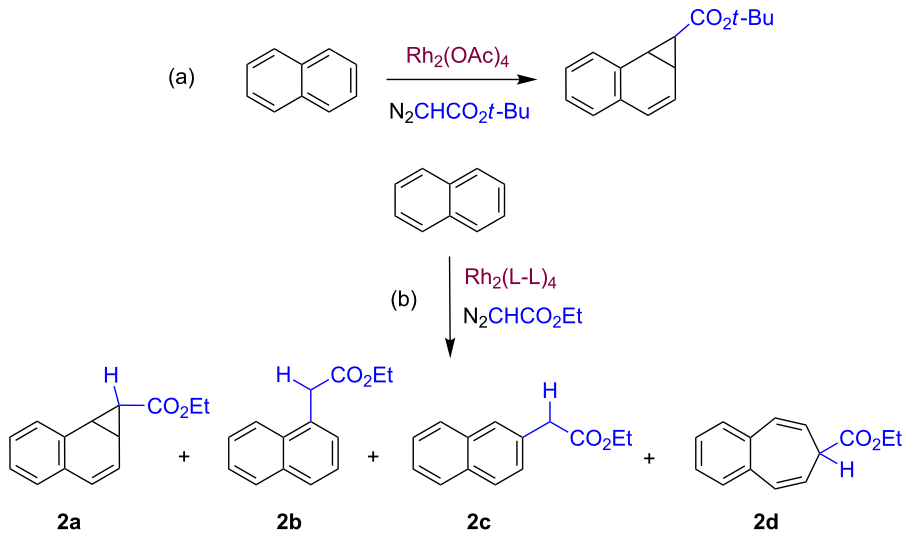
Scheme 1: (a) The Buchner reaction of benzene and ethyl diazoacetate and (b) the Rh-catalyzed version. (c) Both pathways involve the formation of norcaradiene intermediates.

derivatives, formed by the cyclopropanation of one of the double bonds of the naphthalene ring. Later, Müller and co-workers [9] showed the effect of a series of $Rh_2(L\text{-}L)_4$ in the same transformation but with ethyl diazoacetate as the carbene source. A mixture of the products (**2a**–**d**) arising from cyclopropanation, ring opening and the formal insertion of $CHCO_2Et$ into the aromatic C–H bonds were observed, with **2a** being by far the major product (Scheme 2).

In the course of our research, focussed on the development of group 11 metal-based catalysts for carbene transfer reactions from diazo compounds [10], we found that the gold complex IPrAuCl (**1b**) (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) in the presence of one equiv of $NaBAr'_4$ (Ar' = 3,5-bis(trifluoromethyl)phenyl) induced the functionalization of benzene with ethyl diazoacetate to give a mixture of a cycloheptatriene and ethyl 2-phenylacetate [11], the latter being the result of the formal insertion of the $CHCO_2Et$ group into the C–H bond of benzene as well as the major product (Scheme 3). In this contribution, we report the results obtained from the analogous transformation using naphthalene as the substrate, with copper- and gold-based catalysts, not previously described for the functionalization of such fused arenes.



Scheme 3: The gold-catalyzed reaction of benzene and EDA.



Scheme 2: The Buchner reaction applied to naphthalene. (a) Teyssié's system. (b) Müller's system.

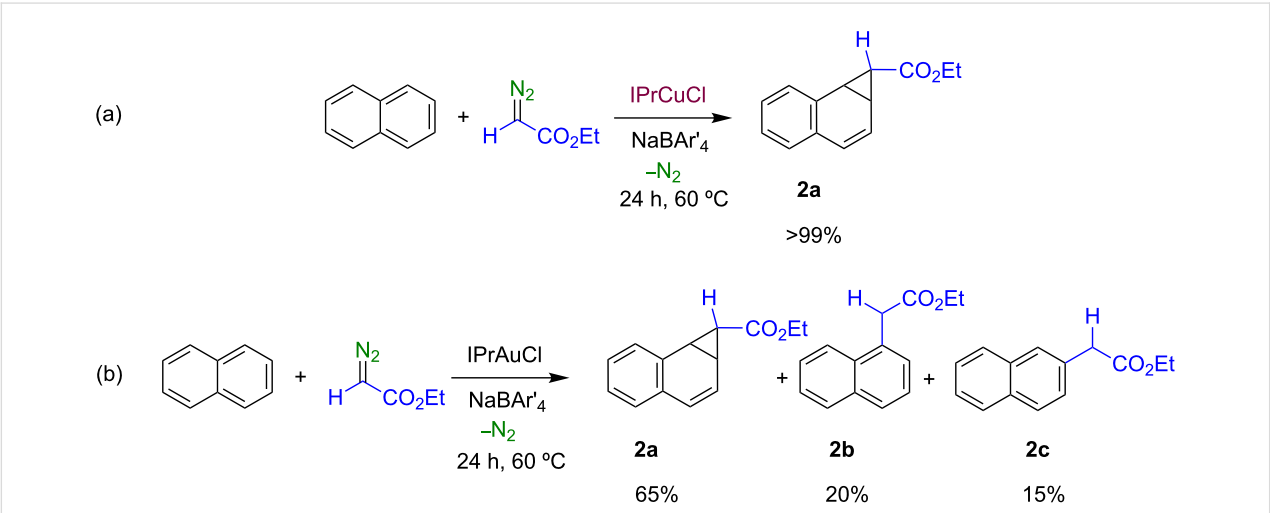
Results and Discussion

Reaction of naphthalene and diazoacetates catalyzed by IPrMCl (M = Cu, Au)

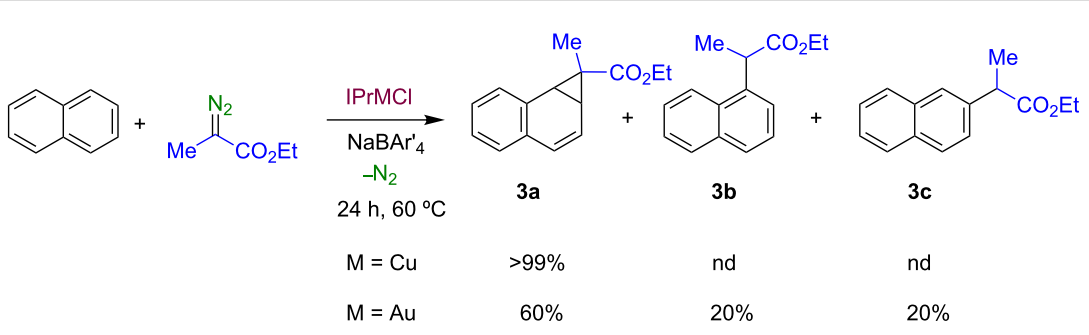
When dichloroethane solutions of naphthalene were treated with ethyl diazoacetate in the presence of catalytic amounts (5%) of a 1:1 mixture of IPrMCl (M = Cu, **1a**; M = Au, **1b**) and $NaBAr'_4$, the diazo compound was consumed after 24 h at 60 °C (no significant reaction was observed at room temperature or at 40 °C). NMR analysis of the crude reaction product revealed that when **1a** was used as the catalyst, only one compound was formed, identified as ethyl 1a,7b-dihydro-1H-cyclopropa[a]naphthalene-1-carboxylate (**2a**), i.e., the product derived from the direct cyclopropanation of the naphthalene C–C double bond (Scheme 4a). By contrast, the use of the gold catalyst IPrAuCl (**1b**) under the same reaction conditions gave a mixture of three compounds, in ca. 65:20:15 ratio, that have been identified as **2a**, ethyl 2-(naphthalen-1-yl)acetate (**2b**) and ethyl 2-(naphthalen-2-yl)acetate (**2c**). Compounds **2b** and **2c**, respectively, are derived from the formal insertion of the carbene group into a C–H bond of naphthalene (Scheme 4b).

The selectivity observed is similar to that reported by Müller's group with $[Rh_2(O_2CC_3F_7)_4]$ (60:22:18) [8]. However, in our case the yield of products (EDA-based) was quantitative: products derived from dimerization of the diazo compound, i.e., diethyl fumarate and maleate, were not detected. The absence of the fused cycloheptatriene **2d** in our system is also noteworthy. Substituted naphthalenes with OMe or Cl substituents at the beta position were also employed as substrates, however, the yields of the desired products were nearly negligible. The former seemed to induce the insertion into the Me groups, whereas in the latter case the aromatic reagent seemed deactivated.

We have expanded this reaction to ethyl 2-diazopropionate as the diazo component. Following a similar protocol, naphthalene was reacted in dichloroethane with ethyl 2-diazopropionate in the presence of a 1:1 mixture of **1a**,**b** and $NaBAr'_4$ (5% with respect to the diazo compound). Similarly to the previous results, the fused norcaradiene **3a** (Scheme 5) was exclusively and quantitatively formed using the copper catalyst **1a**, whilst



Scheme 4: The functionalization of naphthalene with ethyl diazoacetate catalyzed by the complexes (a) **1a** and (b) **1b**.



Scheme 5: The functionalization of naphthalene with ethyl 2-diazopropionate catalyzed by complexes **1a** and **1b**.

the use of **1b** afforded a mixture of three products in a 60:20:20 ratio. The major product was identified as the **3a** and the minor products have been characterized as the insertion products of the carbene $C(Me)CO_2Et$ into the α- and β-C–H bonds of naphthalene, **3b** and **3c**, respectively. When other diazo reagents such as $Me_3SiC(N_2)CO_2Et$ or $PhC(N_2)CO_2Et$ were employed, intractable mixtures of compounds, probably due to multiple insertions, were observed by NMR.

It is also worth mentioning that the above transformations do not compete with the formation of byproducts derived from the catalytic dimerization of the diazo reagents, a common drawback in this methodology [2]. Despite of adding all the diazo compound in one portion at the beginning of the reaction, the final reaction mixture only showed resonances due to the aforementioned insertion and addition products. This is at variance with other reported systems that required the use of slow addition devices to diminish the formation of such byproducts.

Conclusion

The complexes IPrMCl (M = Cu, Au) catalyze the transfer of carbene groups $C(R)CO_2Et$ (R = H, Me) to naphthalene, in the presence of $NaBAr'_4$ as halide scavenger, to give mixtures of products via carbene insertion into a C–H bond or by addition to a double bond. In the case of copper, norcaradiene type compounds are formed quantitatively. The use of the gold analogue also induces the formation of such fused cyclopropanes in addition to the products derived from the formal insertion of the carbene units into the C–H bonds of naphthalene. The system is completely chemoselective with regards to arene functionalization (with no diazo compound dimerization being observed).

Experimental

All reactions and manipulations were carried out under a nitrogen atmosphere. Organic solvents were dried, distilled, and degassed before use. The reagents were purchased from Sigma Aldrich. Complexes IPrMCl (M = Cu, **1a**; M = Au, **1b**), $NaBAr'_4$ and ethyl 2-diazopropionate were prepared by literature procedures [12-16]. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards.

General catalytic experiment

Complex **1** (0.025 mmol) was dissolved in dichloroethane (5 mL) and one equiv of $NaBAr'_4$ added to the solution, which was then added to a solution of naphthalene (8.6 mmol, 10 mL) and heated at 60 °C in dichloroethane (20 mL). After stirring for 15 min, $(R)C(N_2)CO_2Et$ (R = H, Me; 0.5 mmol) was added in one portion, and the mixture stirred for 24 h. Removal of volatiles followed by silica gel column chromatography (1:1 Et_2O:petroleum ether) gave a mixture of products. The products **2a**, **3b** and **3c** were identified by comparison with literature data [17-19], and **2b** and **2c** were compared authentic samples obtained from commercial sources.

Spectroscopic data for **3a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–6.94 (m, 4H), 6.59 (d, 1H), 6.06 (dd, 1H), 4.23 (m, 2H), 3.14 (d, J = 8.7 Hz, 1H), 2.72 (dd, J = 8.8 Hz, 1H), 1.26 (s, 3H), 1.29 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (CO_2Et), 146.4, 134.5, 133.4, 129.6, 128.5, 127.7, 126.6, 125.5 (aromatic), 63.1 ($COCH_2CH_3$), 39.6, 33.3, 31.2 (cyclopropyl), 19.52 (CH_3), 11.8 ($COCH_2CH_3$); MS m/z (%): 228 (70), 199 (30), 182 (100).

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When cyclopropenes meet gold catalysts

Frédéric Miege, Christophe Meyer* and Janine Cossy*

Review

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Address:
Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS (UMR 7084), 10 rue Vauquelin 75231 Paris Cedex 05, France

Email:
Christophe Meyer* - christophe.meyer@espci.fr;
Janine Cossy* - janine.cossy@espci.fr

* Corresponding author

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Abstract

Cyclopropenes as substrates entered the field of gold catalysis in 2008 and have proven to be valuable partners in a variety of gold-catalyzed reactions. The different contributions in this growing research area are summarized in this review.

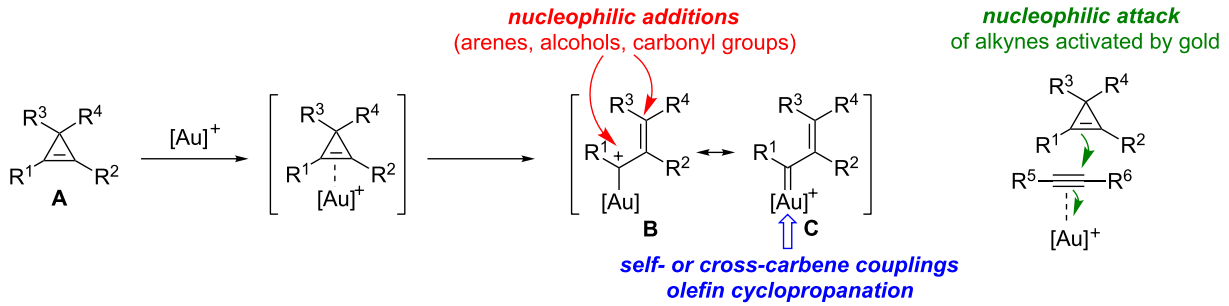
Review

Introduction

Homogeneous gold catalysis has become a particularly active research area over the last decade. The ability of gold catalysts to act as potent carbophilic Lewis acids and hence to chemoselectively activate π bonds towards nucleophilic attack is now well-established and has found many impressive applications for the formation of C–C or C–heteroatom bonds [1-14]. Whereas alkynes, alkenes and allenes have been widely used as substrates or partners in gold-catalyzed reactions, it was only rather recently, in 2008, that cyclopropenes entered the field of gold catalysis despite their well-known high and versatile reactivity in transition metal-catalyzed reactions [15].

As has been observed with other transition metals, the reactivity of cyclopropenes **A** in gold-catalyzed reactions is essentially (but not exclusively) related to their ability to act as ligands for π-acidic gold complexes, and hence, to undergo subsequent ring-opening to produce an organogold species that can be viewed as a hybrid between a gold-stabilized allylic carbocation **B** and a gold carbene **C**. The organogold carbenoid species generated by the ring-opening of cyclopropenes can participate in a variety of reaction types such as nucleophilic addition with, e.g., alcohols, arenes or carbonyl groups, undergo self- or cross-carbene couplings and bring about the cyclopropanation of olefins. The first of these reaction types is often considered to be representative of cationic intermediates whereas the other two are best ascribed to carbene-like reactivity, although this distinction is artificial. Alternatively, cyclopropenes can also behave as nucleophiles and attack other functional groups that are more readily activated by gold complexes, such as alkynes (Scheme 1) [16-26].

This review illustrates the different aspects of the reactivity of cyclopropenes in the presence of gold catalysts and covers the contributions in this field up to February 2011.



Scheme 1: General reactivity of cyclopropenes in the presence of gold catalysts.

Besides their implication in several gold-catalyzed reactions, cyclopropenes have also served as substrates in order to gain insight into the gold-carbon order in the so-called organogold carbenoids. In the broad repertoire of gold-catalyzed organic transformations, gold-stabilized carbocations or, more often gold carbenes, can be found as intermediates in proposed mechanistic pathways, but the true nature of the organogold species had been a matter of debate [27].

Structural considerations: Gold-stabilized carbocations or gold carbenes?

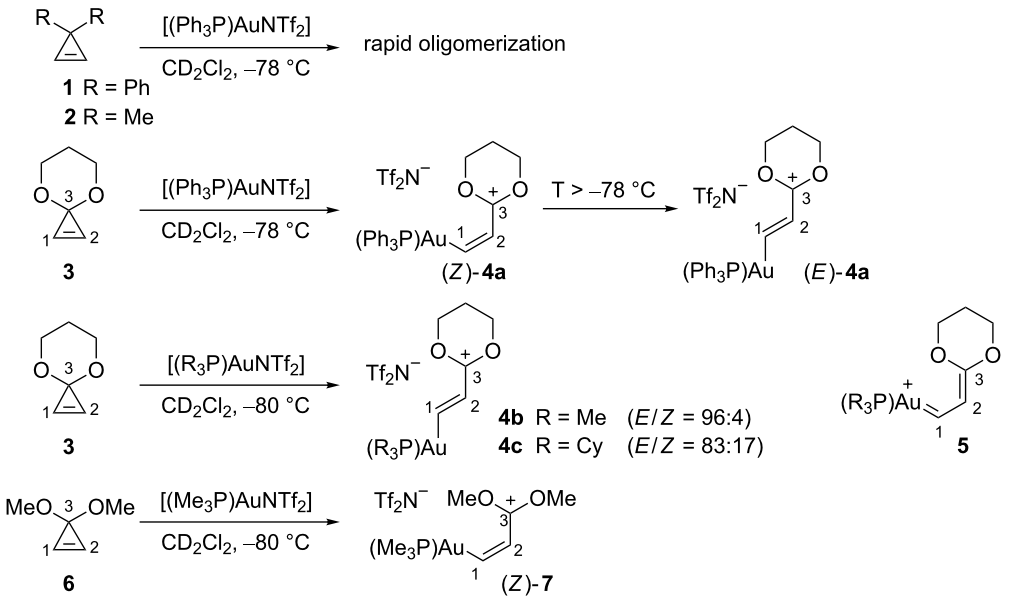
In 2008, Fürstner et al. took advantage of the ring-opening of 3,3-disubstituted cyclopropenes to generate organogold species and characterize them by NMR spectroscopy [16]. Whereas, 3,3-diphenylcyclopropene (**1**) or 3,3-dimethylcyclopropene (**2**) did not generate a defined organogold species upon treatment with Gagosz's complex [$(Ph_3P)AuNTf_2$] [28] (CD_2Cl_2, −78 °C) due to rapid oligomerization, the cyclopropenone acetal **3** gave an organogold species whose NMR spectroscopic data corresponds to the carbocationic structure (*Z*)-**4a**. Upon raising the temperature, organogold (*Z*)-**4a** was found to isomerize into its geometric isomer (*E*)-**4a**. Switching to more electron-donating phosphine ligands such as PMe_3 or PCy_3, also led to the organogold species **4b** and **4c**, respectively, possessing a dioxacarbenium structure, with the predominance of the *E* geometric isomers already at −80 °C. The observed data point towards a high degree of double bond character for the C1–C2 bond, and not the C2–C3 bond, in the organogold species generated by ring-opening of cyclopropenone acetal **3**, with a marginal contribution of the carbene form **5**. The magnitude of the rotational barrier around the C2–C3 bond for **4a** (<30 kJ·mol^{-1}) was in agreement with this result. In the case of the less stable organogold species (*Z*)-**7**, generated from 3,3-dimethoxycyclopropene (**6**) using [$(Me_3P)AuNTf_2$], the broadening of the NMR signals indicated a more restricted rotation around the C2–C3 bond at −80 °C, but the rotation barrier estimated to be 46 ± 1 kJ·mol^{-1} was still comparable in magnitude to rotation around a sterically hindered σ bond (such as in hexachloroethane) (Scheme 2) [16].

These experiments appeared to be useful for the determination of the cationic or carbenic nature of organogold intermediates, but the presence of the two oxygen atoms in cyclopropenone acetals unavoidably led to more favorable cationic forms and hence cannot provide a general answer.

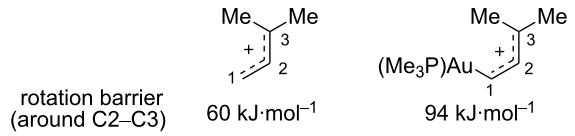
Using the M06 functional of DFT, Toste et al. calculated rotational barriers for (*Z*)-**4a** and (*Z*)-**7** and the results were found to be in agreement with those previously obtained experimentally by Fürstner et al. Thus, with this validated computational method, the barriers to bond rotation in (metal free) 3,3-disubstituted allyl cations, and in the corresponding $(Me_3P)Au$-substituted organogold species, were calculated. Unlike in the case of the allylic cation bearing an acetal moiety at C3, incorporation of the gold center at C1 in the 3,3-dimethyl substituted allylic cation raised the rotation barrier considerably to 94 kJ·mol^{-1}, and hence the latter species should be regarded more as a gold carbene (Scheme 3) [17].

The bond distances and natural atomic charges were calculated for a series of 3,3-disubstituted allylic cations, bearing an acetal, two methyl or two carbomethoxy groups, as well as for their (trimethylphosphine)gold-substituted counterparts. The results indicate that a secondary gold-substituted carbocation (at C1) is as stable as a tertiary dimethyl-substituted carbocation (at C3) and that the magnitude of stabilization from the gold moiety increases with increasing electrophilicity of the allylic cation. Toste et al. investigated the effect of the ligand on the structure of gold-substituted 3,3-dimethyl allyl cations of type **D**. Increasing *trans* σ-donation from the ligand and strongly π-acidic ligands such as phosphites (decreasing back π-donation from gold to C1) led to a longer C1–Au bond and hence a more carbocation-like character for the organogold species. By contrast, those ligands that increase gold-to-C1 back π-donation or decrease C1-to-gold σ-donation will induce a shorter C1–Au bond and a carbene-like reactivity (Scheme 4) [17].

These studies highlighted the tremendous influence of the substitution pattern and the ancillary ligand on the nature of



Scheme 2: Cationic organogold species generated from cyclopropenone acetals.



Scheme 3: Rotation barriers around the C2–C3 bond (M06 DFT calculations).

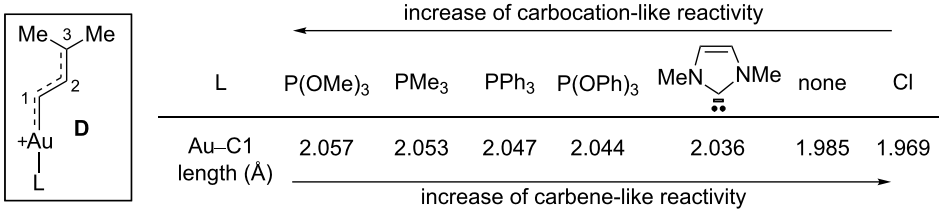
bonding in cationic gold-stabilized intermediates. Interestingly, the organogold species investigated in these computational studies are precisely those that can be generated by the ring-opening of cyclopropenes in the presence of gold complexes. Indeed, as it will be illustrated later in this review, these structural effects were found to have important consequences in terms of reactivity in the case of intermolecular olefin cyclopropanation promoted by gold carbenes generated from cyclopropenes.

In fact, the first reports on gold-catalyzed reactions involving cyclopropenes appeared in the literature before these structural investigations were carried out. In the following presentation of the different chemical transformations involving cyclopropenes, either one of the two forms (i.e., an allylic gold cation or carbene) will be drawn in the mechanistic pathway. In general, little information is available on the modulation and tuning of the reactivity by the choice of the gold ligand.

Nucleophilic addition to gold-stabilized allylic cations generated from cyclopropenes

Intermolecular addition of oxygen nucleophiles

In 2008, Lee et al. reported several gold-catalyzed reactions involving cyclopropenes among which the addition of alcohols to 3-methyl-3-nonylcyclopropene (**8**) was investigated in detail [18]. A variety of primary alcohols reacted with cyclopropene **8** in the presence of either in situ generated [(Ph_3P)AuOTf] or [(Ph_3P)AuNTf_2] (5 mol %) to afford the corresponding *tert*-allylic ethers **9a**–**9f** with very high regioselectivity (>99%). Other catalysts such as $AuCl_3$ or $Rh_2(OAc)_4$ provided mixtures of compounds containing traces of allylic ethers **9** and **9'** and mostly oxidation products (vide infra, enals **16** and **17**). AgOTf



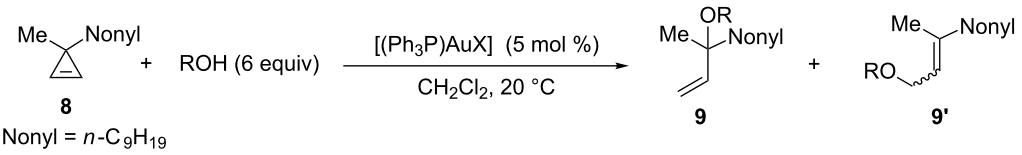
Scheme 4: Au–C1 bond length in organogold species of type **D**.

was less efficient and led to an incomplete conversion whereas no reaction took place with TfOH. Gagosz's catalyst was in general more efficient than [(Ph_3P)AuOTf] and also allowed iPrOH to be used as a nucleophile to provide ether **9g** (70%), however, tertiary alcohols did not react under these conditions. Water in the presence of *t*-BuOH as co-solvent acted as a nucleophile, but the corresponding tertiary alcohol **9i** was isolated in only modest yield (34%) (Scheme 5) [18]. Additional results were subsequently reported by Lee et al. in a full article in 2010 [19]. Due to their lower nucleophilic character compared to alcohols, phenols could not be used. With the optically pure chiral alcohol (*R*)-PhMeCHCH$_2$OH as a nucleophile, the reaction was not diastereoselective and led to the tertiary allylic ether **9k** (65%) as a 1:1 mixture of diastereomers. An unprotected primary and tertiary 1,3-diol reacted chemoselectively with the primary alcohol to furnish monoether **9l** (58%). Addition of neopentyl glycol led to a 1:1 mixture of regioisomeric monoethers **9m** and **9'm** in modest yield (32%) due to the competitive formation of oligomeric by-products. The regioselectivity was found to be highly sensitive to temperature since the tertiary monoether **9m** was selectively obtained (**9m**/**9'm** > 99:1) (33%) when the reaction was carried out at 10 °C (Scheme 5) [18,19].

The reaction was successfully extended to a variety of 3,3-disubstituted cyclopropenes (3-methyl-3-benzylcyclopropene, spiro[2.5]oct-1-ene, 3-benzyl-3-isopropylcyclopropene, 3-*tert*-butyl-3-methylcyclopropene) and the corresponding tertiary allylic ethers were always obtained with high regioselectivities (92:8 to >99:1). However, when 3-methyl-3-phenylcyclopropene (**10**) was used as the substrate the regioselectivity was altered in some cases. With *n*-BuOH as a nucleophile, a 1:1 regioisomeric mixture of allylic ethers **11a** and **11'a** was obtained under the previously used reaction conditions. By lowering the temperature to 10 °C and increasing the quantity of *n*-BuOH (15 equiv), the tertiary allylic ether **11a** (65%) was obtained regioselectively (**11a**/**11'a** > 99:1). Curiously, a complete switch of the regioselectivity took place when phenethyl alcohol was employed as a nucleophile, since in this case the primary allylic ether **11'b** (65%) was obtained (**11b**/**11'b** > 1:99) (Scheme 6) [19].

The formation of the *tert*-allylic ethers **9** can be explained by the regioselective attack of the alcohol at C3 on the organogold species **12**, generated by electrophilic ring-opening of cyclopropene **8**, followed by protodeauration of the resulting vinyl gold species **13**. Using CD_3OD as a nucleophile effectively led to 90% deuterium incorporation at C1 and formation of a mixture of geometric isomers (Scheme 7) [18,19].

Interestingly, an excess of the alcohol (6 equiv) was crucial to achieve high regioselectivities. If the quantity of EtOH was reduced (1 equiv) a 2:1 mixture of the corresponding regioisomeric allylic ethers **9a** and **9'a** was obtained, however, the addition of a protic additive [*t*-BuOH (5 equiv)] restored the high regioselectivity (>99:1) [18,19]. Lee and Hadfield demon-



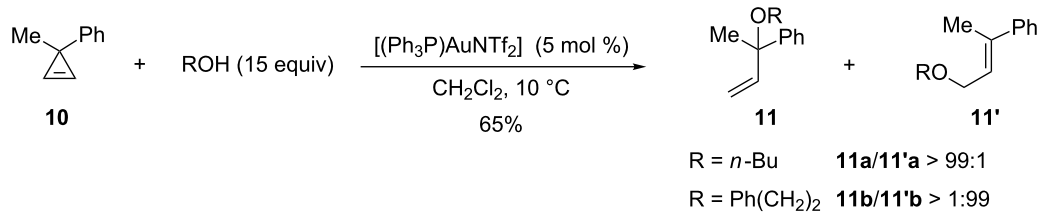
8
Nonyl = *n*-C_9H_{19}

9 **9'**

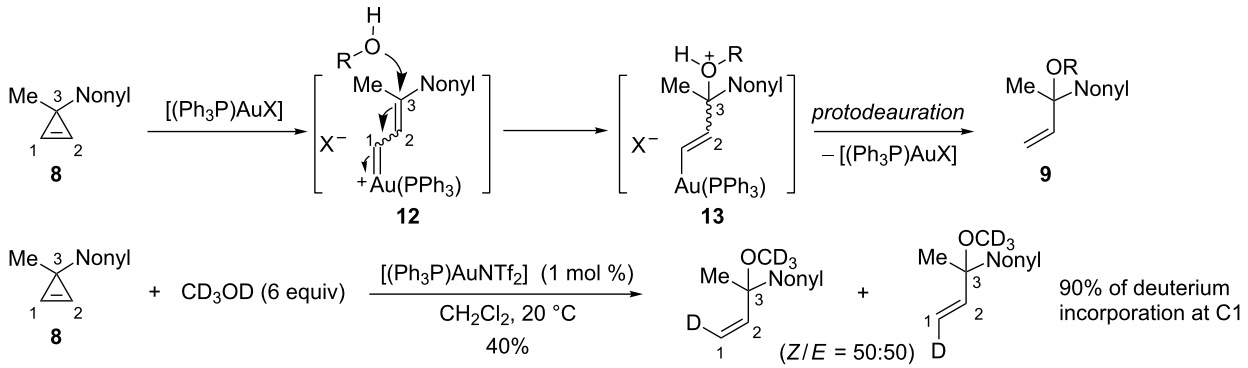
R	X	Product(s)	Yield	Regioselectivity (**9**/**9'**)
Et	OTf	**9a**	64%	>99:1
Et	NTf_2	**9a**	83%	>99:1
Me, Allyl, H_2C=CH(CH_2)$_2$, Ph(CH_2)$_2$	NTf_2	**9b**–**9e**	77–88%	>99:1
Bn	OTf	**9f**	78%	>99:1
iPr	NTf_2	**9g**	70%	97:3
t-Bu	NTf_2	**9h**	traces	—
H[a]	NTf_2	**9i**	34%	>99:1
4-(MeO)C_6H_4	NTf_2	**9j**	—	—
(*R*)-Ph(Me)CHCH$_2$	NTf_2	**9k**[b]	65%	>99:1
$Me_2C(OH)CH_2CH_2$[c]	NTf_2	**9l**	58%	>99:1
$(HOCH_2)CMe_2CH_2$[c]	NTf_2	**9m**,**9'm**	32%	1:1
$(HOCH_2)CMe_2CH_2$[c]	NTf_2	**9m**	33%[d]	>99:1[d]

[a]With *t*-BuOH (15 equiv). [b]1:1 Mixture of diastereomers. [c]2 equiv of 1,3-diol were used. [d]Reaction run at 10 °C.

Scheme 5: Gold-catalyzed addition of alcohols or water to cyclopropene **8**.

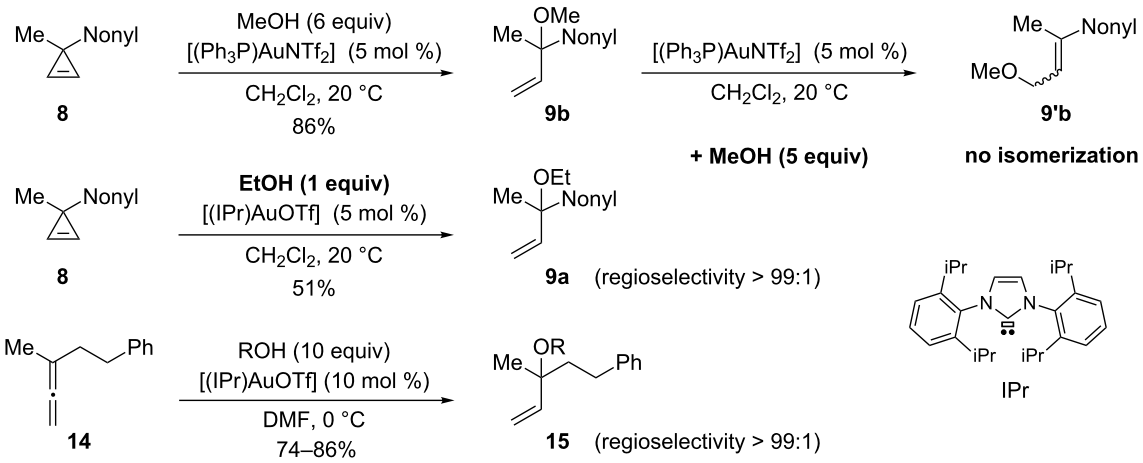


Scheme 6: Gold-catalyzed addition of alcohols to cyclopropene **10**.



Scheme 7: Mechanism of the gold-catalyzed addition of alcohols to cyclopropenes.

strated that the use of an excess of methanol retarded the isomerization of the tertiary allylic ether **9b** into the primary allylic isomer **9'b**, which is also catalyzed by the gold complex [29] (Scheme 8). The isomerization was also found to be catalyst dependent and did not operate in the presence of the NHC–gold complex [(IPr)AuOTf]. Thus, when cyclopropene **8** was treated with a stoichiometric quantity of EtOH in the presence of the latter catalyst (5 mol %), the tertiary allylic ether **9a** was obtained with high regioselectivity (>99:1), but the yield (51%) was not as high as with Gagosz's catalyst (83%). Lee and Hadfield took advantage of these findings to develop the regioselective addition of alcohols (used in excess) to allenes such as **14** catalyzed by [(IPr)AuOTf] (10 mol %) to produce the *tert*-allylic ethers **15** as the kinetic products (Scheme 8) [29].



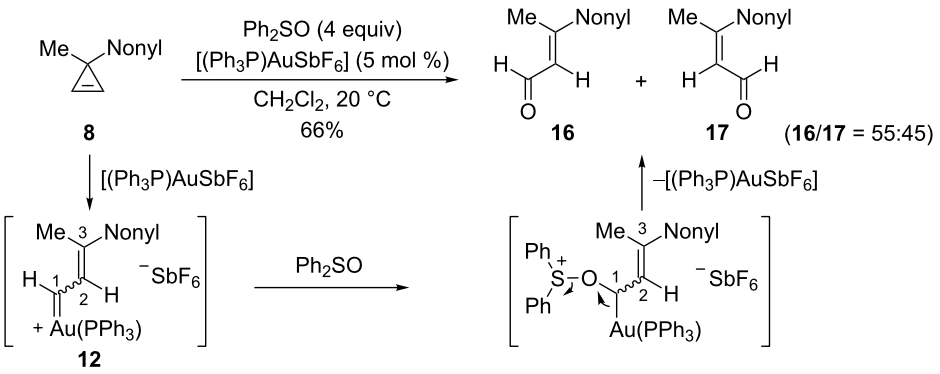
Scheme 8: Synthesis of *tert*-allylic ethers from cyclopropenes and allenes.

During their studies on the addition of alcohols to cyclopropenes, Lee et al. also reported one example of oxidation of the gold carbene intermediate **12**, resulting from the electrophilic ring-opening of 3-methyl-3-nonylcyclopropene (**8**), with diphenylsulfoxide [30]. The reaction proceeds by nucleophilic attack of diphenylsulfoxide at C1 followed by elimination of diphenylsulfide to afford a 55:45 mixture of the *E* and *Z* enals **16** and **17**, respectively (66%) (Scheme 9) [18,19].

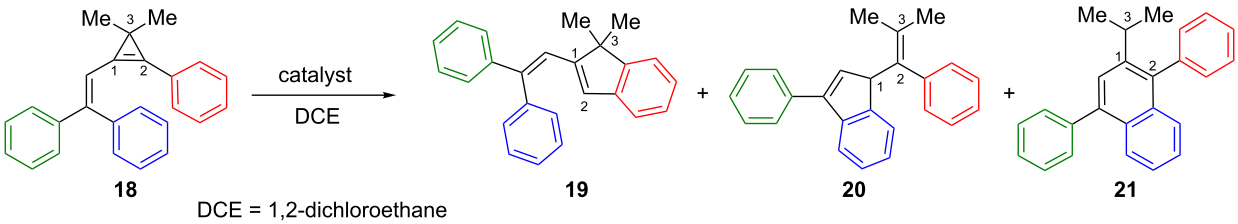
Other examples of nucleophilic attack on organogold species resulting from the ring-opening of cyclopropenes in the presence of gold complexes involve intramolecular Friedel–Crafts reactions and the addition of carbonyl groups.

Intramolecular Friedel–Crafts reactions

In the context of their studies on the Lewis acid-catalyzed rearrangement of strained three-membered ring hydrocarbons, such as methylenecyclopropanes and vinylidenecyclopropanes, Shi et al. investigated the behaviour of 1-(2,2-diarylvinyl)-2-phenylcyclopropenes in the presence of gold catalysts [20]. Upon treatment with [(Ph_3P)AuOTf], vinylcyclopropene **18** was found to produce a mixture of regioisomeric indenes **19** and **20** in a 75:25 ratio (99%). The use of AgOTf alone led to the isomeric substituted naphthalene **21** as the sole product. Shi et al. had previously demonstrated that indene **20** and naphthalene **21** could be selectively formed using $Cu(OTf)_2$ and $BF_3{\cdot}OEt_2$ as catalysts, respectively, thereby highlighting the complementarities of the different electrophilic activators [31]. Since AgOTf and $BF_3{\cdot}OEt_2$ led to the same naphthalene product **21**, the authors suspected that traces of the Brønsted acid (HOTf) present in the silver salt may be the actual catalyst and may also modify the regioselectivity observed in the gold-catalyzed reaction. Thus, several basic additives were screened and it was found that DBU not only inhibited the isomerization of vinylcyclopropene **18** in the presence of AgOTf, but also led to a completely regioselective gold-catalyzed process to afford indene **19** as the sole reaction product (97%) (Scheme 10) [20].



Scheme 9: Oxidation of the intermediate gold–carbene with diphenylsulfoxide.



Catalyst	Additive	Conditions	Products (Yield)
(Ph_3P)AuCl/AgOTf (5 mol %)	--	50 °C, 24 h	**19**/**20** = 75:25 (99%)
AgOTf (5 mol %)	--	50 °C, 24 h	**21** ("single product")
$Cu(OTf)_2$ (10 mol %)	--	50 °C, 5 h	**20** (98%)
$BF_3{\cdot}OEt_2$ (10 mol %)	--	40 °C, 5 h	**21** (60%)
AgOTf (5 mol %)	DBU (50 mol %)	50 °C, 10 h	no reaction
(Ph_3P)AuCl/AgOTf (5 mol %)	DBU (50 mol %)	50 °C, 10 h	**19** (97%)

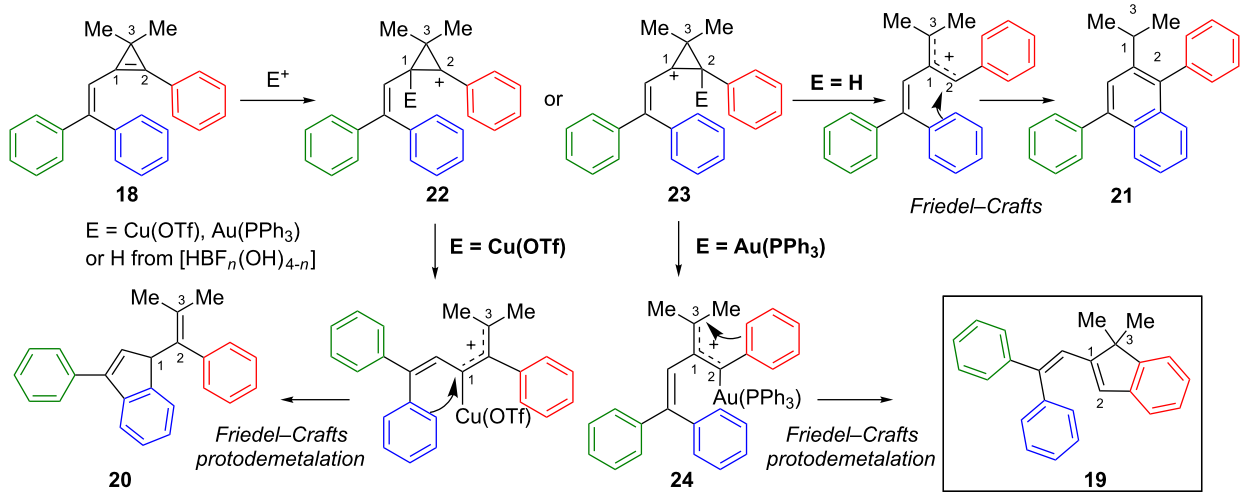
Scheme 10: Gold, copper and Lewis acid-catalyzed reactions of cyclopropene **18**.

Upon electrophilic activation, vinylcyclopropene **18** can give rise to two regioisomeric cyclopropyl cations **22** and **23**. It is worth noting that consideration of these two cation species is only helpful to understand the observed regioselectivities, though they may not be actually involved as intermediates during the ring-opening of cyclopropenes in the presence of electrophilic transition metal complexes. Shi et al. initially suggested that the formation of **22** preferentially occurs with a rather bulky electrophile such as $Cu(OTf)_2$ to avoid repulsion with the aryl group at C2. Conversely, a Brønsted acid (generated by reaction of $BF_3{\cdot}OEt_2$ with traces of water) should favour the formation of the more stable cyclopropyl cation **23**. Afterwards, ring-opening and intramolecular Friedel–Crafts reactions should enable the formation of indene **20** or naphthalene **21**. With the gold catalyst, the formation of indene **19** indicated that electrophilic activation of the cyclopropene **18** also occurred at C2 to afford, after ring-opening, the gold-stabilized allylic cation **24**. However, in contrast to the acid-catalyzed reaction, subsequent intramolecular Friedel–Crafts cyclization occurred by nucleophilic attack by the phenyl group (at C2) on the organogold species at C3, followed by protodeauration (Scheme 11) [20,31].

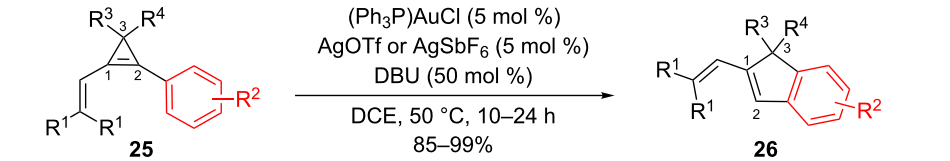
The reaction was generalized with a series of 3,3-disubstituted-1-(2,2-diarylvinyl)-2-arylcyclopropenes of general formula **25**. The catalyst $[(Ph_3P)AuSbF_6]$ was found to provide better results than $[(Ph_3P)AuOTf]$ for substrates having electron-withdrawing substituents on the benzene rings. The corresponding indenes **26** were obtained in good to excellent yields (85–99%) under the previously optimized conditions (Scheme 12) [20].

In the absence of substituents at C3 ($R^3 = R^4 = H$), or when a single substituent was attached to this carbon (R^3 = Me, R^4 = H), the reaction led to a complex mixture of products. The authors attributed these results to the formation of less stable carbocations at C3 (primary or secondary, respectively).

Other examples of gold-catalyzed isomerization of cyclopropenes that involve a Friedel–Crafts cyclization have been reported. In 2009, Wang et al. demonstrated that $[(Ph_3P)AuOTf]$ could smoothly catalyze the isomerization of a variety of 3-substituted 1,2,3-triphenylcyclopropenes **27** into 3-substituted 1,2-diphenyl-1*H*-indenes **28** [21]. The rearrangement occurred rapidly (20–40 min) for substrates **27a**–**27e** and indenes **28a**–**28e** were obtained in excellent yields (97–99%).



Scheme 11: Mechanism of the Lewis acid-catalyzed reactions of cyclopropene **18**.



Scheme 12: Gold-catalyzed rearrangement of vinylcyclopropenes **25**.

A phenylethynyl group could be present at C3, but the rearrangement of substrate **27f** proceeded slowly (rt, 6 h) and gave indene **28f** in only a moderate yield (54%) together with an unknown by-product, presumably because the alkyne competes with the cyclopropene for coordination to the gold catalyst (Scheme 13) [21,26].

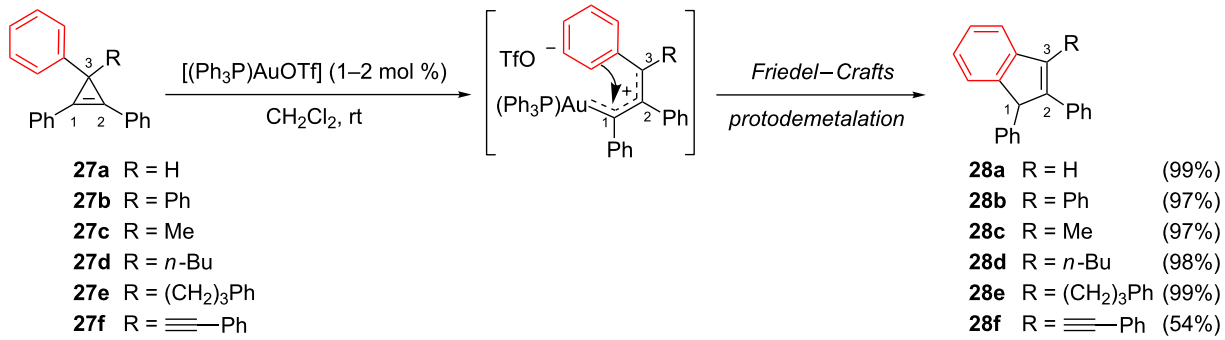
The rearrangement of **27a** to **28a** (95%) had been previously reported by Müller et al. using rhodium(II) perfluorobutyrate as a catalyst (1 mol %, C_6H_6, reflux, 48 h) [32], whereas Padwa et al. showed that the isomerization of **27b** to **28b** was quantitatively catalyzed by $AgClO_4$ (2 mol %, C_6H_6, rt) [33].

Wang et al. also examined the behaviour of 3-arylcyclopropenes bearing a protected hydroxymethyl group at C3: only acetates **29** underwent clean conversion to 1-methylene-2-substituted-1*H*-indenes **30** [21]. The yields were improved by the addition of DBU once the rearrangement was complete. For substrates **29** possessing an unsymmetrically substituted endocyclic olefin, it is worth noting that electrophilic activation of the cyclopropene occurred regioselectively to produce the organogold species **31** (formally resulting from the ring-opening of a secondary benzylic cyclopropyl cation). The gold carbene **31** was captured by the aromatic group at C3 via an intramolecular Friedel–Crafts reaction. Subsequent elimination of AcOH from compound **33** then delivered methylene indene **30** (Scheme 14) [21].

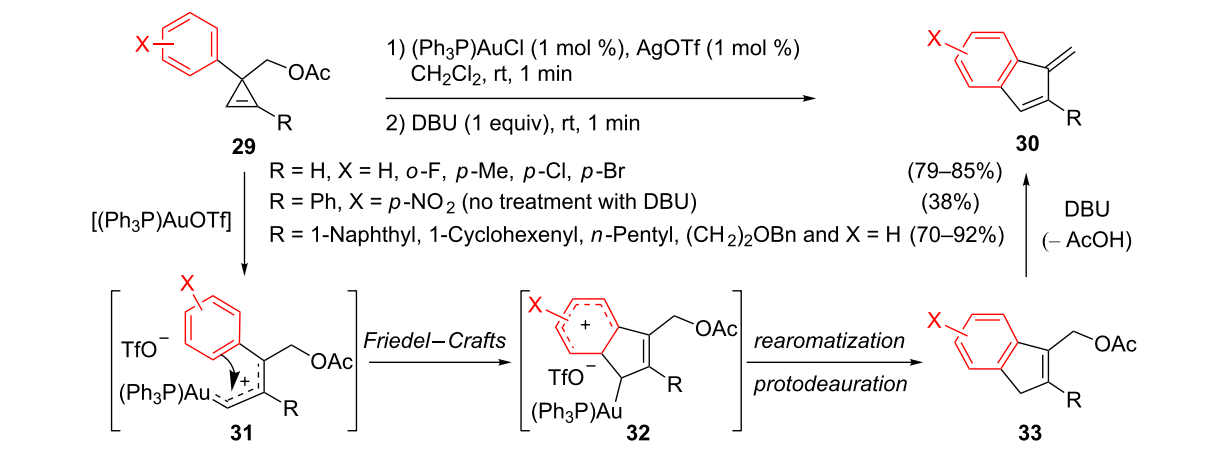
Other gold-catalyzed rearrangements of cyclopropenes that proceed through ring-opening and intramolecular Friedel–Crafts cyclization have been studied using 3-aryl-cyclopropene-3-carboxylates. However, for these latter substrates, the carbonyl group can also play the role of a nucleophile and compete with the aryl group.

Nucleophilic addition of carbonyl groups in competition with Friedel–Crafts reactions

Besides the gold-catalyzed intermolecular addition of alcohols to cyclopropenes, Lee et al. investigated the behaviour of methyl 3-arylcyclopropen-2-yl carboxylates to ascertain whether the organogold species resulting from the ring-opening in the presence of [(Ph_3P)AuOTf] (10 mol %) would be trapped



Scheme 13: Gold-catalyzed rearrangement of cyclopropenes **27** to indenes **28**.

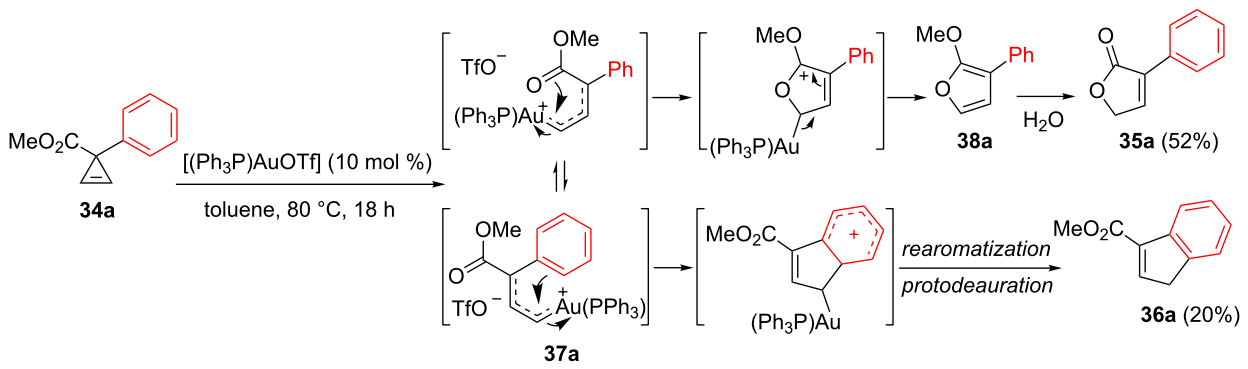


Scheme 14: Gold-catalyzed rearrangement of cyclopropenes **29** to indenes **30**.

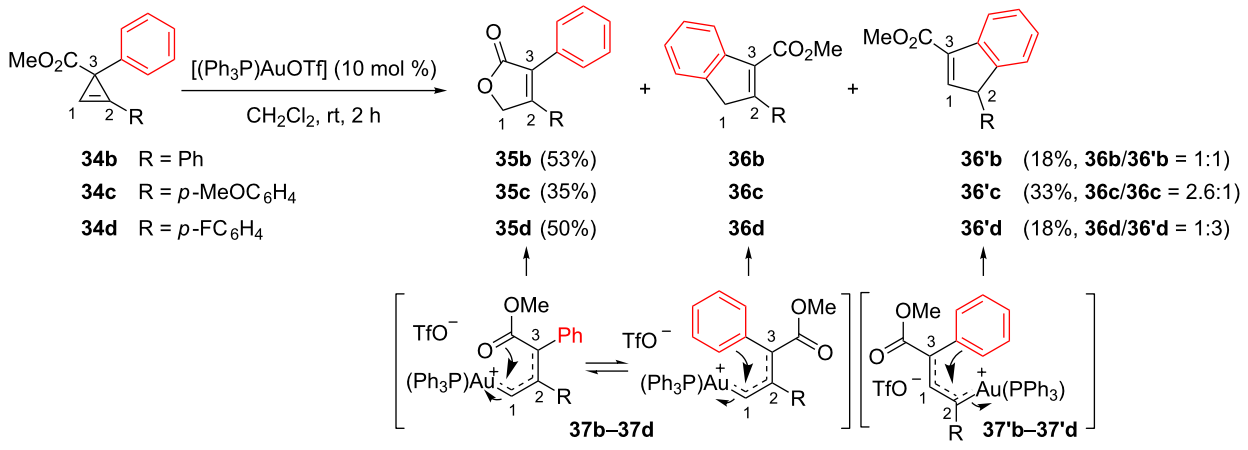
in an intramolecular fashion, either by the oxygen atom of the carbonyl group, or by the phenyl group [18]. For cyclopropene **34a** possessing an unsubstituted endocyclic alkene, heating in toluene (80 °C, 18 h) was required and the reaction afforded two products: Furanone **35a** (52%) and indene **36a** (20%). The former compound arose from intramolecular trapping of the intermediate organogold species **37a** by the carbonyl group of the ester at C3, followed by hydrolysis of the resulting α-methoxyfuran **38a**. A similar result was reported by Wang et al. [21]. Indene **36a** is, as previously mentioned, the product resulting from an intramolecular Friedel–Crafts reaction (Scheme 15).

For unsymmetrical cyclopropenes **34b**–**34d** possessing a trisubstituted endocyclic double bond, the rearrangement took place at rt and invariably led to mixtures of furanones **35b**–**35d**, and mixtures of the inseparable regioisomeric indenes **36b**–**36d** and **36'b**–**36'd**. Electrophilic activation and ring-opening of cyclopropenes **34** favored the formation of the organogold species **37b**–**37d**. Furanones **35b**–**35d** and indenes **36b**–**36d** result from nucleophilic attack on these latter intermediates at C1 by the carbonyl or the phenyl group, respectively. By contrast, the regioisomeric indenes **36'b**–**36'd** would arise from the initial formation of organogold species **37'b**–**37'd** and subsequent Friedel–Crafts cyclization (Scheme 16) [18].

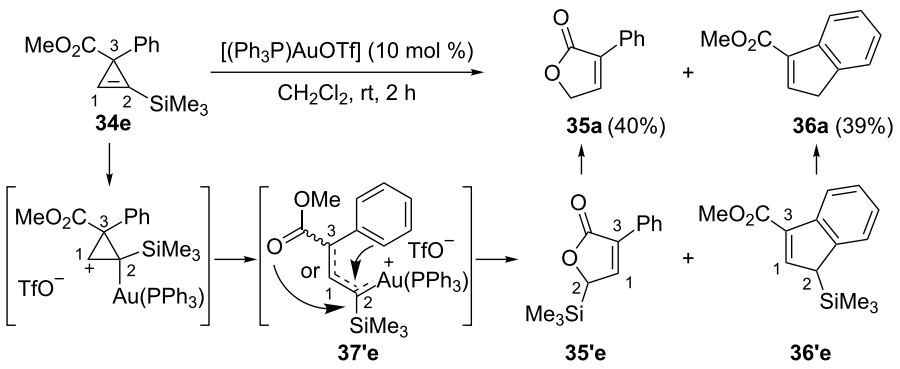
Interestingly, the gold-catalyzed rearrangement of cyclopropenylsilane **34e** provided two compounds: Furanone **35a** (40%) and indene **36a** (39%) both devoid of a trimethylsilyl group. Since protodesilylation took place readily, it is likely that the allylic silanes **35'e** and **36'e** were the initially generated products. Their formation could be explained by regioselective electrophilic activation and ring-opening of the cyclopropenylsilane leading to the organogold **37'e** (formally arising from ring-opening of a cyclopropyl cation at the β-position of the trimethylsilyl group). Subsequent nucleophilic attack by the carbonyl and the phenyl would produce **35'e** and **36'e**, though this was not discussed by the authors (Scheme 17) [18].



Scheme 15: Gold-catalyzed rearrangement of cyclopropenyl ester **34a**.



Scheme 16: Gold-catalyzed reactions of cyclopropenyl esters **34b**–**34d**.



Scheme 17: Gold-catalyzed reactions of cyclopropenylsilane **34e**.

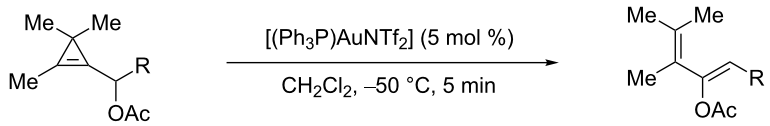
It is worth noting that for substrates bearing two electron-withdrawing groups at C3 (COMe and CO_2Me), no gold-catalyzed rearrangement took place under similar conditions. However, such cyclopropenes have been converted to furans in the presence of CuI or $PdCl_2(MeCN)_2$ as catalysts [34].

Rearrangement of cyclopropenylmethyl acetates

Propargylic carboxylates have proven to be particularly interesting substrates in gold-catalyzed reactions that have led to the development of useful synthetic processes relying on 1,3- or 1,2-acyloxy migration as the key step, depending on the substitution pattern [35,36]. Due to their high strain and π-electron density, cyclopropenes exhibit reactivity often comparable to that of alkynes in transition metal-catalyzed reactions. Not surprisingly, the reactivity of cyclopropenylmethyl carboxylates in the presence of gold catalysts has been investigated as reported in 2010 by Ariafard, Hyland et al. [22]. These authors reported that 2,3,3-trimethyl-cyclopropenylmethyl acetates **39** underwent a gold-catalyzed rearrangement into the corresponding 2-acetoxydienes **40**, and a screening of gold catalysts indicated the superior activity of Gagosz's complex $[(Ph_3P)AuNTf_2]$ in terms of yield and selectivity. Starting from arylcyclopropenylmethyl acetates **39a**–**39e** substituted by a phenyl group or an electron-deficient aromatic ring, a low temperature (CH_2Cl_2, −50 °C) was essential to obtain the 2-acetoxydienes **40a**–**40e** with high *Z*-selectivity (*Z*/*E* = 10:1–41:1). Cyclopropenylmethyl acetate **39f** substituted by the electron-rich *p*-tolyl group effectively underwent rearrangement, but the corresponding diene **40f** decomposed rapidly. A low selectivity (*Z*:*E* = 1.8:1) was observed for the 2-acetoxydiene **40g** resulting from the rearrangement of cyclopropenylmethyl acetate **39g** substituted by an *n*-alkyl group (Scheme 18) [22].

Among the conceivable mechanisms, DFT calculations indicated that the kinetically favored pathway involved an initial regioselective electrophilic activation of the cyclopropene followed by ring-opening to yield the gold-stabilized allylic carbocation **41**. Subsequent 1,2-migration of the acetoxy group proceeded via the formation of five-membered intermediates **42** or **42'**, which then collapsed to the geometric isomers of the corresponding 2-acetoxydiene. For steric reasons, the energy barrier was found to be significantly lower for the pathway leading to the *Z* isomer, with a larger calculated difference when a phenyl group was present (R = Ph, 5.7 kcal·mol^{-1}) compared to an *n*-alkyl substituent (R = Et, 1.6 kcal·mol^{-1}), which correlates well with the experimental results (Scheme 19) [22].

The gold-catalyzed reactions involving cyclopropenes examined so far in this review have involved capture of the organogold intermediates, resulting from electrophilic activation and ring-opening, by an external or an internal nucleo-

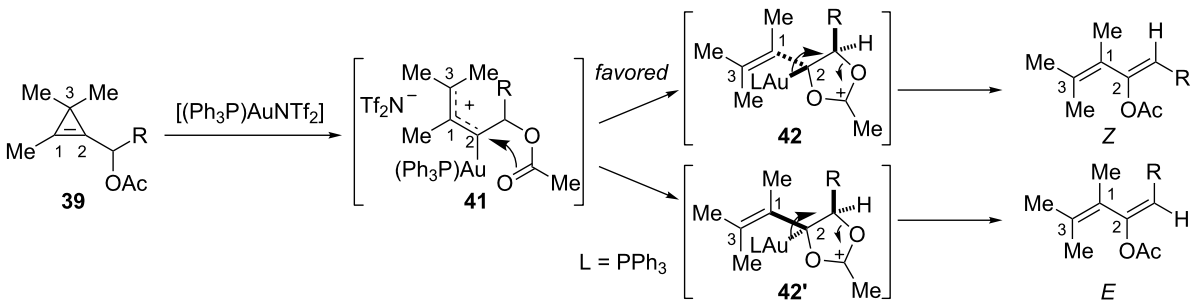


39a–**39e** R = Ph, *o*-ClC_6H_4, *o*-BrC_6H_4, *p*-FC_6H_4, *p*-$NO_2C_6H_4$ **40a**–**40e** (81–99%, *Z*/*E* = 10:1 to 41:1)

39f R = *p*-MeC_6H_4 **40f** product decomposition

39g R = *n*-$C_{11}H_{23}$ **40g** (80%, *Z*/*E* = 1.8:1)

Scheme 18: Gold-catalyzed rearrangement of cyclopropenylmethyl acetates.



Scheme 19: Mechanism of the gold-catalyzed rearrangement of cyclopropenes **39**.

phile. Cyclopropanation of olefins, a reaction classically attributed to the carbene-like reactivity, will now be examined.

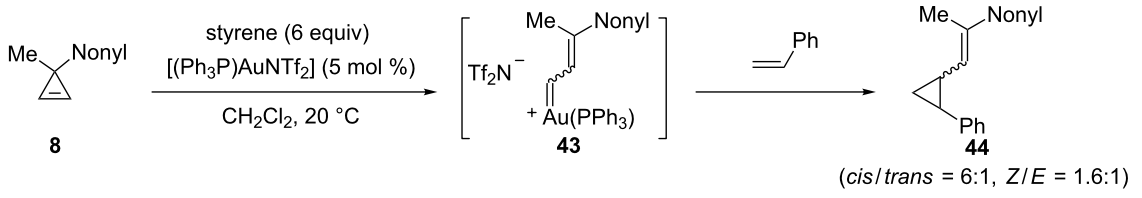
Cyclopropanation of olefins with gold carbenes generated from cyclopropenes

Intermolecular cyclopropanation of olefins

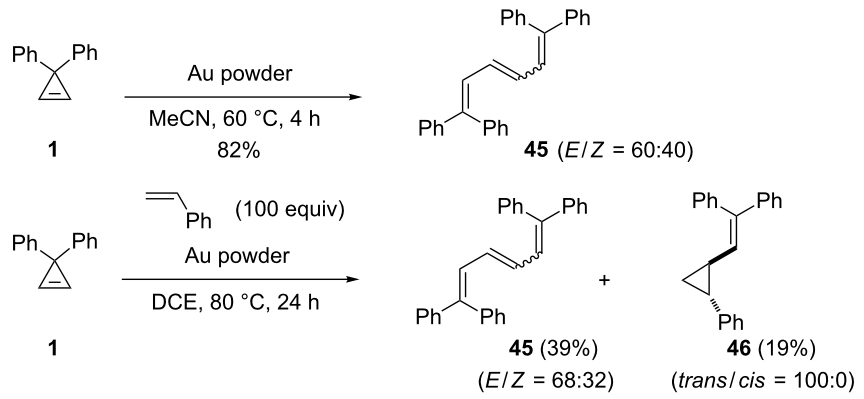
In 2008, Lee et al. disclosed several representative gold-catalyzed reactions with cyclopropenes and reported one example of cyclopropanation achieved via the gold-carbene intermediate. Thus, when 3-methyl-3-nonylcyclopropene (**8**) was treated with a catalytic amount of $[(Ph_3P)AuNTf_2]$ in the presence of excess styrene, the alkenyl cyclopropane **44**, resulting from intermolecular cyclopropanation triggered by the gold carbene **43**, was isolated in 72% yield as a 6:1 mixture of *cis*/*trans* diastereomers and a 1.6:1 mixture of *Z*/*E*-geometric isomers (Scheme 20) [18].

Angelici, Woo, et al. reported several catalytic reactions of carbene precursors on bulk gold metal powder consisting of particles (5–50 μm size) prepared by reduction of $HAuCl_4$ with hydroquinone [23]. Upon treatment with this gold powder (MeCN, 60 °C), 3,3-diphenylcyclopropene (**1**) gave 1,1,6,6-tetraphenylhexa-1,3,5-triene (**45**), arising from self-coupling of a surface bound gold carbene, as a 40:60 mixture of *Z*/*E*-geometric isomers (82%). Cross-couplings of carbenes derived from cyclopropene **1** and phenyldiazomethane or ethyl diazoacetate on bulk gold powder were also studied, but mixtures of self- and cross-coupling products were invariably obtained with negligible selectivity. Interestingly, the authors investigated the intermolecular cyclopropanation of styrene by the surface bound gold carbene generated from cyclopropene **1**. Though a large excess of styrene (100 equiv) was used, triene **45** resulting from the self-coupling of **1** still predominated, and the cyclopropanation product **46** was isolated in low yield (19%) as a single *trans* diastereomer (Scheme 21) [23].

In their investigations on the bonding model for gold(I) carbenoid complexes, Toste et al. highlighted the importance of the substitution pattern and the ligands (Scheme 4). Interestingly, DFT calculations were carried out for organogold species that can actually be generated by ring-opening of cyclopropenes, and therefore the authors examined experimentally the impact of cationic versus carbene-like species on the reactivity in olefin cyclopropanation [17]. In the presence of an olefin and a cationic gold(I) catalyst, cyclopropenone acetal **3** did not provide any cyclopropanation product, which is in agreement with the fact that the organogold species generated by ring-opening of **3** should instead react as a gold-stabilized carbocation due to the presence of oxygen atoms that can stabilize the cationic intermediate. However, it is worth pointing out that Boger and Brotherton previously reported that cyclopropenone acetals could cyclopropanate electron-deficient olefins, via charged intermediates, under simple thermal conditions [37]. In contrast to the behaviour of cyclopropenone acetal **3**, Toste et al. observed that the reaction of the 3,3-disubstituted cyclopropene **47** and (*Z*)-stilbene in the presence of a cationic



Scheme 20: Gold-catalyzed cyclopropanation of styrene with cyclopropene **8**.



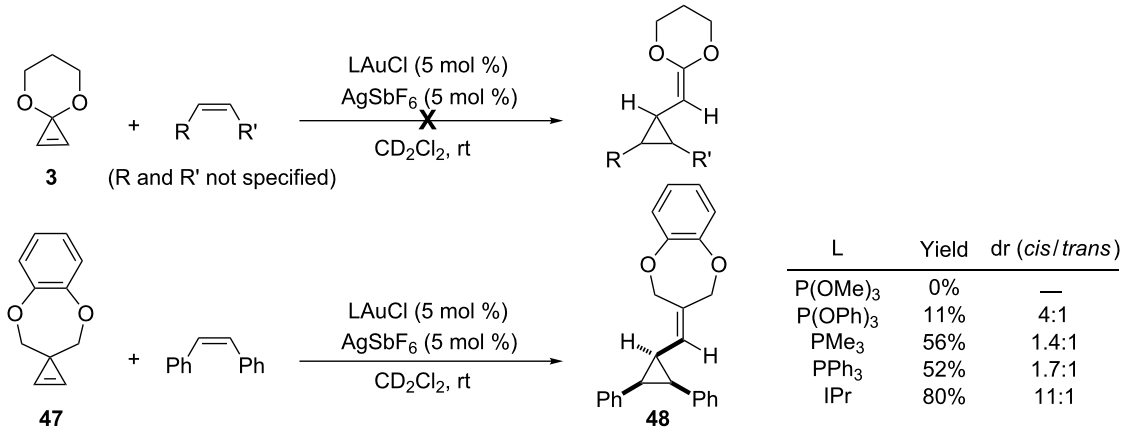
Scheme 21: Representative reactions of carbene precursors on gold metal.

gold catalyst could effectively provide the desired cyclopropanation product **48**, but the yield and the diastereoselectivity were highly dependent on the gold ligand. As anticipated from the structural studies, π-acidic phosphites that increase cation-like reactivity gave little or none of the cyclopropanation product **48**. Phosphines gave moderate results, whereas the highest yield and diastereoselectivity was obtained when the strong σ donor and weak π acceptor N-heterocyclic carbene IPr was the ligand. The latter was indeed anticipated to give an organogold with a higher carbene-like reactivity which favors olefin cyclopropanation. AuCl was unreactive under these conditions (Scheme 22) [17].

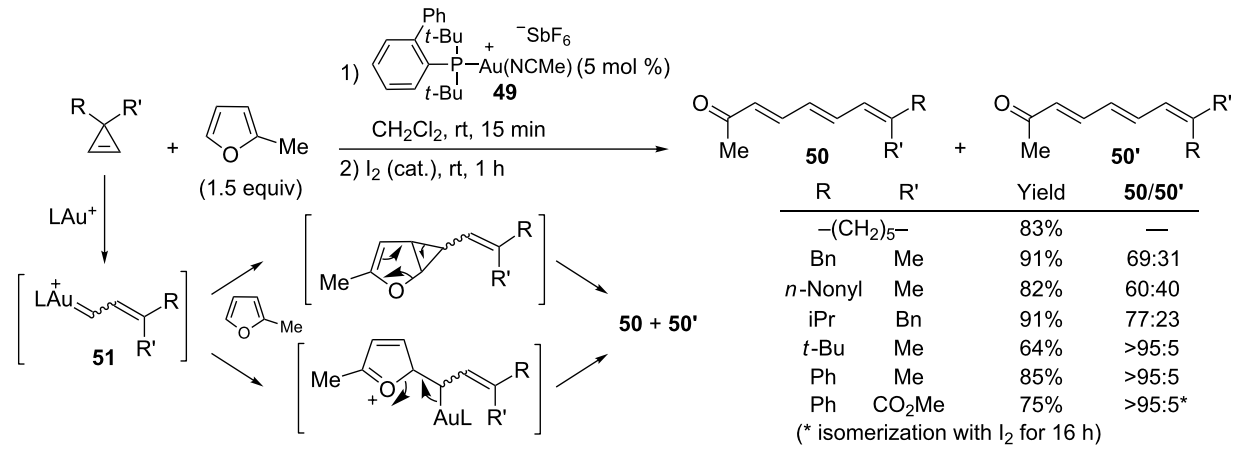
Intermolecular cyclopropanation of furans: Synthesis of conjugated trienes

In 2011, Lee and Hadfield reported the synthesis of conjugated trienes by gold-catalyzed intermolecular reaction of cyclopropenes with furans [24]. Several catalysts such as $[(Ph_3P)AuNTf_2]$, or IPrAuCl in combination with different silver salts could be used successfully, but the highest yields were obtained with the cationic gold catalyst **49**. In the presence of 2-methylfuran, a variety of 3,3-disubstituted cyclopropenes led to trienes **50**/**50'**, and the initially generated mixture of geometric isomers was isomerized by treatment with a catalytic amount of iodine. Trienes **50**/**50'** were isolated in good yields and with satisfactory levels of stereoselectivity when the steric bulk of the two substituents (R and R') were significantly different or if a phenyl group was present. Although no cyclopropane derivative was obtained from this reaction, this transformation has been included in this section because one of the possible mechanisms involves an initial cyclopropanation of the less hindered olefin in 2-methylfuran by the organogold intermediate **51**, followed by ring-opening. The alternative mechanism involves nucleophilic attack of 2-methylfuran on the gold carbene **51**, followed by elimination (Scheme 23) [24].

The reaction was more difficult to carry out with cyclopropene carboxylates **52** and **53** possessing tetrasubstituted alkene structures. The former substrate required harsher conditions (DCE, 80 °C), but the corresponding tetrasubstituted triene **54** was still



Scheme 22: Intermolecular olefin cyclopropanation with gold carbenes generated from cyclopropenes.

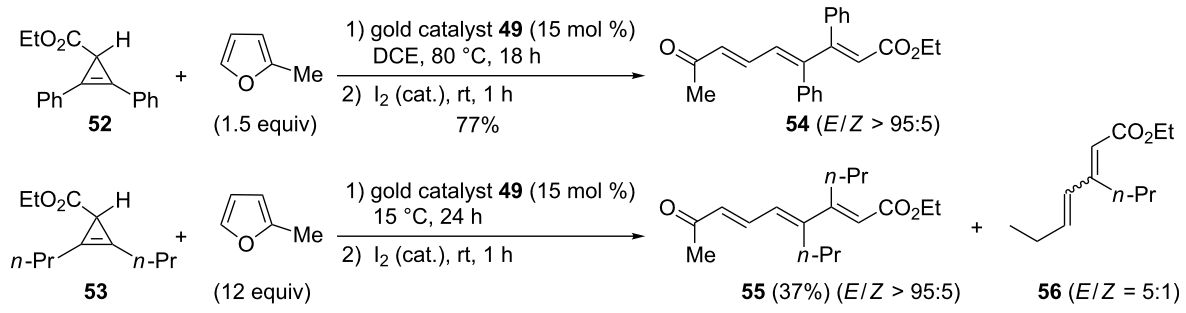


Scheme 23: Gold-catalyzed formation of trienes from cyclopropenes and furans.

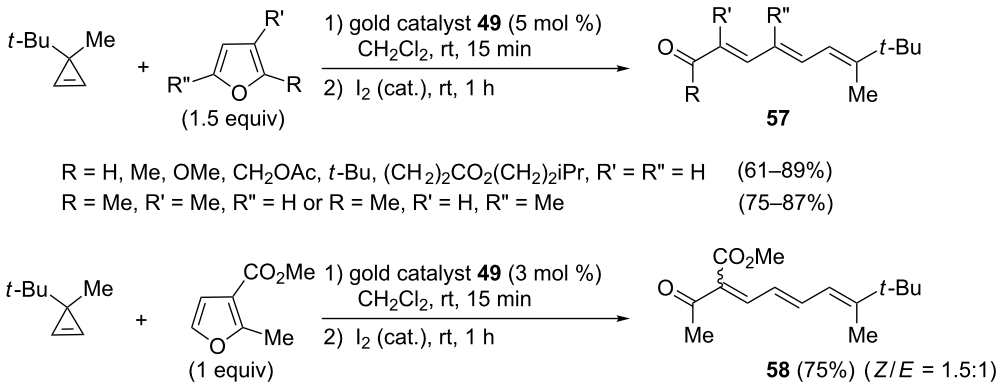
obtained in good yield (77%). For the latter substrate, the reaction was conducted in an excess of 2-methylfuran and triene **55** was isolated in low yield (37%), accompanied by dienoate **56** as a by-product (Scheme 24) [24].

Other mono- or disubstituted furans can be successfully used as partners, as illustrated by the gold-catalyzed reactions involving 3-*tert*-butyl-3-methylcyclopropene as substrate that led to the corresponding tetra- or pentasubstituted trienes of type **57** or triene **58** bearing two geminal electron-deficient groups (Scheme 25) [24].

Besides these examples of intermolecular cyclopropanations, examples of intramolecular cyclopropanation of olefins by gold carbenes generated from cyclopropenes have been investigated in our group.



Scheme 24: Gold-catalyzed formation of trienes from cyclopropenes and furans.



Scheme 25: Gold-catalyzed formation of trienes from cyclopropenes and furans.

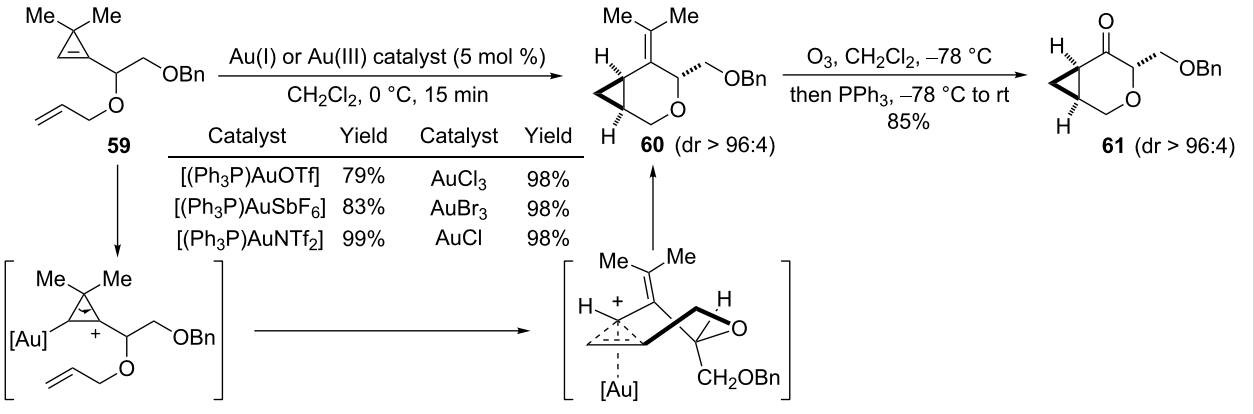
Intramolecular cyclopropanation: cycloisomerization of cyclopropene-enes

In 1981, Padwa et al. reported that 1,2-diphenylcyclopropenes, substituted by allyl, methallyl, crotyl groups at C3, rearranged to the corresponding 1,2-diphenylbicyclo[3.1.0]hex-2-enes upon treatment with nearly stoichiometric quantities of $AgClO_4$ and prolonged heating in C_6H_6 or MeOH at reflux [33,38]. These reactions appear to constitute the first examples of intramolecular olefin cyclopropanation promoted by a silver carbenoid generated by ring-opening of a cyclopropene.

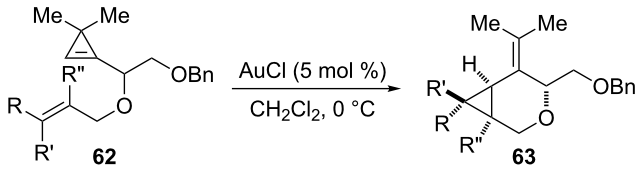
We envisioned that the gold carbene resulting from the ring-opening of appropriately substituted cyclopropenes could also be involved in intramolecular olefin cyclopropanation in order to access [n.1.0] bicyclic ring systems. Rather than examining the behaviour of cyclopropenes bearing an allylic chain at C3, and in order to avoid aryl-substituted cyclopropenes that have routinely been used as substrates, allylic ethers derived from cyclopropenyl carbinols were selected as substrates. Cyclopropenyl carbinols have recently emerged as synthetically useful building blocks [39] and are readily available by the condensation of an in situ generated cyclopropenyl organolithium with an aldehyde [39,40]. Additionally, they can be obtained in an enantiomerically enriched form by Sharpless kinetic resolution [41]. In order to ensure regioselective ring-opening of the cyclopropene ring, cyclopropenyl carbinols possessing a trisubstituted endocyclic alkene were considered with the hope that a secondary cyclopropyl cation would be preferentially formed upon coordination of a gold complex. However, this implies that substituents have to be present at C3 in order to handle stable substrates. Thus, allyl 3,3-dimethylcyclopropenylcarbinyl ether **59** was prepared and several gold(I) and gold(III) species {$AuCl_3$, $AuBr_3$, AuCl, [$(Ph_3P)AuNTf_2$], [$(Ph_3P)AuSbF_6$] or [$(Ph_3P)AuOTf$]} were found to catalyze smoothly the cycloisomerization and yield the desired oxabicyclic compound **60** in high yields and with excellent diastereoselectivity (dr > 96:4) [25]. The observed stereochemical outcome has been tentatively rationalized by considering a twist-boat transition state model in which the gold center and the allylic benzyloxymethyl substituents both occupy axial positions in order to avoid 1,3-allylic strain with the vinylic methyl groups. The isopropylidene group in compound **60** can be cleaved by ozonolysis to give the corresponding 3-oxabicyclo[4.1.0]heptanone **61** (85%), and hence, the 3,3-dimethylcyclopropene moiety appears to be an excellent surrogate of an α-diazoketone (Scheme 26) [25,42].

Further studies were carried out using AuCl as a catalyst and the reaction was generalized for a variety of substituted allylic ethers **62a**–**62f**. Excellent results were obtained with allylic ethers bearing one (**62a**, **62b**) or two substituents (**62c**–**62e**) at the terminal position of the olefin and the corresponding oxabicyclic compounds were isolated in high yields (93–99%). The stereospecificity of the cyclopropanation process was highlighted by the behaviour of geranyl ether **62d** and neryl ether **62e**, which furnished the epimeric cycloisomerization products **63d** and **63e**, respectively. The stereoselectivity was lower for methallyl ether **62f** which afforded compound **63f** as an 87:13 mixture of diastereomers (Scheme 27) [25].

The influence of the substituent at the α-position of the oxygen atom and the cyclopropene has also been examined. Diastereoselectivities and yields were always high when this substituent was branched, whatever the relative configuration of the additional stereocenter, as shown with substrates **64a**–**64e** and **66** which led to the oxabicyclic products **65a**–**65e** and **67**, respectively. The substituent could also be a longer linear *n*-alkyl chain functionalized at the remote position by a benzyl ether, as illustrated for the cycloisomerization of **68** to **69**. Interestingly, the azabicyclic compound **71** was obtained in excellent yield (99%)



Scheme 26: Gold-catalyzed cycloisomerization of cyclopropene-ene **59**.



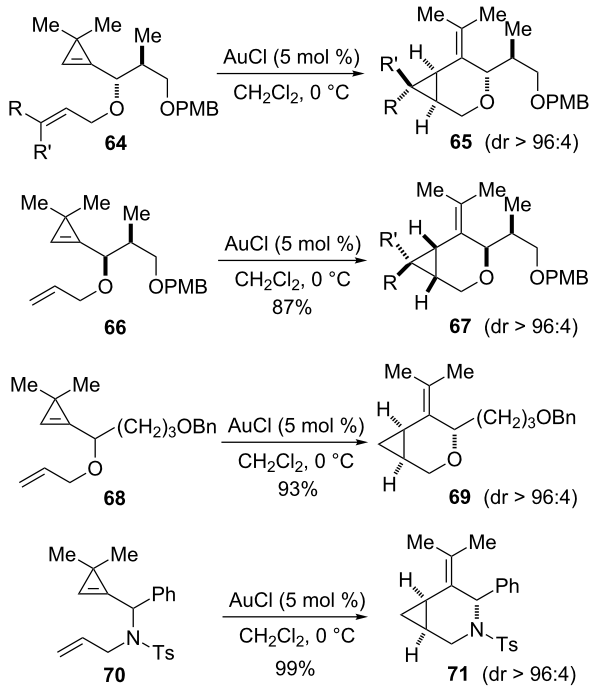
Substrate	R	R'	R"	Product	dr	Yield
62a	Ph	H	H	**63a**	>96:4	98%
62b	$CH_2OTBDPS$	H	H	**63b**	>96:4	93%
62c	Me	Me	H	**63c**	>96:4	97%
62d	$(CH_2)_2CH=CMe_2$	Me	H	**63d**	>96:4	97%
62e	Me	$(CH_2)_2CH=CMe_2$	H	**63e**	>96:4	99%
62f	H	H	Me	**63f**	87:13	72%*

(* isolated yield of the major diastereomer)

Scheme 27: Gold-catalyzed cycloisomerization of substituted allyl cyclopropenyl carbinyl ethers **62a**–**62f**.

and with high diastereoselectivity (dr > 96:4) by gold-catalyzed cycloisomerization of the *N*-allyl sulfonamide **70** (Scheme 28) [25].

	Product	Yield
65a	R = R '= H	93%
65b	R = R' = Me	90%
65c	R = Ph, R' = H	84%
65d	R = $(CH_2)_2CH=CMe_2$, R' = H	98%
65e	R = H, R' = $(CH_2)_2CH=CMe_2$	97%

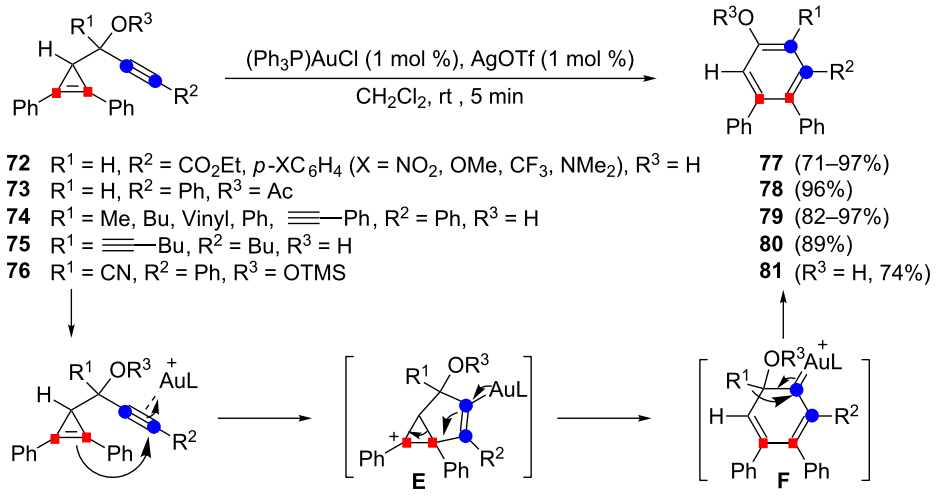


Scheme 28: Gold-catalyzed cycloisomerization of cyclopropene-enes.

The success of the gold-catalyzed cycloisomerization of cyclopropene-enes, proceeding with intramolecular cyclopropanation of the olefin, lies in the chemoselective activation of the cyclopropene, in preference to the alkene, which allows the generation of a gold carbene intermediate. The relative reactivity of cyclopropenes compared to alkynes is an interesting issue that has been addressed by Wang et al. during their studies on the gold-catalyzed cycloisomerization of cyclopropene-ynes [26].

Cycloisomerization of cyclopropene-ynes

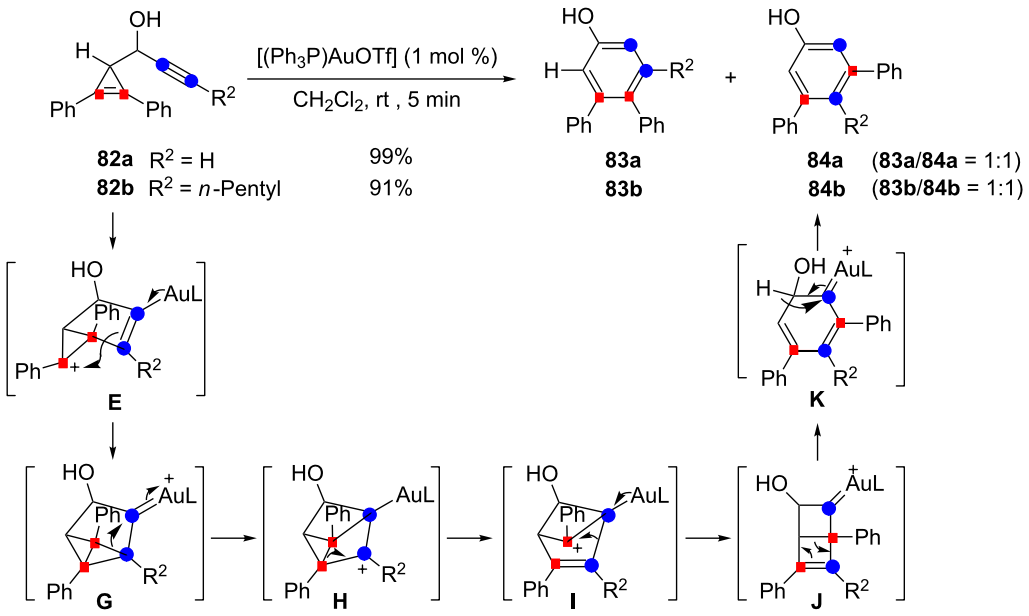
Upon treatment with [(Ph_3P)AuOTf] (5 mol %), several propargylic alcohols possessing a 2,3-diphenylcycloprop-2-enyl substituent were smoothly converted (CH_2Cl_2, rt, 5 min) to substituted 4,5-diphenylphenols. The scope of the reaction is quite broad since it could be applied to secondary propargylic alcohols **72** (or an acetate derivative **73**), to tertiary alcohols such as **74** or **75** and even to the *O*-trimethylsilyl cyanohydrin **76**. The corresponding cycloisomerization products **77**–**81** were isolated in good to excellent yields (71–97%). The hydroxyl group did not exert a particular role in this process since 1,2-diphenyl-3-propargylcyclopropene was rearranged to 1,2-diphenylbenzene (97%) under the same conditions [26]. The formation of phenols (and their derivatives) **77**–**81** could be explained by an initial chemoselective activation of the alkyne by the gold catalyst with subsequent intramolecular nucleophlic attack of the cyclopropene olefin. Ring-opening of the cyclopropyl cation **E** to generate the 1,3-cyclohexadiene **F** and a 1,2-shift of the R^1 group would then lead to the substituted 4,5-diphenylphenol. In this mechanistic pathway, the cyclopropene carbon atoms become directly linked to those of the alkyne with no skeletal rearrangement (Scheme 29) [26].



Scheme 29: Gold-catalyzed cycloisomerization of cyclopropene-ynes.

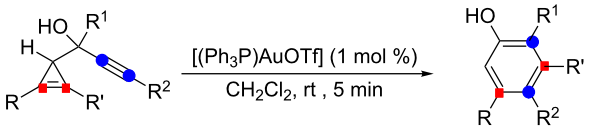
However, the substituents were found to exert an important influence on the outcome of the reaction. Indeed, the secondary propargylic alcohols **82a** and **82b**, in which the alkyne is terminal or substituted by an *n*-pentyl group, afforded an equimolar mixture of two regioisomeric phenols (91–99%). Whereas 4,5-diphenylphenols **83a** and **83b** correspond to the previously observed rearrangement pathway, the structure of the symmetrical phenols **84a** and **84b** indicates that cleavage of both the cyclopropene double bond and the alkyne had occurred. To explain the formation of the latter double cleavage products, Wang et al. proposed a mechanistic scenario in which back donation from gold in the initially formed vinyl gold species **E** led to the highly strained gold carbene **G** possessing a tricyclo[3.1.0.0^{2,6}]hexane structure. Rearrangement of **G** by consecutive 1,2-alkyl shifts, proceeding through carbocations **H** and **I** and Dewar-type benzene **J** as intermediates, followed by ring-opening and a 1,2-hydrogen shift, ultimately led to **84a** or **84b** (Scheme 30) [26].

Since intermediates **G**–**J** are all sterically crowded, this double cleavage mechanistic pathway should be favored for cyclopropenes bearing smaller substituents. In fact, for cyclo-



Scheme 30: Formation of products arising from a double cleavage process in the gold-catalyzed cycloisomerization of cyclopropene-ynes.

propenes **85a**–**85c** having two *n*-butyl substituents or cyclopropenes **86a**–**86d** with one *n*-butyl and one trimethylsilyl group (the latter ensuring regioselective attack of the cyclopropene onto the activated alkyne to form a β-silylcyclopropyl cation), the gold-catalyzed rearrangement led exclusively to the phenols **87a**–**87c** and **88a**–**88d** (84–93%), respectively, resulting from a double cleavage process, whatever the substituent on the alkyne (Scheme 31) [26].



Substrate	R	R'	R^1	R^2	Product	Yield
85a	*n*-Bu	*n*-Bu	H	H	**87a**	87%
85b	*n*-Bu	*n*-Bu	H	Ph	**87b**	90%
85c	*n*-Bu	*n*-Bu	H	CO_2Et	**87c**	87%
86a	*n*-Bu	$SiMe_3$	H	H	**88a**	84%
86b	*n*-Bu	$SiMe_3$	H	Ph	**88b**	93%
86c	*n*-Bu	$SiMe_3$	H	CO_2Et	**88c**	86%
86d	*n*-Bu	$SiMe_3$	Me	Ph	**88d**	89%

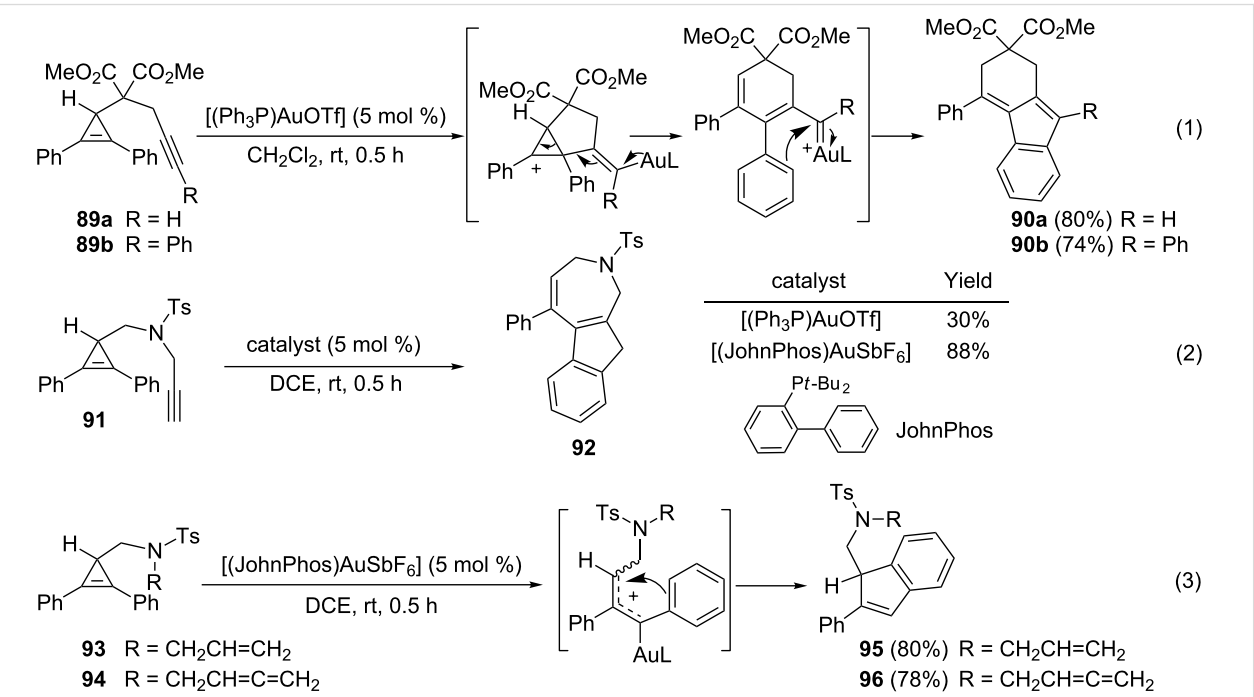
Scheme 31: Gold-catalyzed cycloisomerization of cyclopropene-ynes involving a double cleavage process.

Wang et al. also examined the behaviour of other cyclopropen-1,n-ynes. For substrates **89a** and **89b** possessing a 1,6-enyne moiety, the gold-catalyzed cycloisomerization led to the tricyclic hydrocarbons **90a** (80%) and **90b** (74%), respectively. The alkyne, chemoselectively activated by the gold complex, underwent nucleophilic attack by the cyclopropene in a 5-*exo*-dig manner followed by ring-opening. A subsequent Friedel–Crafts cyclization allowed the formation of the indene subunit (Equation 1, Scheme 32). Sulfonamide **91** contains a 1,7-enyne subunit and its gold-catalyzed cycloisomerization delivered tricyclic compound **92** incorporating a seven-membered nitrogen heterocycle. The yield of this transformation was found to be greatly improved when in situ generated [(JohnPhos)$AuSbF_6$] was used as the catalyst (88%) instead of [(Ph_3P)AuOTf] (30%) (Equation 2, Scheme 32). When the alkyne was replaced by an alkene or an allene, the corresponding substrates **93** and **94** underwent a gold-catalyzed rearrangement to afford indenes **95** (80%) and **96** (78%), respectively. Interestingly, only the cyclopropene reacted by ring-opening followed by Friedel–Crafts cyclization: The alkene and the allene units were unaffected (Equation 3, Scheme 32) [26].

Thus, alkynes appear to be chemoselectively activated in the presence of gold complexes in preference to cyclopropenes, whereas the latter moiety is more reactive than alkenes and possibly allenes, although in the latter case only a single example of competition was reported.

Conclusion

Though relatively recent, the entry of cyclopropenes into the area of gold catalysis has already led to interesting contribu-



Scheme 32: Gold-catalyzed reaction of cyclopropene-ynes, cyclopropene-enes and cyclopropene-allenes.

tions exploiting different aspects of the reactivity of alkenyl organogold carbenoids. It is obvious that the possibility to generate gold carbenes from cyclopropenes opens new possibilities and further synthetic developments in this field will certainly be reported.

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Beilstein Journal of Organic Chemistry

A racemic formal total synthesis of clavukerin A using gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes as the key strategy

Jae Youp Cheong and Young Ho Rhee*

Letter

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Address:
Department of Chemistry, POSTECH (Pohang University of Science and Technology), Hyoja-dong san 31, Nam-gu, Pohang, Kyungbook, Republic of Korea 790-784

Email:
Young Ho Rhee* - yhrhee@postech.ac.kr

* Corresponding author

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Abstract

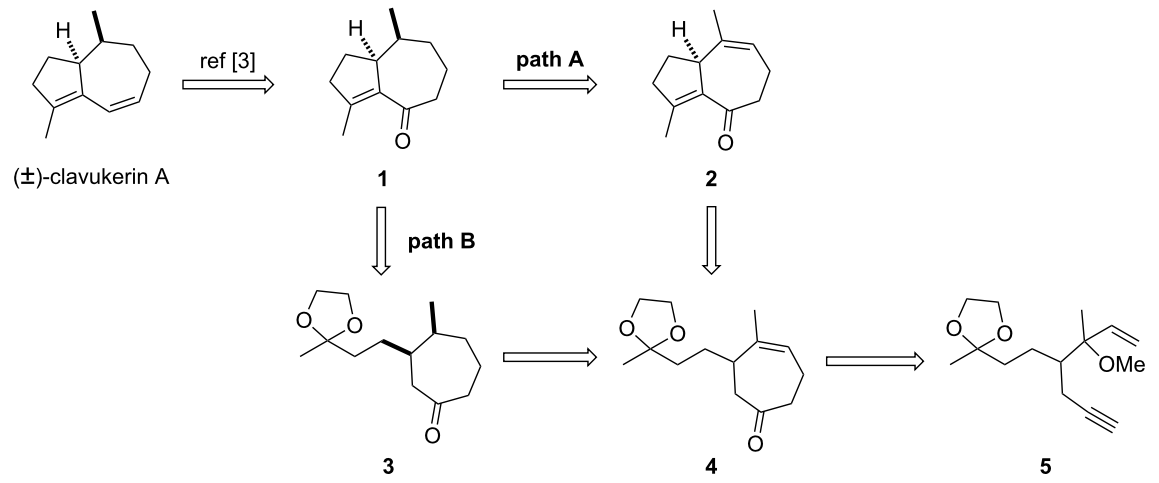
An efficient formal total synthesis of (±)-clavukerin A was accomplished via a gold-catalyzed cycloisomerization of a 3-methoxy-1,6-enyne **5** as the key strategy followed by Rh-catalyzed stereoselective hydrogenation of the cycloheptenone **4**.

Findings

Clavukerin A is a member of marine trinorguaiane sesquiterpene natural products. It was first isolated in 1983, by the group of Kitawara, from the Okinawa soft coral *Clavularia koellikeri*. The structure of clavukerin A was established by CD spectra and X-ray diffraction [1]. The first total synthesis of clavukerin A was reported by Asaoka in 1991, which was followed by several other racemic and enantioselective syntheses [2-14]. Herein, we report a short formal total synthesis of racemic clavukerin A employing the gold(I)-catalyzed cycloisomerization of a 3-methoxy-1,6-enyne as the key strategy, which was recently developed by us [15]. This reaction provides cycloheptane frameworks in a unique manner and illustrates the utility of the gold-catalyzed reactions [16-23].

From a retrosynthetic point of view, we envisioned two different approaches to the key enone intermediate **1** [3] to clavukerin A, starting from the cycloheptenone **4** (Scheme 1). In the first approach, enone **1** could be prepared by the sequential cyclization and the chemo- and stereoselective hydrogenation from cycloheptenone **4** (path A). Alternatively, enone **1** could be accessed by the hydrogenation of **4** and the subsequent cyclization (path B). The cycloheptenone **4** could then be synthesized from the enyne substrate **5** by gold(I)-catalyzed cycloisomerization.

The synthesis of enyne substrate **5** commenced with the alkylation of methyl acetoacetate with the known bromide **6** [24] to

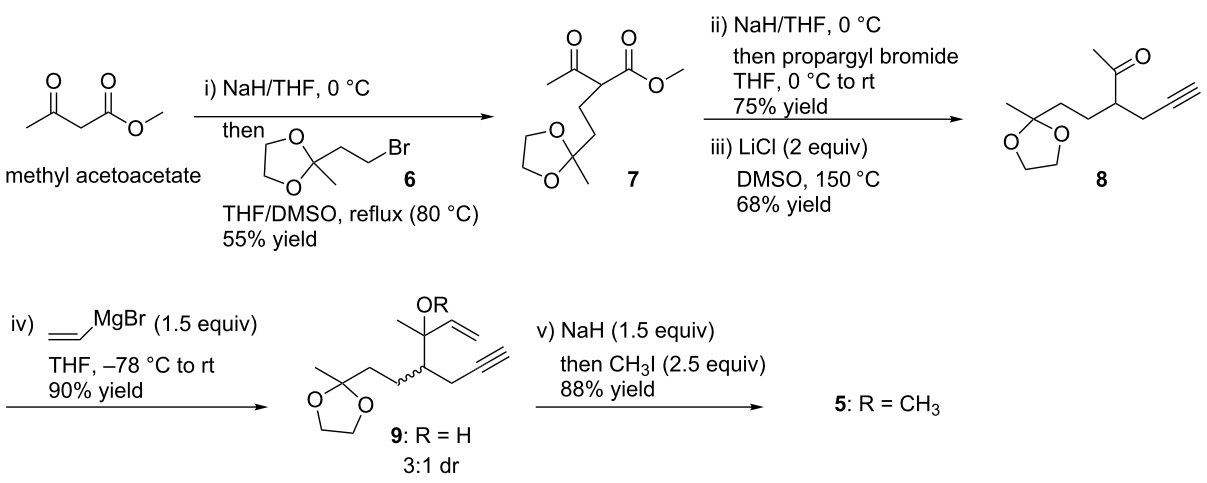


Scheme 1: Retrosynthetic analysis.

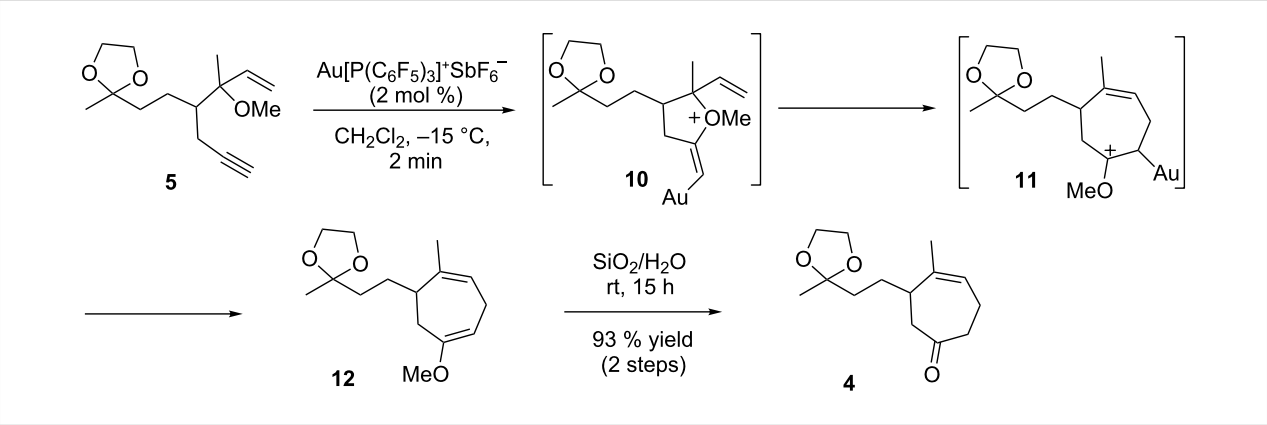
provide compound **7** in 55% yield (Scheme 2). Propargylation of **7** followed by the decarbomethoxylation with LiCl [25] gave the ketone **8** in 51% yield (over two steps). Addition of the vinyl group to this ketone gave the alkynol **9** in 90% yield as an inseparable 3:1 mixture of diastereomers. The diastereomeric ratio was determined by integration of the ^{1}H NMR spectrum of the crude reaction product. Subsequent methylation gave the 1,6-enyne **5** in 88% yield.

We then investigated the gold-catalyzed cycloisomerization of enyne **5** using the optimized conditions from our previous study [15]. The use of the pre-generated complex $Au[P(C_6F_5)_3]^+SbF_6^-$ (2 mol %) provided the relatively unstable enol ether **12**, which was then immediately treated with aqueous silica gel to give the ketone **4** in 93% yield over two steps. Formation of **12** was unambiguously confirmed by the analysis of ^{1}H NMR data of the crude reaction mixture. From a mechanistic viewpoint, the reaction presumably proceeds via the initial heterocyclization intermediate **10** and the subsequently rearranged intermediate **11** (Scheme 3). Notably, when the gold(I)-catalyzed reaction was carried out on a multi-mmol scale, there was no decrease in the yield at the same catalyst loading.

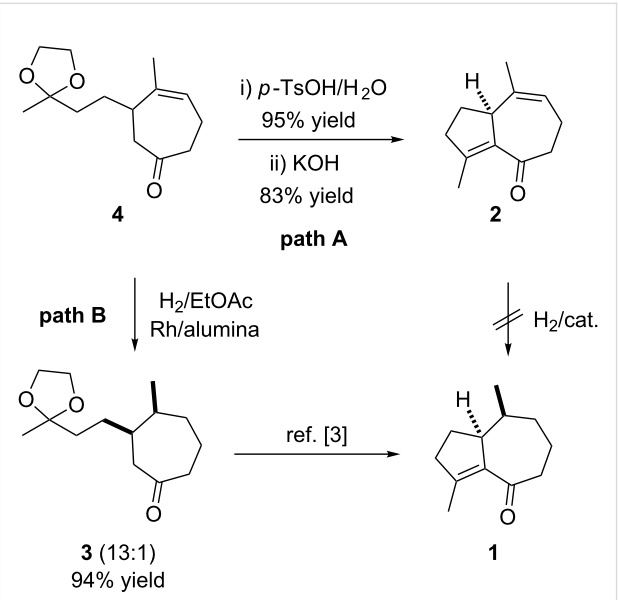
With ketone **4** in hand, the final stage in the formal synthesis of clavukerin A was explored. We first investigated the cyclization–hydrogenation strategy (path A in Scheme 4). Deprotection of **4** and the aldol condensation of the resulting diketone under basic conditions proceeded smoothly to give the enone **2** in good yield. However, extensive attempts at the chemoselective hydrogenation of the trisubstituted olefin **2** gave only compound **1** with poor selectivity. For example, various metal (Pd



Scheme 2: Preparation of compound **5**.



Scheme 3: Synthesis of the cycloheptenone **4**.



Scheme 4: Completion of the formal synthesis of clavukerin A.

or Rh)-catalyzed hydrogenations resulted in a mixture of **1** and **3**. This problem was also noted in another work on the synthesis of clavukerin A [13].

Thus, we decided to investigate the alternative strategy that involved sequential hydrogenation–cyclization of **4**. Initial efforts using various Pd catalysts or Wilkinson catalyst again showed poor stereoselectivity for the hydrogenation. However, with a Rh/alumina catalyst the selectivity was significantly improved and afforded the *cis*-ketone **3** in 94% yield with ~13:1 selectivity. The structure of **3** was unambiguously confirmed by comparison of the ^{1}H and ^{13}C data with those in the literature [3]. Because the ketone **3** was previously transformed into the enone **1** [3], synthesis of **3** represents the completion of the formal synthesis of clavukerin A.

In summary, a formal synthesis of racemic clavukerin A was accomplished via the gold(I)-catalyzed cycloisomerization of a 3-methoxy-1,6-enyne as the key strategy and stereoselective Rh-catalyzed hydrogenation. Notably, the gold(I)-catalyzed reaction was compatible with the acid-sensitive functional group. Further application of the gold(I)-catalyzed cycloisomerization reaction of 3-methoxy-1,6-enynes to the enantioselective synthesis of more structurally complex cycloheptane natural products is in progress, and will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental section for the preparation of compounds **2**–**12**, and ^{1}H and ^{13}C NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-84-S1.pdf]

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Synthetic applications of gold-catalyzed ring expansions

David Garayalde and Cristina Nevado*

Review

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Address:
Organic Chemistry Institute, University of Zürich, Winterthurerstr. 190, CH-8057, Zürich, Switzerland

Email:
David Garayalde - dgh@oci.uzh.ch; Cristina Nevado* - nevado@oci.uzh.ch

* Corresponding author

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Abstract

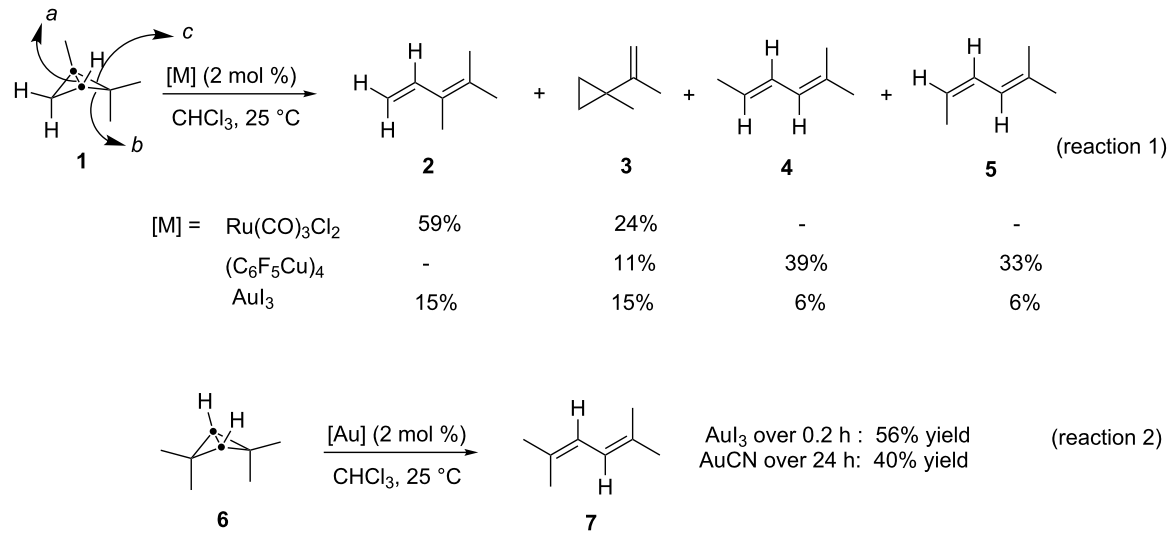
The development of new methodologies catalyzed by late transition metals involving cycloisomerizations of strained rings can open new venues for the synthesis of structurally complex molecules with interesting biological activities. Herein we summarize, from both a synthetic as well as a mechanistic point of view, the most recent developments in gold-catalyzed ring expansions.

Introduction

Over the past twenty years, the image of gold has evolved, from being considered a dead-entity in terms of chemical reactivity, to playing a key role in catalytic processes. The vast array of gold-mediated transformations reported so far share a common feature: The ability of gold(I) and gold(III) species to activate unsaturated moieties due to the strong relativistic effects governing its coordination behavior [1-6]. However, beyond its Lewis acidity properties towards alkynes, allenes or alkenes, gold has also proved to be extremely powerful in triggering ring-expansion processes to introduce structural complexity into organic molecules. The gold-catalyzed ring expansion of strained rings is viewed nowadays as a flexible synthetic tool in organic synthesis [7-9].

In this review, we aim to summarize the most recent developments in gold-catalyzed ring expansions, from both a synthetic and a mechanistic point of view. A deeper understanding of the processes governing gold-chemistry allows organic chemists to become more creative in designing novel processes, which might provide access to architectures that were so far inaccessible.

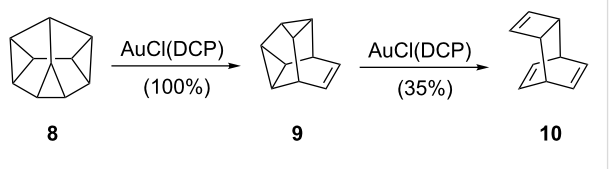
After the first examples on the perchlorination of naphthalene with $AuCl_3$ or AuCl by Schwemberger and Gordon in 1935 [10], almost forty years passed without a single report on the catalytic ability of gold salts, due to its presumed lack of reactivity. In 1972, Paul G. Gassman reported several



Scheme 1: Transition metal promoted rearrangements of bicyclo[1.1.0]butanes.

studies on transition metal promoted rearrangements of bicyclo[1.1.0]butanes [11]. Thus Ru–carbonyl complexes promote the rearrangement of 1,2,2-trimethylbicyclo[1.1.0]butane (**1**) to yield diene **2** and the cyclopropyl derivative **3** (Scheme 1, reaction 1: a,b for **2** and **3**), whilst pentafluorophenylcopper tetramer affords predominately dienes **4** and **5** (Scheme 1, reaction 1: c for **4** and **5**). By contrast, gold salts show almost no preference for the activated C–C sigma bond in the substrate. However, in the case of 2,2,4,4-tetramethylbicyclo[1.1.0]butane (**6**), the reaction was completely selective and gave 2,5-dimethyl-2,4-hexadiene (**7**) in moderate yields when either AuI_3 or AuCN were used as catalysts (Scheme 1, reaction 2).

Only four years later, de Meijere reported a gold-catalyzed rearrangement of strained small ring hydrocarbons [12]. Although heterogeneous catalysis seemed to be operating in this case, homogeneous complexes such as AuCl(DCP) (DCP = dicyclopentadiene) were able to trigger the quantitative rearrangement of diademane (**8**) to snoutene (**9**) and, at least partially, the rearrangement of the latter into basketene (**10**) (Scheme 2).



Scheme 2: Gold-catalyzed rearrangements of strained rings.

Although the structures of the final products in these transformations are rather simple and the low selectivities limit the synthetic potential of these methods, the fact that gold was able to activate strained ring systems opened up a new research area that is still highly active to date, as will be shown in the following sections of this review.

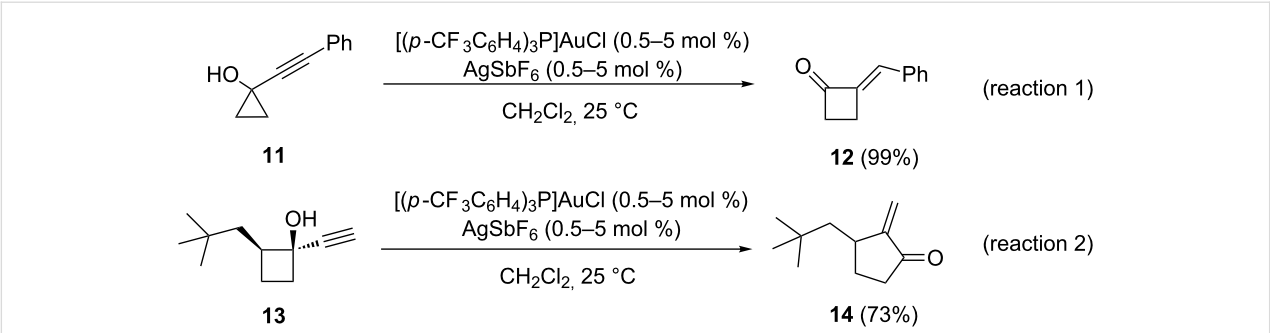
Review

1 Ring expansions involving oxygenated functions

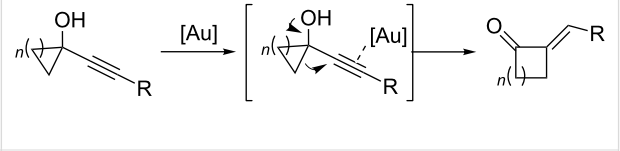
1.1 Cyclopropanols and cyclobutanols

Substituted cyclobutanones [13-15] and cyclopentanones [16-18] constitute valuable building blocks in organic synthesis due to their rich chemistry. In addition, they are common motifs in numerous natural products. Among the various approaches to access these ubiquitous scaffolds, the gold(I)-catalyzed ring expansion of cyclopropanols and cyclobutanols is considered one of the most powerful and versatile methods. In 2005, Toste and co-workers reported the treatment of 1-(phenylethynyl)cyclopropanol (**11**) with tris(4-trifluoromethylphenyl)phosphine gold(I) to give alkylidenecyclobutanone **12** quantitatively (Scheme 3, reaction 1) [19]. In an analogous manner, alkynylcyclobutanols were suitable substrates for gold(I)-catalyzed ring expansions only when a terminal alkyne group was present (Scheme 3, reaction 2). Thus, cyclobutanol **13** gave 2-methylene-3-neopentylcyclopentanone (**14**) in 73% yield.

Both processes were rationalized as a result of the π-activation of the alkyne in the presence of gold, followed by migration of the C–C bond, and a final 1,4-H shift (Scheme 4) [20].

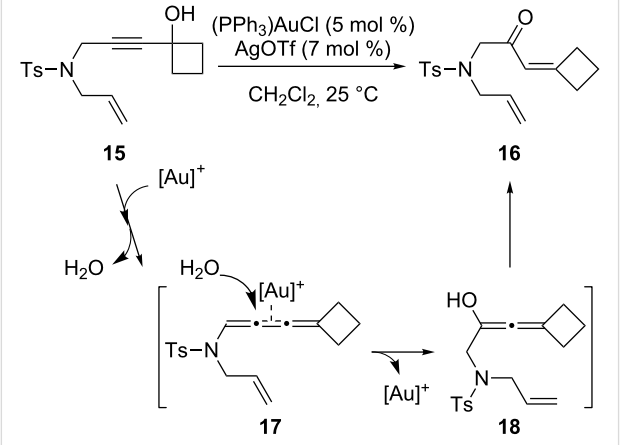


Scheme 3: Gold-catalyzed ring expansions of cyclopropanols and cyclobutanols.



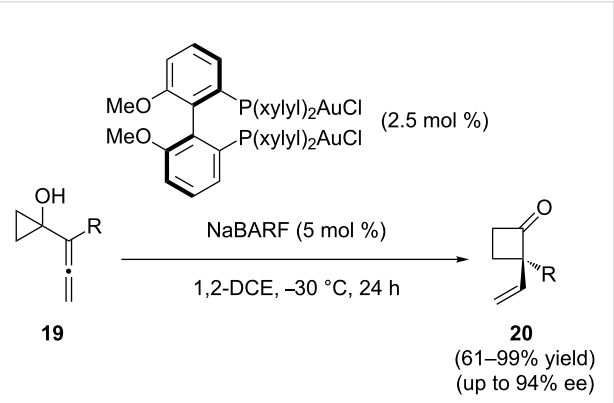
Scheme 4: Mechanism of the cycloisomerization of alkynyl cyclopropanols and cyclobutanols.

Interestingly, the use of internal alkynyl cyclobutanols such as **15**, reported in 2007 by Chung and co-workers [21], led to a completely different outcome (Scheme 5). This transformation did not lead to the expected cyclopentanones. Instead, α,β-unsaturated ketones **16** were isolated in good yields. The proposed mechanism (Scheme 5) involves nucleophilic attack by a molecule of water on the activated alkyne moiety, followed by dehydration to give the cumulene intermediate **17**. Attack on **17** by a second water molecule regenerates the catalyst with the formation of intermediate **18**, which then tautomerizes to afford the observed product.



Scheme 5: Proposed mechanism for the Au-catalyzed isomerization of alkynyl cyclobutanols.

1-Allenyl cyclopropanols **19** can be transformed into cyclobutanones **20** with absolute stereocontrol at the quaternary stereogenic center generated during the reaction by the use of a binuclear chiral gold-phosphine complex, as shown in Scheme 6 [22]. Bicyclic cyclopentanones can also be obtained in a related transformation starting from allenyl cyclobutanols [23].

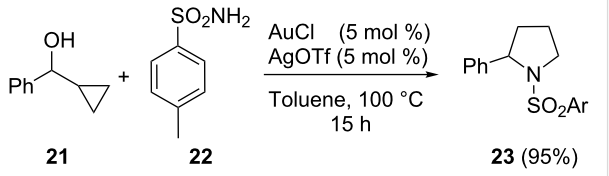


Scheme 6: Gold-catalyzed cycloisomerization of 1-allenylcyclopropanols.

1.2 Cyclopropylmethanols

Cyclopropyl methanols can be used, alternatively, as pre-electrophiles in gold-catalyzed reactions. In 2008 Chan and co-workers developed an efficient synthetic route to pyrrolidines via a tandem amination/ring expansion of these substrates in the presence of sulfonamides [24]. Phenylcyclopropylalcohol **21** was efficiently transformed into sulfonyl pyrrolidine **23** in the presence of 5 mol % of the cationic complex AuOTf (Scheme 7). The reaction was applicable to a wide range of activated and non-activated cyclopropylmethanols, sulfonamides containing electron-withdrawing, electron-donating, and sterically demanding substituents. This transformation is thought to proceed through activation of the substituted cyclopropylmethanol by the gold catalyst, which leads to the ionization of the alcohol followed by the subsequent cyclopropyl ring

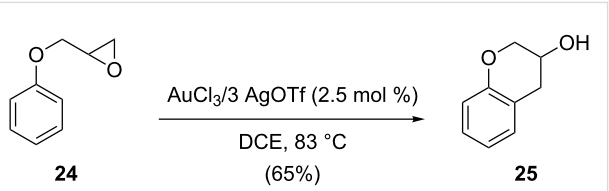
opening and trapping of the carbocation by the sulfonamide. Subsequent intramolecular hydroamination gave the pyrrolidine products.



Scheme 7: Gold-catalyzed cycloisomerization of cyclopropylmethanols.

1.3 Oxiranes

As an oxophilic Lewis acid, gold can activate epoxides towards the attack of nucleophiles. A good example is the $AuCl_3$ catalyzed ring opening of aryl alkyl epoxide **24** to give 3-chromanol **25**, which was reported by He and co-workers in 2004 (Scheme 8) [25].



Scheme 8: Gold-catalyzed cycloisomerization of aryl alkyl epoxides.

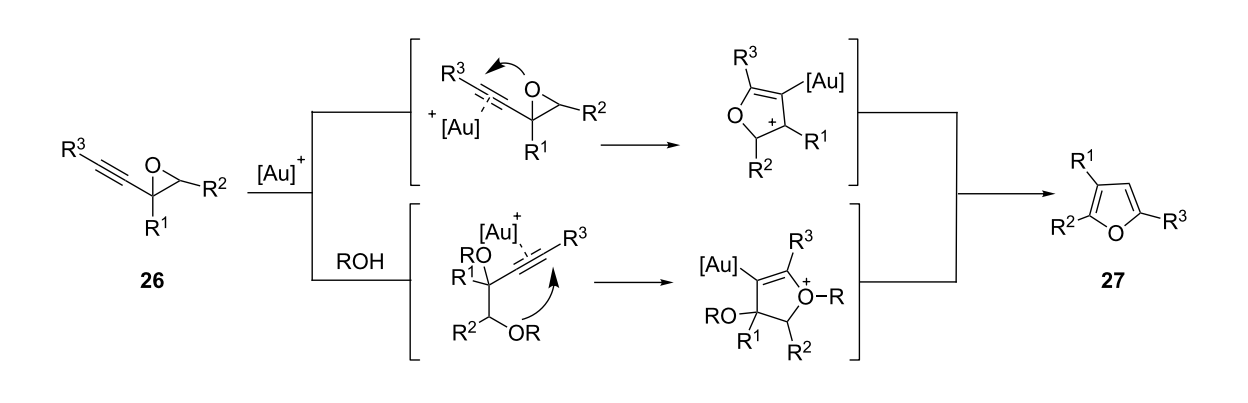
The same year, Hashmi and co-workers described the first example of a gold-catalyzed conversion of alkynyl epoxides **26** into furans **27** [26,27]. Mechanistic studies performed later by Pale and co-workers [28] seem to rule out the usually proposed mechanism, that is, via the intramolecular nucleophilic addition of the oxirane oxygen on the π-metal–alkyne complex (Scheme 9, upper row). Instead, the reaction seems to proceed through a cascade initiated by an internal or external nucleophilic (the hydroxy group in the substrate or adventitious water or alcohol present in the reaction media) opening of the three membered ring, followed by metal activation of the triple bond to trigger the cyclization (Scheme 9, lower row). In both cases, aromatization and protodeauration would afford the observed products.

Acyloxylated alkynyl oxiranes **28** and **30** have also proved to be versatile building blocks for the synthesis of divinyl ketones **29** [29], 2,5-disubstituted furans **31** [30] and difurylmethane derivatives **32** [31], respectively (Scheme 10).

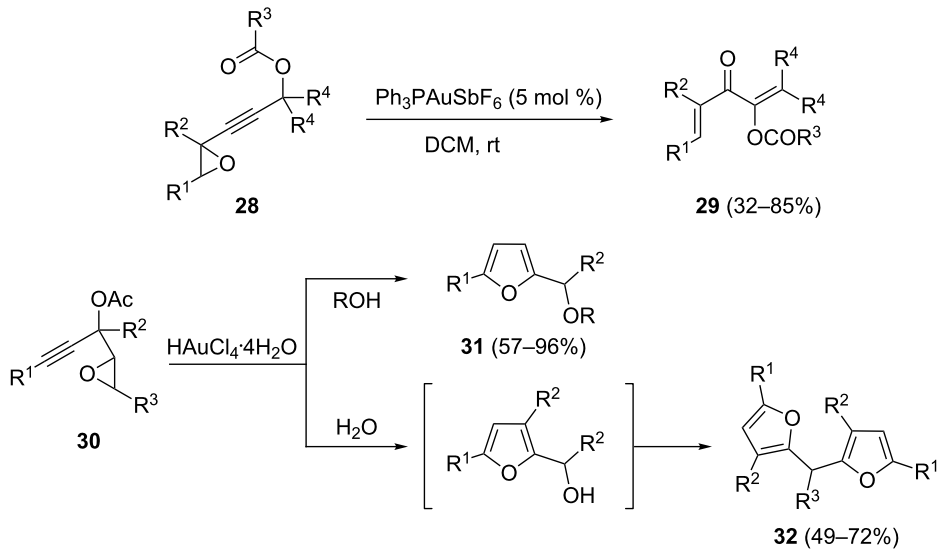
Epoxy alkynes can also be transformed with high stereoselectivity into ketals in the presence of catalytic amounts of gold and an external nucleophile such as water or an alcohol (Scheme 11) [32]. The reaction seems to commence with the epoxide ring opening in the presence of the nucleophile to give intermediate **33** (as already proposed in Scheme 9) followed by activation of the alkyne and intramolecular nucleophilic attack of the alcohol function to give **34**. Reactivation of the olefin and subsequent incorporation of a second molecule of nucleophile (intramolecularly in the case of water, intermolecularly in the case of alcohols) affords ketals **35** and **36**, respectively. The reaction can also proceed in an intramolecular manner, if the substrate contains an alcohol functionality [33,34].

2 Ring expansions involving cyclopropyl alkynes

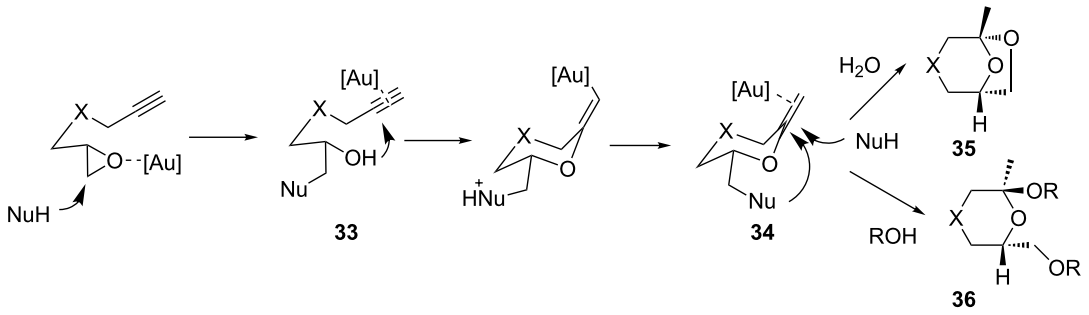
The metal-catalyzed ring expansion of cyclopropyl alkyne derivatives represents a versatile method to access a wide range of building blocks [35-38]. Upon gold activation of the triple bond in **37** two possible pathways can arise. In the first, the cyclobutyl cation **38** is formed by ring expansion, which is subsequently trapped by an external nucleophile (Scheme 12,



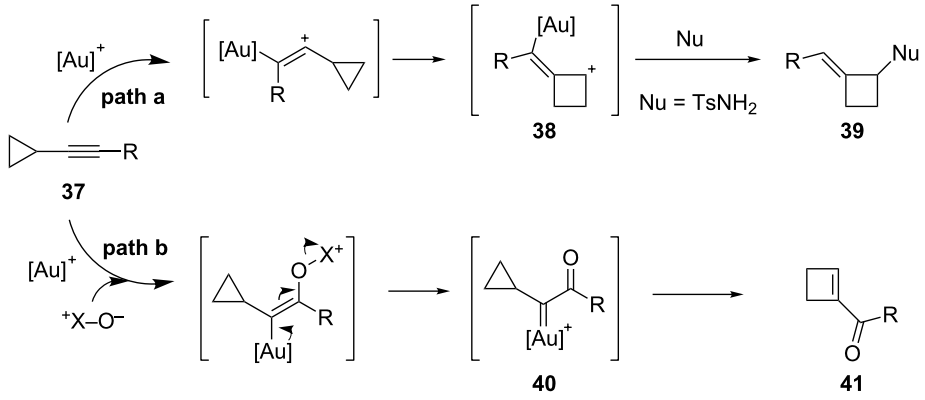
Scheme 9: Gold-catalyzed synthesis of furans.



Scheme 10: Transformations of alkynyl oxiranes.



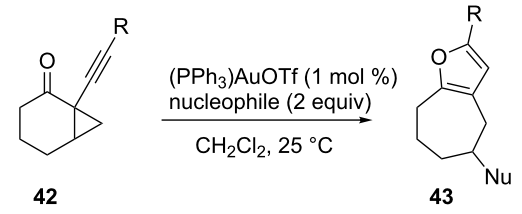
Scheme 11: Transformations of alkynyl oxiranes into ketals.



Scheme 12: Gold-catalyzed cycloisomerization of cyclopropyl alkynes.

path a). In 2010, the group of Yu developed a new route for the synthesis of cyclobutanamines **39** according to this reaction mode [39]. Alternatively, in the presence of an external oxidant, a nucleophilic addition can occur to form carbene **40**, which rearranges to cyclobutenone **41** (Scheme 12, path b). Liu recently reported the use of diphenylsulfoxide as an external nucleophilic oxidant in this context [40].

The gold-catalyzed intramolecular nucleophilic attack of heteroatoms on alkynes, followed by ring expansion, represents an appropriate method for the synthesis of furans and pyrroles. In 2006, Schmalz and co-workers reported a gold-catalyzed cascade reaction of alkynyl cyclopropyl ketones **42**, which makes use of the carbonyl group as a nucleophile, and yields substituted furans **43** (Scheme 13) [41].

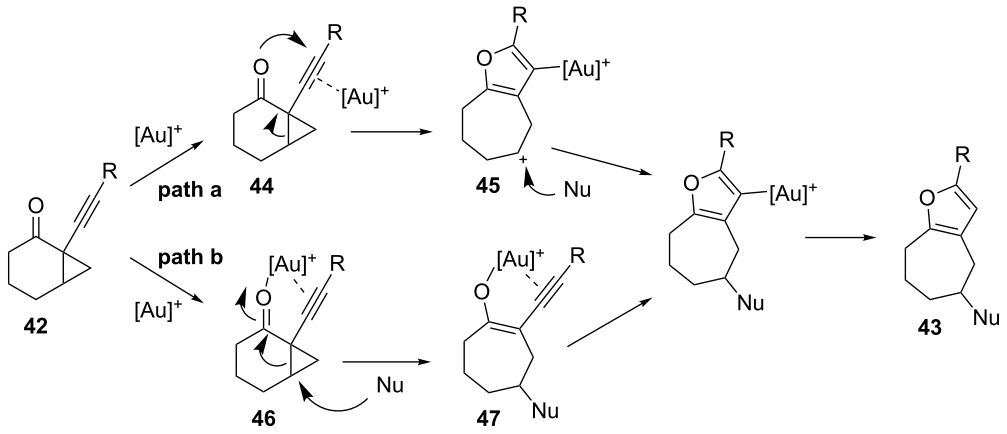


Scheme 13: Gold-catalyzed synthesis of substituted furans.

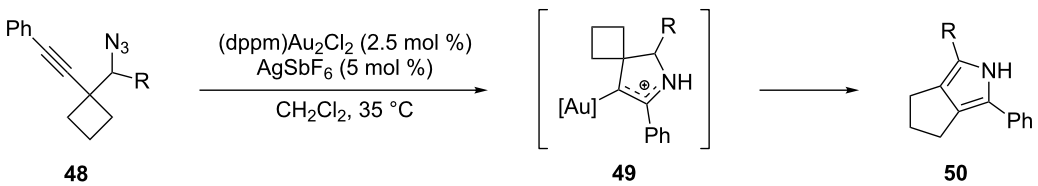
Two possible mechanisms were proposed for this transformation. Nucleophilic attack of the carbonyl oxygen atom onto the activated alkynyl moiety can trigger the cyclopropyl ring opening to give carbocation **45,** which is then trapped in the presence of an external nucleophile to give, after protonolysis, furans **43** (Scheme 14, path a). Alternatively, gold can complex both of the unsaturated moieties as in **46**, triggering the cyclopropyl ring opening through an intermolecular nucleophilic attack to give intermediate **47**, which upon cycloisomerization affords the aromatic product (Scheme 14, path b).

Toste and co-workers reported an intramolecular acetylenic Schmidt reaction using azides as internal nucleophiles to give substituted pyrroles (Scheme 15) [42]. Gold activation of the alkyne in **48**, addition of the azide moiety followed by a loss of dinitrogen affords a gold-stabilized cationic intermediate **49**. A subsequent 1,2-H shift gave, after tautomerization, the 1*H*-pyrrole **50**. Epoxides can also be used as nucleophiles for the preparation of heterocarbocycles via gold-catalyzed ring expansion of 1-oxiranyl-1-alkynylcyclopropanes [43,44].

An alternative method for obtaining disubstituted pyrroles via gold-catalyzed ring expansion was reported by Davies and co-workers who employed alkynyl aziridines **51** as intramolecular nucleophiles [45]. Ring expansion from the aziridines onto



Scheme 14: Proposed mechanism for the isomerization of alkynyl cyclopropyl ketones.



Scheme 15: Cycloisomerization of cyclobutylazides.

the adjacent alkyne afforded the 2,5-disubstituted pyrroles **52** in high yields (Scheme 16).

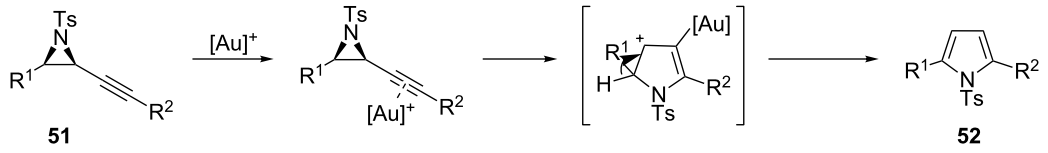
In 2011, Barluenga et al. developed a new methodology for the preparation of 1,6-disubstituted regioisomeric cyclohexadienes **54** and **54'** (Scheme 17) [46]. The process resulted in a five-to-six-membered ring expansion which involves the cleavage of the bridging C–C bond and a formal [1,2]-alkynyl shift. A mixture of regioisomers resulted due to an unexpected equilibration of the starting material **53** to **53'** via 6-*endo* cyclization of the olefin with the gold-activated alkyne.

3 Ring expansions of cyclopropenes

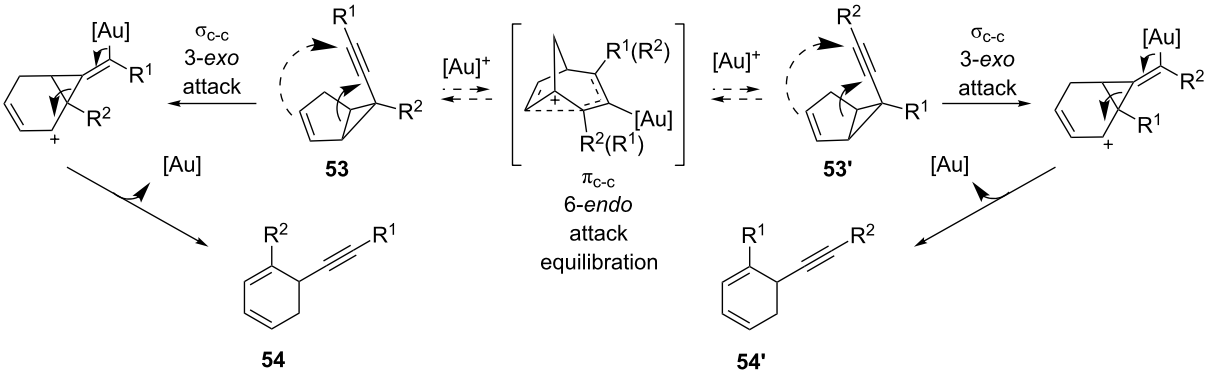
Highly strained cyclopropenes can undergo a wide variety of transformations in the presence of Lewis acids. Shi and co-workers reported in 2008 a gold-catalyzed cycloisomerization of aryl vinyl cyclopropenes to produce, selectively, 2-vinyl-1*H*-indene derivatives in high yields (Scheme 18). Upon activation of the cyclopropene, cation **55** is formed. C–C bond cleavage of the cyclopropyl ring followed by a Friedel–Crafts reaction affords, after recovery of aromaticity, the observed products [47].

4 Ring expansions involving annulation reactions

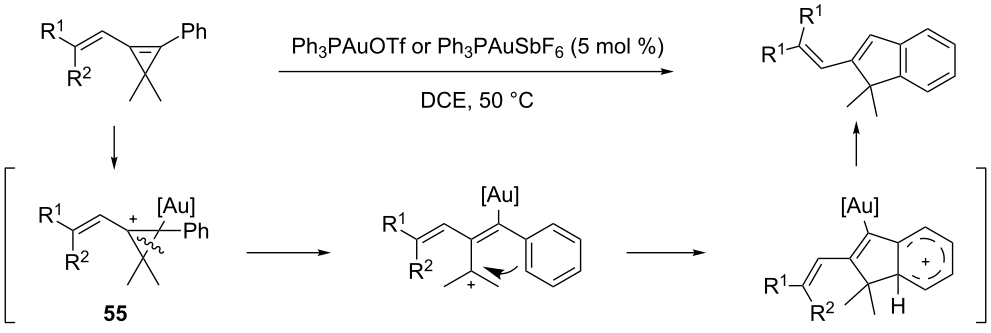
Diels–Alder, [1,3]-dipolar-, [2 + 2]- and [4 + 3]-cycloadditions are just some of the relevant available methods employed by organic chemists to increase the molecular complexity of products originating from rather straightforward starting materials. In contrast to the vast number of precedents involving Rh-catalyzed [4 + 3]-cycloaddition reactions to form 7-membered-rings in a stereocontrolled manner [48,49], the use



Scheme 16: Cycloisomerization of alkynyl aziridines.

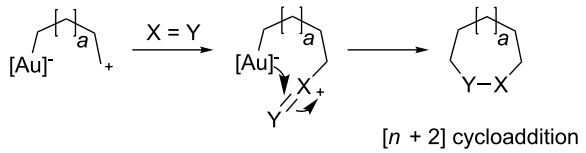


Scheme 17: Gold-catalyzed synthesis of disubstituted cyclohexadienes.



Scheme 18: Gold-catalyzed synthesis of indenes.

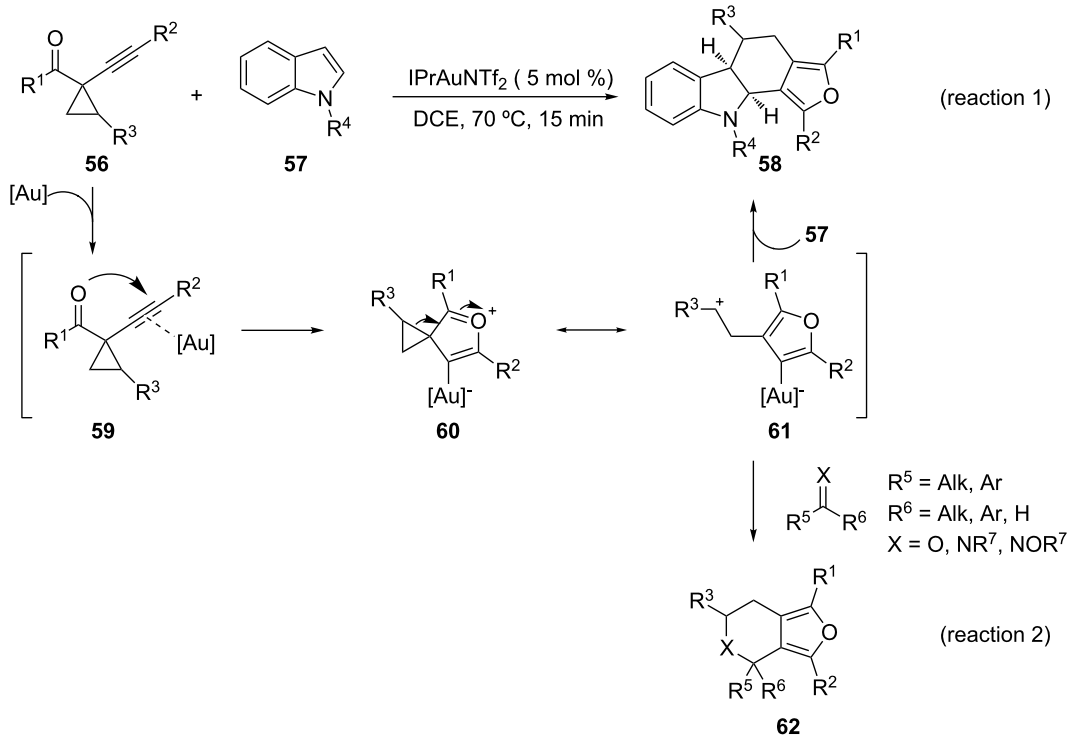
of the analogous gold-catalyzed transformations has remained, until recently, largely unexplored. Usually, 1,*n*-dipoles are elusive intermediate species, which can undergo many side reactions preceding the desired annulation/cyclization processes. Zhang envisioned that if the negative terminus of the dipole could be stabilized in the presence of gold, a better handling of these species could be achieved to trigger [*n* + *m*] annulation processes. In fact, the cationic end of the dipole was proposed to react in a bimolecular process in the presence of a dipolarophile, such that the nucleophilic C–Au bond could intercept the newly generated delta positive charge (Scheme 19).



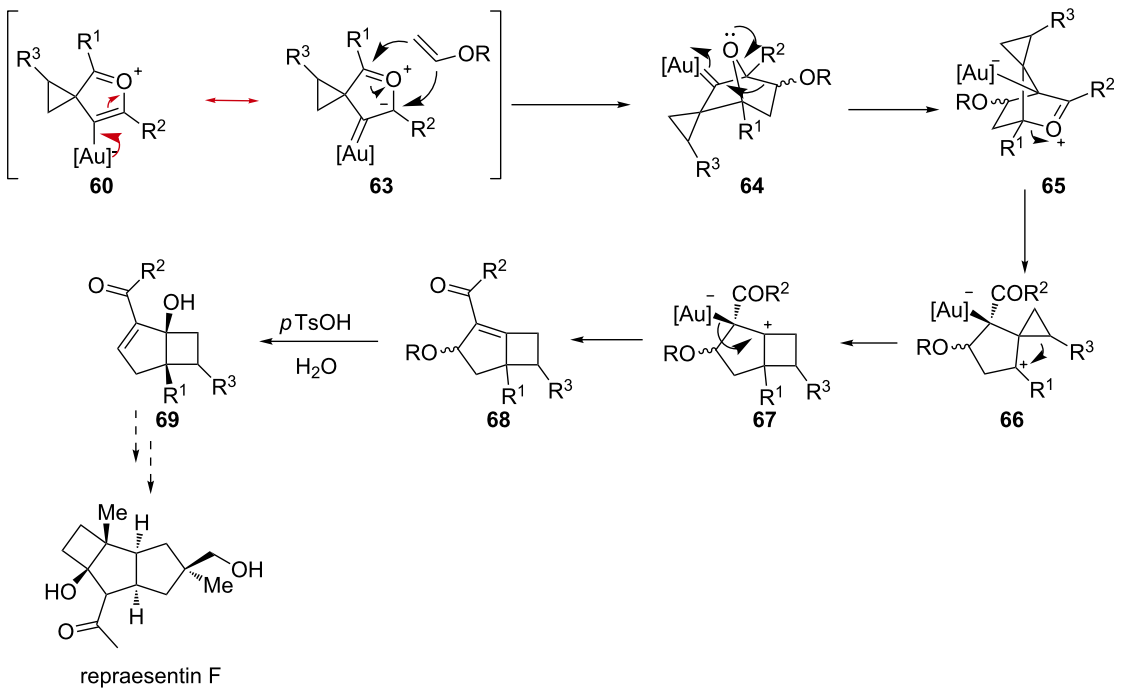
Scheme 19: Gold-catalyzed [*n* + *m*] annulation processes.

This concept, successfully applied to self cyclization processes [50], could be enforced in its intermolecular version by generation of gold-1,4-dipoles, which minimize self cyclization events [51]. 1-(1-Alkynyl)cyclopropyl ketones **56** proved to be versatile building blocks for this purpose and gave, in the presence of indoles **57** as dipolarophiles, tetracyclic furans **58** in excellent yields (Scheme 20, reaction 1). NHC carbenes are preferred as ancillary ligands on the metal center. Upon coordination of the metal to the alkyne **59**, the 1,4-dipole **61** can be formed from oxocarbenium **60**. Carbonyl compounds and carbonyl derivatives, such as imines or silyl enol ethers, can also be used as dipolarophiles to generate bicyclic furans **62** in fairly good yields (Scheme 20, reaction 2). Nitrones also reacted as dipolarophiles in the presence of $AuCl_3$, even if in some cases copper catalysts were found to be more effective at triggering the corresponding annulations [52].

By contrast, when alkoxy vinyl ethers were employed as dipolarophiles, the cycloaddition takes place prior to the formation of the 1,4-furan dipole (Scheme 21). In fact, a resonance structure of **60** can be envisaged entailing a gold–carbene and a carbonyl ylide **63**. Upon 1,3-dipolar cycloaddition with the alkoxy vinyl ether, bridged bicycle **64** is formed. 1,2-Alkyl migration and bridge opening produces a spiro cation **66**, such that a consecutive cyclopropyl ring expansion affords the bicyclic [3.2.0]heptane skeleton **68** in excellent yield and selectivity [53]. Treatment of **68** with a protic acid in water should activate the enone system triggering the nucleophilic attack of



Scheme 20: Gold-catalyzed generation of 1,4-dipoles.

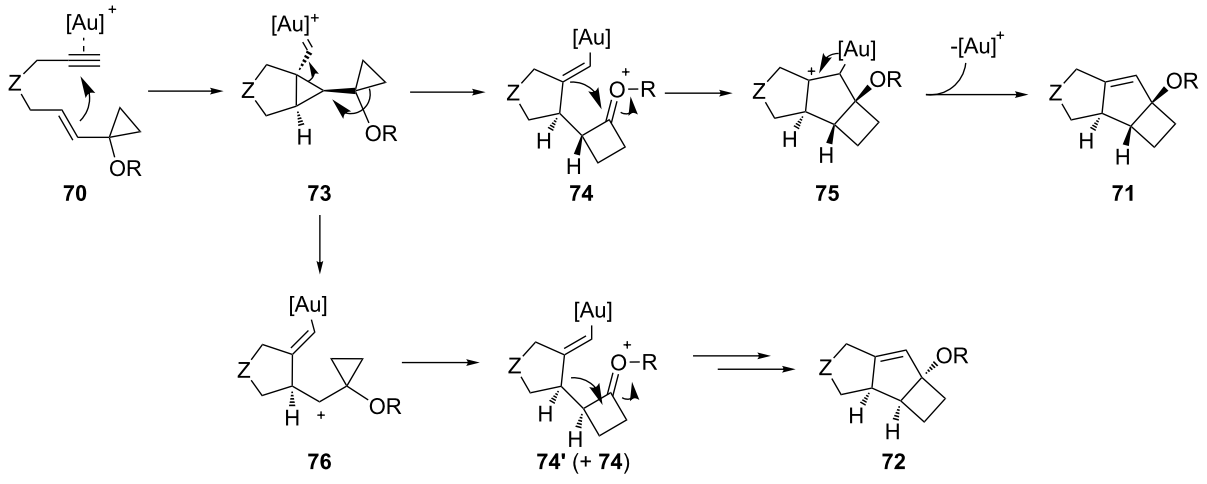


Scheme 21: Gold-catalyzed synthesis of repraesentin F.

water to give hydroxy ketones **69**. The synthetic utility of the method can be easily recognized by an examination of the structure of natural products such as repraesentin F, whose core largely comprises the structural motifs generated in this gold-catalyzed cascade.

5 Ring expansions involving enynes

The gold-catalyzed heteroatom-assisted 1,2-shift already summarized in section 1 of this review, can offer further synthetic potential in combination with 1,6-enyne substrates. Echavarren successfully developed a gold-catalyzed Prins cyclization of enynes **70** to afford *trans*- and *cis*-octahydrocyclobuta[*a*]pentalene skeletons **71** and **72**, respectively (Scheme 22) [54]. In most cases *trans* products were favored. The reaction is proposed to proceed via the cyclopropyl carbene **73**, which undergoes ring expansion to form the alkenyl–gold intermediate **74**. Reaction of the latter with the oxonium cation produces **75**, which upon gold departure forms tricycles **71**. If a



Scheme 22: Gold-catalyzed ring expansion of cyclopropyl 1,6-enynes.

non-concerted process takes place, then cyclopropyl carbene **73** evolves towards cyclopropyl cation **76**, which upon non-stereospecific ring expansion and cyclization could explain the formation of both *cis* and *trans* reaction products **71** and **72**, respectively.

Toste and co-workers also reported a remarkable synthetic application of a gold-catalyzed ring expansion of cyclopropanols in enynic substrates [55]. Vinyl cyclopropanol **77** reacts with Ph_3PAuBF_4 via cyclization, followed by a selective semi-pinacol shift via carbocationic intermediate **78**, to give cyclobutanone **79**, which is readily transformed into the angular triquinane ventricosene in six steps (Scheme 23).

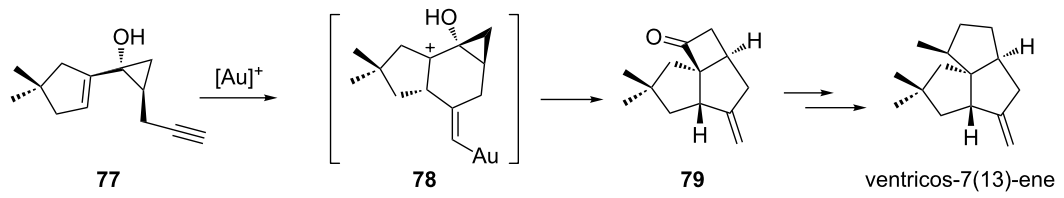
6 Ring expansions involving propargyl acyloxy rearrangements

Propargyl carboxylates **80** can be π-activated by gold towards 1,2-acyloxy migration and/or [3,3]-sigmatropic rearrangement. Two different, but mechanistically related, intermediates characterize these competitive processes, i.e., 1,2-migration via metal "carbenoid" **81** formation and [3,3]-sigmatropic rearrangement via allenyl acetate **82** as an intermediate (Scheme 24) [5,56,57].

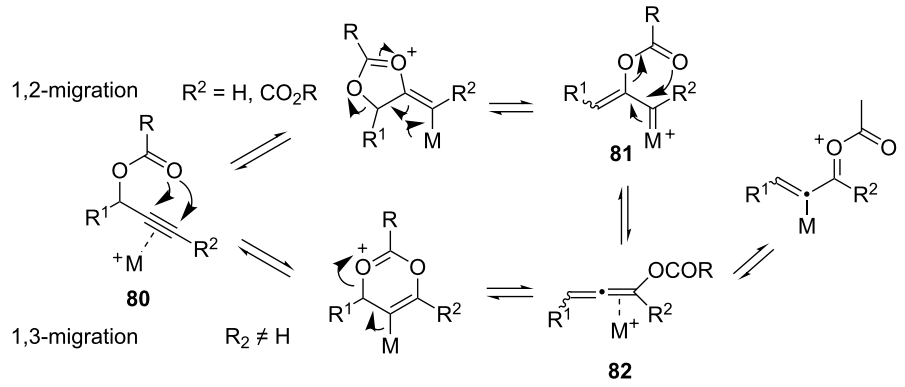
In 2008, Toste and co-workers reported a gold(I)-catalyzed cycloisomerization of *cis*-pivaloyloxy vinyl alkynyl cyclopropanes **85** to give arenes **86**, **87** and cycloheptatriene **88** derivatives through 5-*endo-dig* and 6-*endo-dig* cyclization reactions, respectively, under careful control of the reaction conditions (Scheme 25) [58].

A mechanistic rationale for these transformations is shown in Scheme 26. Cyclopropanes **85a** are generated in situ by intermolecular cyclopropanation of enyne **84** and a carbene resulting from the rearrangement of propargyl ester **83**. When tertiary propargyl esters are used, the 5-*endo-dig* cyclization generates the carbocation **89**. Migration of the pivaloyloxy group affords the allylic cations **90** and **91** by delocalization of the positive charge onto gold. The aromatic intermediate **92** is probably converted, via **93**, into **86** and **87** by E1 and S_N1 mechanisms, respectively. When secondary esters are employed, 6-*endo-dig* cyclization occurs to give **94**, which forms the cycloheptatriene derivate **88** upon cyclopropyl ring expansion.

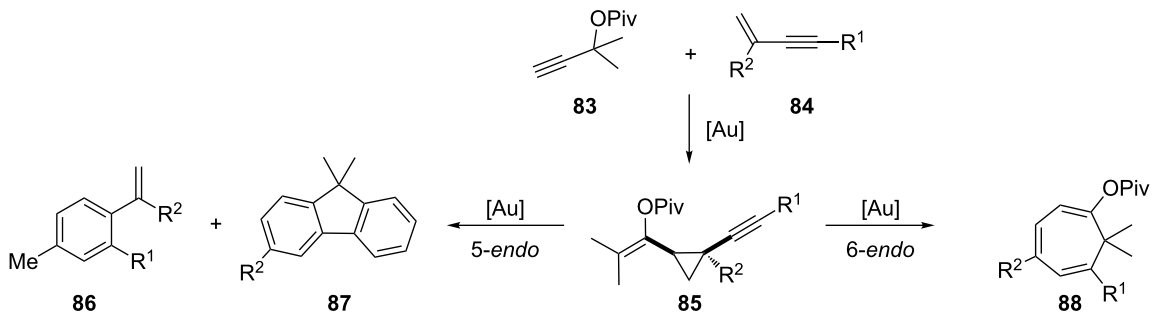
Nevado and co-workers [59] have also recently used cyclopropyl intermediates, generated in situ via alkene cyclopropanations mediated by gold carbenes, for the stereocontrolled synthesis of 5- and 7-membered-rings (Scheme 27). This method was subsequently applied in a formal enantioselective synthesis of frondosin A, a marine norsesquiterpenoid with promising biological activities (Scheme 28) [48]. Treatment of pivalate **95** and 6,6-dimethyl-1-vinylcyclohexene (**96**) with (*S*)-MeO-



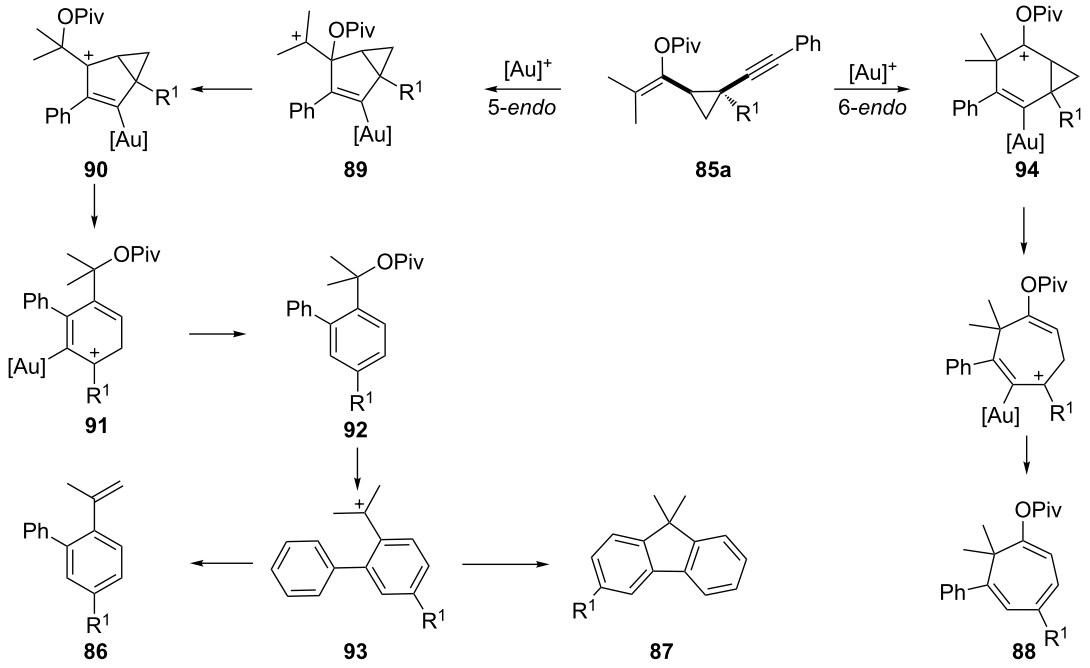
Scheme 23: Gold-catalyzed synthesis of ventricos-7(13)-ene.



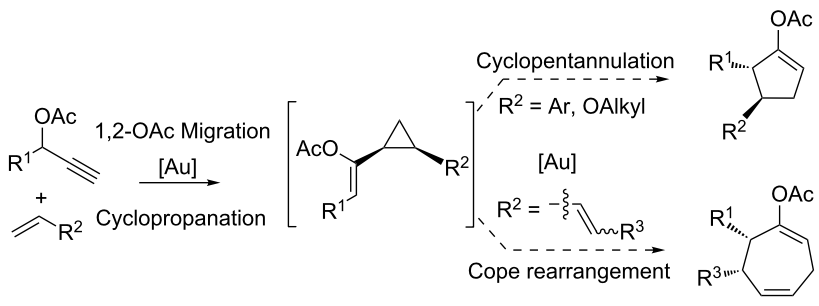
Scheme 24: 1,2- vs 1,3-Carboxylate migration.



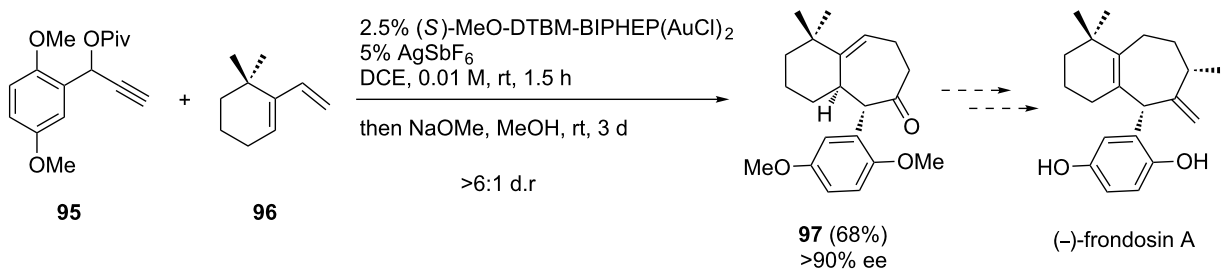
Scheme 25: Gold-catalyzed cycloisomerization of vinyl alkynyl cyclopropanes.



Scheme 26: Proposed mechanism for the cycloisomerization of vinyl alkynyl cyclopropanes.



Scheme 27: Gold-catalyzed 1,2-acyloxy rearrangement/cyclopropanation/cycloisomerization cascades.



Scheme 28: Formal total synthesis of frondosin A.

DTBM-BIPHEP-gold(I) complex afforded the corresponding bicyclic cycloheptenyl pivalate quantitatively. In situ hydrolysis and subsequent equilibration with NaOMe/MeOH yielded thermodynamically favored ketone **97** in 68% yield and >90% ee. Since this bicyclic enone has been recently elaborated to frondosins A and B [60,61] this approach represents a streamlined formal enantioselective synthesis of both molecules.

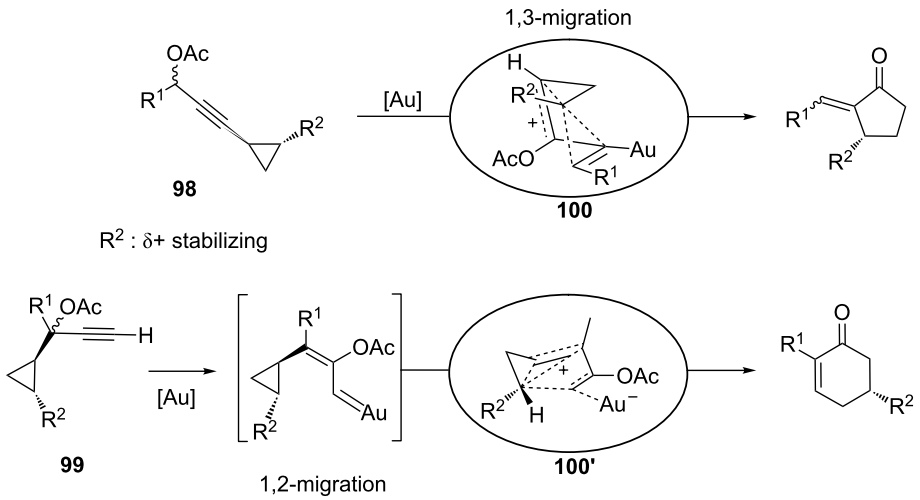
In addition, 3- and 1-substituted cyclopropyl propargylic acetates **98** and **99** have also been intensively studied and provide access to 5- and 6-membered ring enones, respectively (Scheme 29) [62-64]. In the former substrates, experimental as well as computational evidence was gathered which proved the reversible nature of the [3,3]-rearrangement in these cyclopropane probes. However, these transformations proved to be stereospecific in nature through gold-stabilized non-classical carbocations **100** and **100'**, even if the stereochemical information transfer to the product is sometimes incomplete. This may arise due to a competitive gold-promoted cyclopropyl ring opening/epimerization/ring closure, both in *cis* and *trans*-cyclopropyl settings, which competes with the cyclization event, thus eroding the overall transfer of stereochemical information.

Conclusion

From the early examples reported by Gassman and de Meijere, the field of gold-catalyzed ring expansions has experienced a continuous and sustained growth. Recently, the development of chiral gold catalysts, and the implementation of highly stereocontrolled transformations, has opened up the avenue for the application of these methodologies into more complex settings, such as natural product synthesis. In summary, gold-catalyzed ring expansions of strained rings can now be considered a mature tool for the construction of molecular complexity and thus are to be incorporated in to the toolbox of the synthetic organic chemist.

Acknowledgements

The authors would like to thank the Organic Chemistry Institute of the University of Zürich for the continuous support and the Swiss National Science Foundation for funding to D.G.



Scheme 29: Gold-catalyzed rearrangement/cycloisomerization of cyclopropyl propargyl acetates.

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Highly efficient gold(I)-catalyzed Overman rearrangement in water

Dong Xing and Dan Yang*

Letter

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Address:
Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China

Email:
Dong Xing - xingdong@hku.hk; Dan Yang* - yangdan@hku.hk

* Corresponding author

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Abstract

A highly efficient gold(I)-catalyzed Overman rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides in water is reported. With this environmentally benign and scalable protocol, a series of C3-alkyl substituted allylic trichloroacetamides were synthesized in good to high yields.

Introduction

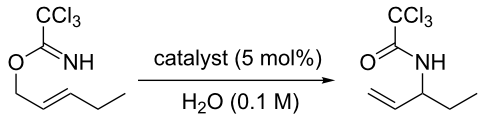
The aza-Claisen rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides (Overman rearrangement) is a powerful and attractive strategy for the synthesis of allylic amines from readily available allylic alcohols [1,2]. This transformation can be conducted thermally at high temperatures or by transition metal catalysis under very mild conditions [3-7]. Asymmetric induction has been achieved with certain types of transition metal catalysts (e.g., palladium complexes) in combination with chiral ancillary ligands [8-13]. However, although a large number of late transition metal catalysts have been used for different types of [3,3]-sigmatropic rearrangements [14,15], only Pd(II) and Hg(II) salts have found wide application in Overman rearrangements. In recent years, gold catalysts have been successfully applied to a series of [3,3]-sigmatropic rearrangements, such as the rearrangement of propargylic esters to allenyl esters [16-21], allenyl carbinol esters to 1,3-butadien-2-ol esters [22] and the isomerization of allylic acetates [23,24]. However, when they were used as catalysts for the Overman rearrangement, the substrate scope was limited and only poor to moderate yields were achieved [25-28]. Very recently, our group developed an efficient gold(I)-catalyzed decarboxylative aza-Claisen rearrangement of allylic *N*-tosylcarbamates for the synthesis of *N*-tosyl allylic amines [29]. This reaction was performed in water and therefore represented an environ-

mentally benign protocol [30-34]. We decided to apply this extremely mild catalytic system to the Overman rearrangement of allylic trichloroacetimidates.

Results and Discussion

Trichloroacetimidate **1a** was prepared by the DBU-catalyzed addition of *trans*-2-penten-1-ol to trichloroacetonitrile [10,35]. With this substrate, the catalytic activities of different gold(I) complexes in H_2O were examined. When **1a** was subjected to the optimal catalytic conditions previously reported by our group (5 mol % AuCl/AgOTf at 75 °C) [29], the desired allylic trichloroacetamide **2a** was obtained in 91% yield in a reaction time of 1 h (Table 1, entry 1). Gold(I) complexes with phosphine ligands, $Au(PPh_3)Cl$ or $Au[P(t\text{-}Bu)_2(o\text{-}Ph)Ph]Cl$, in place of AuCl gave none of the desired product (Table 1, entries 2 and 3). Further screening revealed that AuCl alone could catalyze this reaction with high efficiency to give **2a** in 92% yield in 2 h (Table 1, entry 4). On the other hand, with only AgOTf as the catalyst, the formation of **2a** was not observed and substrate **1a** decomposed completely (Table 1, entry 5). In the absence of AuCl, substrate **1a** remained unreacted, even when the temperature was increased to 100 °C for 3 h (Table 1, entry 6), indicating that the gold(I) catalyst is indispensible for this transformation. This gold(I)-catalyzed reaction could be performed at room temperature, albeit with a prolonged reaction time (Table 1, entry 7). When the temperature was raised to 55 °C the reaction was complete within 2 h and in excellent yield (94%; Table 1, entry 8).

Table 1: Optimization of reaction conditions.[a]



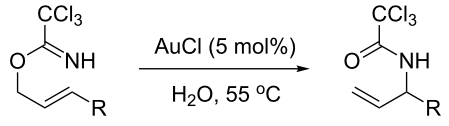
1a **2a**

Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)[b]
1	AuCl/AgOTf	75	2	91
2	$AuPPh_3Cl$/AgOTf	75	12	<5
3	$Au[P(t\text{-}Bu)_2(o\text{-}Ph)Ph]Cl$ /AgOTf	75	12	<5
4	AuCl	75	2	92
5	AgOTf	75	12	<5
6	–	100	3	<5
7	AuCl	rt	12	90
8	AuCl	55	2	94

[a]Reaction conditions: 0.3 mmol of substrate, 5 mol % of the catalyst, 3 mL H_2O; [b]yield determined by ^1H NMR with nitrobenzene as internal standard.

With the optimized reaction conditions in hand, the substrate scope of this gold(I)-catalyzed Overman rearrangement was surveyed. Different alkyl substituents at the C1 position of allylic trichloroacetimidates, including methyl (**1b**), ethyl (**1a**), *n*-propyl (**1c**) and phenethyl (**1d**) groups, underwent the desired transformation smoothly to afford the corresponding C3-alkyl substituted allylic trichloroacetamides in high yields (Table 2, entries 1–4). The C1-diethylmethyl substituted substrate (**1e**) also underwent the desired rearrangement, affording the desired

Table 2: Gold(I)-catalyzed Overman rearrangement in H_2O.[a]



1 **2**

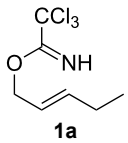
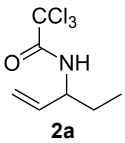
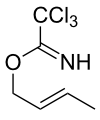
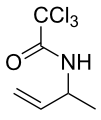
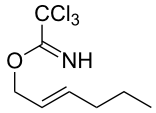
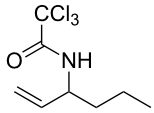
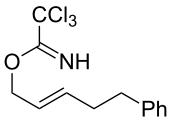
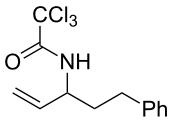
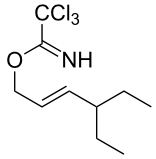
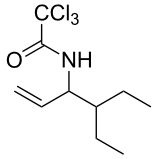
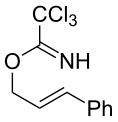
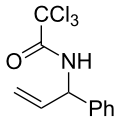
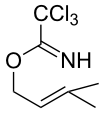
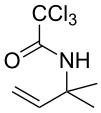
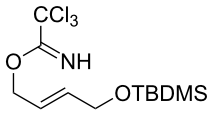
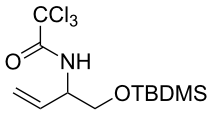
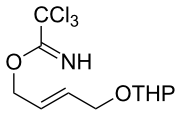
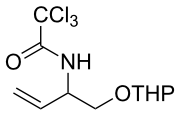
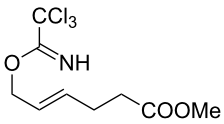
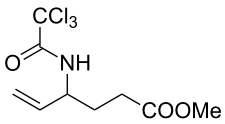
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	2	92
2	 **1b**	 **2b**	2	96

Table 2: Gold(I)-catalyzed Overman rearrangement in H_2O.[a] (continued)

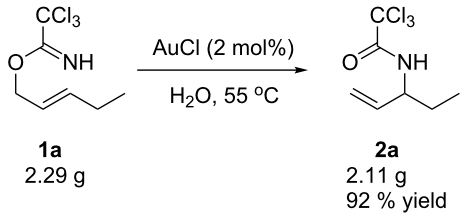
3	 **1c**	 **2c**	2	95
4	 **1d**	 **2d**	2	90
5	 **1e**	 **2e**	3	67[c]
6	 **1f**	 **2f**	3	n.d.[d]
7	 **1g**	 **2g**	3	n.d.[d]
8	 **1h**	 **2h**	3	86
9	 **1i**	 **2i**	2	79
10	 **1j**	 **2j**	6	71[c]

[a]Unless otherwise indicated, all reactions were carried out on a 0.5 mmol scale with 5 mol % of AuCl in 5 mL H_2O at 55 °C for the indicated time; [b]unless otherwise indicated, crude yields were reported with >95% purities as determined by ^{1}H NMR; [c]isolated yield after flash chromatography; [d]n.d. = not detected.

product (**2e**) in 67% isolated yield (Table 2, entry 5). However, neither the substrates with phenyl (**1f**) nor dimethyl (**1g**) substituents at the C1 position gave the rearranged product (Table 2, entries 6 and 7), indicating that both electronic and steric effects at the C1 position play roles in the rearrangement. Although the substrate scope is currently limited to C1-alkyl substituted trichloroacetimidates, this method is still very convenient and attractive for the preparation of synthetically useful allylic amines. For example, substrates containing either TBDMS- or THP-protected hydroxy groups (**1h** and **1i**) efficiently underwent the desired rearrangement to afford the corresponding products, which are precursors for the synthesis of a variety of β-substituted β-amino alcohols (Table 2, entries 8 and 9). Compound **2j** was also obtained in 71% yield under the reaction conditions from the corresponding trichloroacetimidate **1j** (Table 2, entry 10). Trichloroacetamide **2j** could be

transformed to vigabatrin, a GABA aminotransaminase inhibitor [36], in one single step [37].

One of the most remarkable features of this gold(I)-catalyzed Overman rearrangement is that it is performed in water under very mild reaction conditions. Moreover, this method is extremely clean. After completion of the reaction, simple extraction gave the desired product in high purity, and no further purification step was required. To illustrate the potential utility of this method for industrial applications, a gram-scale synthesis of **2a** was performed with 2 mol % of AuCl in H_2O (Scheme 1). After reacting at 55 °C for 4 h, the desired product was obtained in 92% yield.



Scheme 1: Gram-scale synthesis of **2a**.

Conclusion

In summary, we have developed an efficient gold(I)-catalyzed Overman rearrangement for the synthesis of a series of C3-alkyl substituted allylic trichloroacetamides. This transformation was performed in water under very mild reaction conditions and could be carried out on the gram-scale with low catalyst loading and simple work-up procedure, making it potentially applicable to the industrial community for large-scale synthesis. Further exploration of the substrate scope and the development of an asymmetric version of this transformation are currently underway in our group.

Experimental

Typical procedure: Synthesis of 2,2,2-trichloro-N-(pent-1-en-3-yl)acetamide (2a)

AuCl (5.8 mg, 0.025 mmol) was added to a solution of (*E*)-pent-2-enyl 2,2,2-trichloroacetimidate (**1a**) (115 mg, 0.5 mmol) in H_2O (5 mL) with vigorously stirring in a 25 mL reaction tube. The reaction mixture was heated at 55 °C for 2 h, then cooled to room temperature, diluted with H_2O and extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$, filtered through a short pad of celite and concentrated in vacuo to provide 107 mg of 2,2,2-trichloro-*N*-(pent-1-en-3-yl)acetamide (**2a**) (>95% purity as determined by ^{1}H NMR). Products **2a**–**2d, 2h** and **2j** are known compounds and their data were identical to those reported in the literature.

Supporting Information

Supporting Information File 1

^{1}H NMR data and NMR spectra of products **2a**–**2d**, **2g**–**2i**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-88-S1.pdf]

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Solvent- and ligand-induced switch of selectivity in gold(I)-catalyzed tandem reactions of 3-propargylindoles

Estela Álvarez[1], Delia Miguel[1], Patricia García-García[1], Manuel A. Fernández-Rodríguez[1], Félix Rodríguez[2] and Roberto Sanz[*1]

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Address:
[1]Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001 Burgos, Spain and [2]Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, C/Julián Clavería 8, 33006 Oviedo, Spain

Email:
Roberto Sanz[*] - rsd@ubu.es

* Corresponding author

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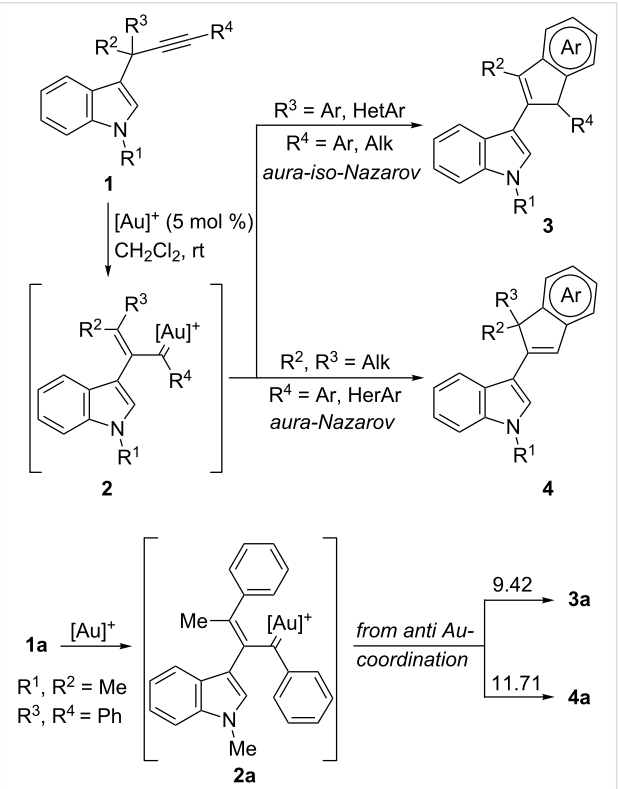
Abstract

The selectivity of our previously described gold-catalyzed tandem reaction, 1,2-indole migration followed by aura-iso-Nazarov cyclization, of 3-propargylindoles bearing (hetero)aromatic substituents at both the propargylic and terminal positions, was reversed by the proper choice of the catalyst and the reaction conditions. Thus, 3-(inden-2-yl)indoles, derived from an aura-Nazarov cyclization (instead of an aura-iso-Nazarov cyclization), were obtained in moderate to good yields from a variety of 3-propargylindoles.

Introduction

Catalysis with gold complexes as carbophilic π-acids has become a highly developed area in the last decade [1-7]. In particular, 1,2-acyl migration reactions of propargylic esters have been extensively investigated. In these processes the gold-carbenoid species generated are able to undergo a wide variety of further transformations [8-11]. In addition, propargylic sulfides have also been reported as useful substrates for this type of process, participating in related 1,2-sulfur migrations [12]. Within this area we have reported the first examples of gold-catalyzed migration reactions in propargylic systems that involve a carbon-centered moiety, implying that carbon–carbon bonds are broken and formed instead of carbon–heteroatom bonds [13,14]. Based on the nucleophilic nature of indoles [15], which are known to react with gold-activated alkynes or allenes [16,17], and by taking advantage of our reported methodology for the synthesis of 3-propargylindoles [18,19], we have shown that the indole nucleus is able to participate in gold-catalyzed 1,2-migration reactions of propargylic systems. Thus, 3-prop-

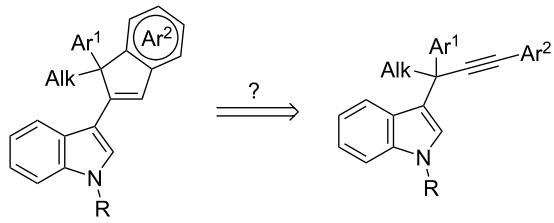
argylindoles **1** give rise to α,β-unsaturated gold-carbenoid intermediates **2** that evolve through different pathways depending on the substituents at the propargylic and terminal positions of the alkyne moiety (Scheme 1). If (hetero)aromatic substituents are present at either of these positions, they undergo further cyclizations to afford 3-(inden-2-yl)indoles **3** or **4** (Scheme 1). An analysis of the aromaticity of the transition state structures for these cyclizations by DFT calculations revealed that these electrocyclic ring closures could be considered as gold variants of the Nazarov (cyclization from **2** to **4**) or iso-Nazarov reactions (cyclization from **2** to **3**) [14]. These theoretical calculations also showed that in those cases where both cyclization pathways are possible (for example in **2a** arising from **1a**; Scheme 1), the calculated energy barriers for the two cyclization modes favored the iso-Nazarov-product **3a** (9.42 kcal/mol vs 11.71 kcal/mol for the Nazarov cyclization assuming that the initial gold coordination to the alkyne is *anti* to the indole). This is in complete agreement with the experimental data, as we always observed the selective formation of cyclization products **3** in those cases where both **3** and **4** could be obtained. However, for the model compound **1a**, similar energy profiles were obtained for the corresponding iso-Nazarov and Nazarov pathways (ΔE = 2.29 kcal/mol) [20]. Since there are several examples reported in the literature that show that the reactivity and selectivity of reactions catalyzed by gold complexes can be appropriately tuned [21-27], we thought that it should be possible to reverse the selectivity of our tandem reaction in favor of the iso-Nazarov pathway, to obtain compounds **4** by a proper setting of the reaction conditions (modulation of the electronic properties of the ligands, counter ion, solvent, substitution pattern of the substrates, etc.). Herein, we report our efforts to control the two competing pathways in the evolution of gold-carbenoid intermediates generated by an initial 1,2-indole migration in 3-propargylindoles.



Scheme 1: Formation of 3-(inden-2-yl)indoles **3** and **4** from 3-propargylindoles. Energy barriers (kcal/mol) for the cyclization reactions of gold-carbenoid intermediate **2a**.

Results and Discussion

It is an intriguing possibility that the aura-Nazarov reaction may also take place with substrates bearing aromatic substituents at both the propargylic and terminal positions, and thus allow access to new functionalized indole derivatives (Scheme 2). It should be remarked that, until now, only the aura-Nazarov cyclization to give products **4** from substrates **1** (without an aromatic substituent at the propargylic position, see R^2, R^3 in Scheme 1) has been observed.

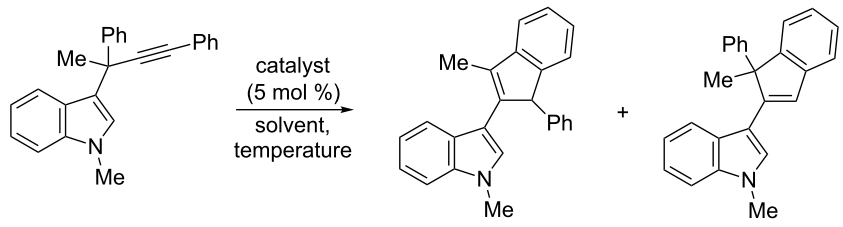


Scheme 2: Tandem 1,2-indole migration/aura-Nazarov cyclization from 3-propargylindoles bearing an aromatic substituent at the propargylic position.

For the initial selectivity control experiments, 1-methyl-3-(1-methyl-1,3-diphenylprop-2-ynyl)-1*H*-indole (**1a**) was selected as the model compound and was treated with several gold catalysts under different reaction conditions (Table 1). As expected, under our standard reported conditions ($(Ph_3P)AuCl/AgSbF_6$ in CH_2Cl_2 at room temperature), the 3-(inden-2-yl)indole **3a** was obtained as the major product. However, a minor isomer **4a** was also isolated along with **3a** in a ca. 3.5/1 ratio (Table 1, entry 1). The structure of the minor compound **4a** was established by X-ray diffraction (Figure 1), confirming that the gold-carbenoid intermediate **2a** could also undergo the aura-Nazarov cyclization [28,29].

The use of cationic gold complexes bearing different types of phosphane ligands always provided the iso-Nazarov product **3a** as the major isomer, with a small increase in the competing Nazarov product **4a** on switching the ligand to SPhos (Table 1, entries 1–4). The use of complexes bearing N-heterocyclic

Table 1: Effect of the catalyst and reaction conditions on the reactivity of **1a**.[a]



1a **3a** **4a**

Entry	Catalyst	Solvent	Ratio[b] **3a**/**4a**
1	$(Ph_3P)AuCl/AgSbF_6$	CH_2Cl_2	3.5/1
2	$(Ph_3P)AuNTf_2$	CH_2Cl_2	3.3/1
3	SPhosAuNTf$_2$[c]	CH_2Cl_2	2.5/1
4	$(Et_3P)AuCl/AgSbF_6$	CH_2Cl_2	3.3/1[d]
5	IMeAuCl[e]/$AgSbF_6$	CH_2Cl_2	2.5/1
6	IPrAuCl[f]/$AgSbF_6$	CH_2Cl_2	3/1
7	$[(PhO)_3P]AuCl/AgSbF_6$	CH_2Cl_2	2.2/1
8	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgSbF_6$	CH_2Cl_2	1.5/1
9	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgBF_4$	CH_2Cl_2	1.5/1
10	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgNTf_2$	CH_2Cl_2	2/1
11	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgOTs$	CH_2Cl_2	1.5/1
12	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgOTf$	CH_2Cl_2	1.4/1
13	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgSbF_6$	DME	1.4/1
14	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgSbF_6$	THF	1.4/1
15	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgSbF_6$	toluene	1/1.8
16	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgSbF_6$	toluene[g]	1/2.3
17	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgSbF_6$	toluene[h]	1/4[i]

[a]Reactions carried out until complete consumption of the starting material **1a**, as judged by GC-MS and/or TLC analysis, unless otherwise stated. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]SPhos = 2-dicyclohexylphosphino-2´,6´-dimethoxybiphenyl. [d]66% of conversion after 24 h. [e]IMe = 1,3,4,5-tetramethylimidazol-2-ylidene. [f]IPr = 1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene. [g]Conducted at 0 °C. A similar result was obtained by using AgOTf as a silver salt. [h]Carried out at −20 °C. [i]50% conversion after 24 h.

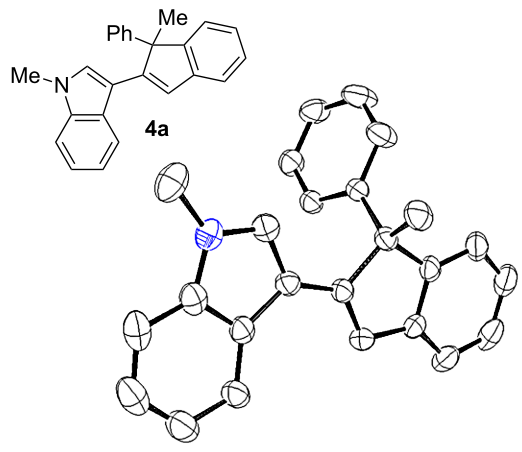


Figure 1: ORTEP diagram for **4a**. Ellipsoids are shown at 30% level (hydrogen atoms are omitted for clarity).

carbene ligands [30] also produced **3a** as the major compound of the corresponding mixtures (Table 1, entries 5 and 6). It was decided to increase the π-acceptor character of the ligand [31], and, in this case, the employment of a triphenylphosphite–gold(I) complex led to a slight increase in the ratio of **4a** (Table 1, entry 7). Finally, the use of the bulky phosphite ligand tris(2,4-di-*t*-butylphenyl)phosphite, gave rise to a 1.5/1 ratio of **3a**/**4a** (Table 1, entry 8) [32].

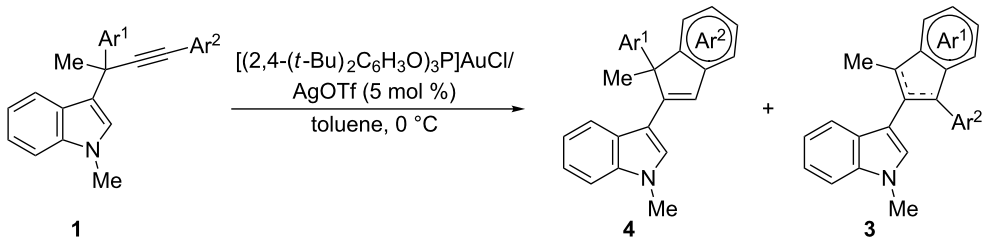
Once tris(2,4-di-*t*-butylphenyl)phosphite was selected as the best ligand to favor the desired tandem process, the influence of the metal counter ion was then studied. Thus, several silver salts were employed for the generation of the cationic catalytic active gold(I) complex, and it was concluded that the effect on the selectivity is almost negligible (Table 1, entries 9–12). Nevertheless, it should be noted that no reaction occurred when AgOBz was employed whilst the reactions with $AgBF_4$,

$AgNTf_2$ and AgOTs were relatively slow. Therefore, AgOTf and $AgSbF_6$ were selected as silver salts, due to their availability and higher reactivity, and subsequently the effect of the solvent was studied. Ethereal solvents, such as DME and THF, led to similar results as CH_2Cl_2 (Table 1, entries 13 and 14), whereas acetonitrile proved to be unsuitable for the reaction. Gratifyingly, it was found that the use of toluene as the solvent reverses the selectivity of the reaction, and, with this solvent, the Nazarov product **4a** became the major isomer in the mixture (Table 1, entry 15). Finally, the effect of the temperature in toluene was investigated: It was found that carrying out the reaction at 0 °C afforded a 2.3/1 ratio of isomers in favor of **4a** (Table 1, entry 16). If the temperature is lowered to −20 °C the ratio in favor of **4a** was even higher, although only a 50% conversion was observed after 24 h (Table 1, entry 17). Under the optimized and synthetically useful reaction conditions, i.e., toluene at 0 °C, with $[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl$/AgOTf as the catalytic system, **4a** was obtained in 60% isolated yield.

At this point it was unclear whether the observed change of selectivity in favor of the Nazarov product **4a** was mainly a solvent effect, or if the nature of the ligand also exerted an influence on the selectivity. To clear up this point the initial catalyst $[(Ph_3P)AuCl/AgOTf]$ was revisited, and **1a** was treated with this catalytic system in toluene. Since the reaction was very slow at 0 °C, the temperature was increased to rt. Under these conditions the observed **3a**/**4a** ratio was 1/1.5. By comparing this result with that in entry 1 of Table 1 led to the conclusion that the change of solvent is the main factor responsible for the selectivity switch in favor of the Nazarov product. Nevertheless, the beneficial effect of the bulky phosphite ligand is also significant factor with regards to both reactivity and selectivity.

To examine further the scope of this switch of selectivity in favor of the Nazarov pathway in tandem gold-catalyzed reactions of 3-propargylindoles initiated by 1,2-indole migrations, a selection of substrates **1a**–**i**, bearing a methyl group at one of the propargylic positions and different (hetero)aromatic groups at both the other propargylic and terminal positions, were reacted under the established conditions (Table 2). From the results obtained, the selectivity in favor of the Nazarov products **4** seems to be general for the selected indoles **1a**–**h** (Table 2, entries 1–8). N-unsubstituted indole **1b** also showed a

Table 2: Synthesis of 3-(inden-2-yl)indoles **4** by gold-catalyzed tandem 1,2-indole migration/Nazarov-type cyclization of 3-propargylindoles **1**.



1 **4** **3**

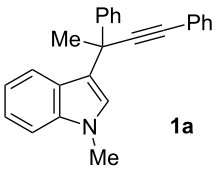
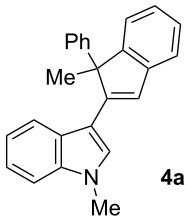
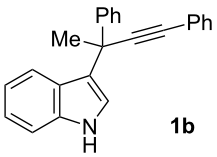
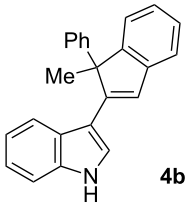
Entry	Substrate	Ratio Nazarov (**4**)/ iso-Nazarov (**3**)[a]	Product	Yield (%)[b]
1	 **1a**	2.3/1	 **4a**	60
2	 **1b**	1.8/1	 **4b**	41

Table 2: Synthesis of 3-(inden-2-yl)indoles **4** by gold-catalyzed tandem 1,2-indole migration/Nazarov-type cyclization of 3-propargylindoles **1**. (continued)

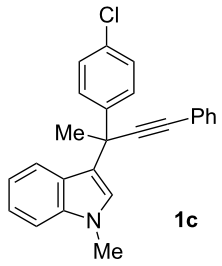
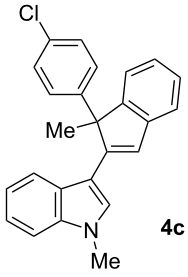
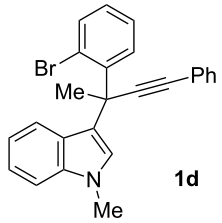
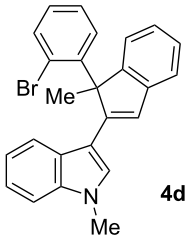
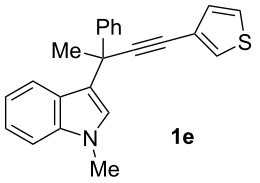
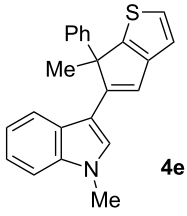
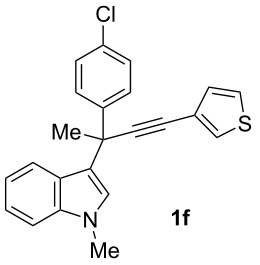
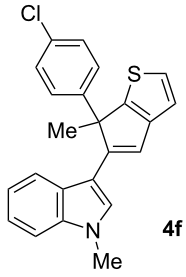
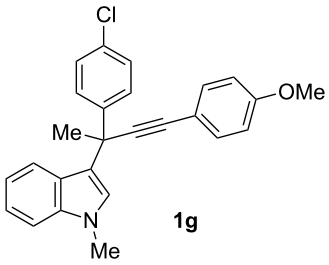
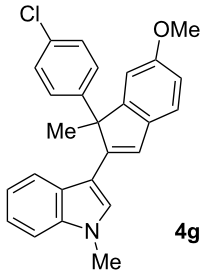
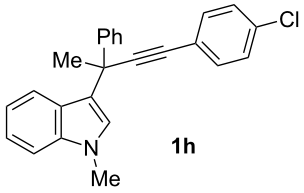
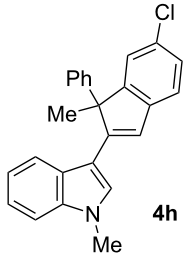
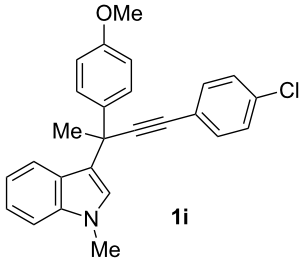
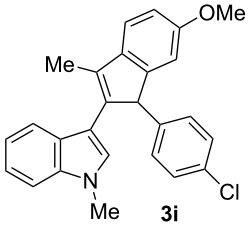
3	 **1c**	3/1	 **4c**	67
4	 **1d**	>10/1	 **4d**	86
5	 **1e**	3/1	 **4e**	62
6	 **1f**	4/1	 **4f**	71
7	 **1g**	3/1	 **4g**	60
8	 **1h**	1.2/1	 **4h**	47[c]

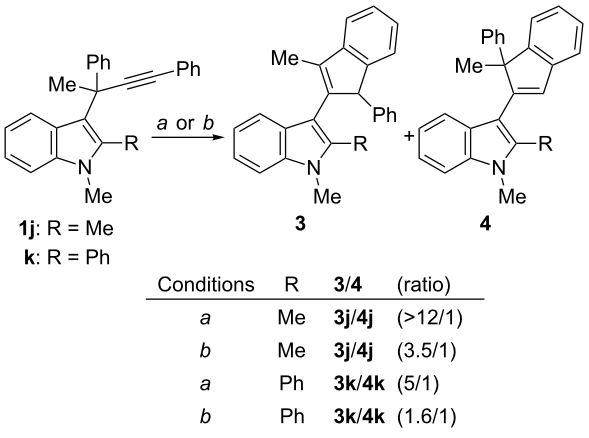
Table 2: Synthesis of 3-(inden-2-yl)indoles **4** by gold-catalyzed tandem 1,2-indole migration/Nazarov-type cyclization of 3-propargylindoles **1**. (continued)

9	 **1i**		<1/10	 **3i**	88[d]

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of compounds **4** after column chromatography, unless otherwise stated. [c]Determined by NMR from the mixture of **3h** and **4h**.[d]Combined yield for **3i** and **3´i**, in which the double bond has isomerized. Both compounds have been isolated and characterized. See Supporting Information File 1 (Experimental and analytical data) and Supporting Information File 2 (NMR spectra).

preference for the corresponding Nazarov product **4b**, although in this case the selectivity was slightly lower compared to **1a** (Table 2, entry 2), and the reaction gave a poorer overall yield. When an electron-withdrawing substituent was present on the aryl group at the propargylic position, selectivity in favor of Nazarov products **4** appeared to be slightly increased (Table 2, entry 3) [33]. Substrate **1d**, with a bulky electron-withdrawing substituent at one of the *ortho* positions of the aromatic propargylic group, afforded almost exclusively the Nazarov product **4d** in high yield (Table 2, entry 4). Similarly, the presence of a π-electron rich heteroaromatic group or an electron-rich aromatic group at the terminal position of the triple bond also favors the Nazarov pathway (Table 2, entries 5–7). On the other hand, the use of 3-propargylindole **1h** as starting material, bearing an electron-withdrawing substituent on the aromatic ring at the terminal position, led to a slight decrease in the selectivity (Table 2, entry 8). Moreover, the introduction of an electron-donating group on the aromatic ring at the propargylic position gave rise to the almost exclusive formation of the iso-Nazarov product **3i** (Table 2, entry 9). A comparison of these selectivities with that obtained for the parent indole **1a**, leads to the conclusion that the electronic nature of the aryl groups at both the propargylic and terminal positions also has a significant influence on the preferred cyclization pathway. The Nazarov products **4** seem to be more favored when electron-withdrawing groups are present at the propargylic position and electron-donating substituents are present at the terminal position. Under these optimized conditions, new and interesting 3-(inden-2-yl)indoles **4a**–**h** were isolated in good yields.

By contrast, it was previously observed that substitution at C-2 of the starting 3-propargylindole led almost exclusively to the formation of iso-Nazarov products **3** [13,14]. For instance, indoles **1j** and **1k**, bearing a methyl and a phenyl group at C-2, respectively, provided the corresponding indole derivatives **3j** and **3k** with high selectivity when the reaction was conducted in CH_2Cl_2 with $(Ph_3P)AuCl/AgSbF_6$ as catalyst (Scheme 3). Interestingly, under the new conditions developed herein, i.e., treatment with a cationic phosphite–gold complex in toluene, the reaction of **1j** afforded a ca. 3.5/1 mixture of **3j**/**4j**, whereas **1k** gave rise to a ca. 1.6/1 mixture of **3k**/**4k** (Scheme 3). These results again show that the change of selectivity in the competitive iso-Nazarov/Nazarov pathways could be induced by a change of ligand and solvent, although complete reversal of selectivity was not achieved for these substrates.

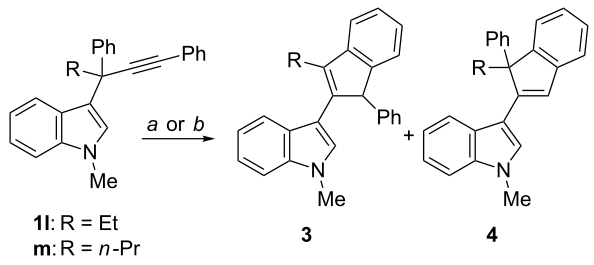


Conditions	R	3/4	(ratio)
a	Me	**3j**/**4j**	(>12/1)
b	Me	**3j**/**4j**	(3.5/1)
a	Ph	**3k**/**4k**	(5/1)
b	Ph	**3k**/**4k**	(1.6/1)

Scheme 3: Comparison of the reactivity of C-2 substituted indoles **1j** and **1k**. Conditions: *a*) $(Ph_3P)AuCl/AgSbF_6$ (5 mol %), CH_2Cl_2, rt; *b*) $[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgOTf$ (5 mol %), toluene, 0 °C.

It has also been observed that reactions of 3-propargylindoles bearing alkyl substituents bulkier than methyl at the propargylic position, such as **1l** and **1m**, almost exclusively produced the corresponding iso-Nazarov products **3l** and **3m**

with $(Ph_3P)AuCl/AgSbF_6$ as catalyst in CH_2Cl_2 (Scheme 4) [13,14]. Again, the use of the phosphite–gold complex as catalyst and toluene as solvent slightly favored the Nazarov pathway: Approximately 3/1 ratios of the corresponding indole derivatives **3l, m**/**4l, m** were obtained (Scheme 4) [32]. In addition, we were able to isolate the new Nazarov compounds **4l** and **4m**, albeit in low yields (Scheme 4). Finally, when the more sterically demanding isopropyl group was present at the propargylic position, the corresponding iso-Nazarov product was produced exclusively irrespective of the conditions employed. Although these results show that the change of the methyl group at the propargylic position of the starting indole **1** to a bulkier alkyl group strongly favors the iso-Nazarov pathway, they also show that our new reported conditions make the Nazarov pathway more accessible.



Conditions	R	**3**/**4** ratio	Isolated yields (%)
a	Et	>12/1	**3l** (79%)
a	*n*-Pr	>12/1	**3m** (75%)
b	Et	3/1	**3l** (53%) + **4l** (20%)
b	*n*-Pr	3/1	**3m** (52%) + **4m** (19%)

Scheme 4: Reactions of 3-propargylindoles **1l** and **1m** with bulky alkyl substituents at the propargylic position. Conditions: *a*) $(Ph_3P)AuCl/AgSbF_6$ (5 mol %), CH_2Cl_2, rt; *b*) $[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgOTf$ (5 mol %), toluene, 0 °C.

Conclusion

We have studied the effect of the ligands and counter ion of the catalyst, as well as the electronic nature of the aryl substituents and the reaction conditions (solvent, temperature), in the gold(I)-catalyzed tandem reactions of 3-propargylindoles initiated by 1,2-indole migrations. We have been able to switch the preference of 3-propargylindoles, bearing (hetero)aromatic substituents at both propargylic and terminal positions of the alkyne moiety, from undergoing an aura-iso-Nazarov cyclization in favor of an aura-Nazarov cyclization. The two competitive pathways are influenced mainly by the electronic and steric properties of the aryl substituent at the propargylic position, as well as the ligand of the catalyst and the solvent used. In this way, new and interesting 3-(inden-2-yl)indoles were obtained in good yields.

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. Copies of ^1H NMR and ^{13}C NMR spectra for new compounds.

Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-89-S1.pdf]

Supporting Information File 2

NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-89-S2.pdf]

Acknowledgements

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29. In our first communication [13] the structure of the minor isomer obtained from an analogous 3-propargylindole bearing an ethyl group at the propargylic position was erroneously assigned to a 3-(inden-1-yl)indole derivative arising from a competitive hydroarylation of the triple bond by the propargylic phenyl group.
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32. When [(2,4-(*t*-Bu)$_2$C$_6$H$_3$O)$_3$P]AuCl was used as catalyst the iso-Nazarov products were obtained as a mixture of **3** and **3´**, in which the double bond is isomerized. So, the ratio of isomers **3**/**4** reflects the ratio of both the iso-Nazarov compounds **3** and **3´** against the Nazarov product **4**.
33. We have also checked that **1b** affords a ca. 2.2/1 mixture of **3b**/**4b** when (Ph$_3$P)AuCl/AgSbF$_6$ was used as catalytic system in CH_2Cl_2, also proving the effect of the electron-withdrawing substituent on the phenyl group at the propargylic position.

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High chemoselectivity in the phenol synthesis

Matthias Rudolph[1], Melissa Q. McCreery[2], Wolfgang Frey[2] and A. Stephen K. Hashmi*[1,2]

Full Research Paper

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Address:
[1]Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany and [2]Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany

Email:
A. Stephen K. Hashmi* - hashmi@hashmi.de

* Corresponding author

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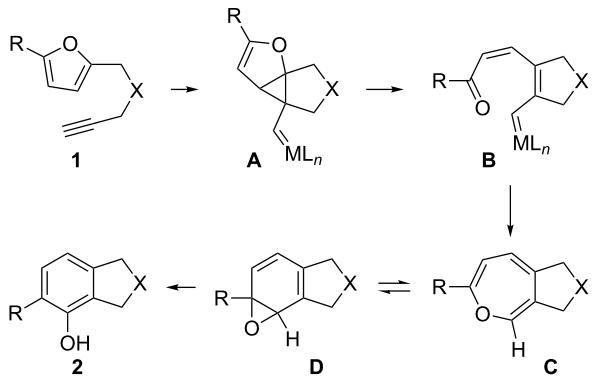
Abstract

Efforts to trap early intermediates of the gold-catalyzed phenol synthesis failed. Neither inter- nor intramolecularly offered vinyl groups, ketones or alcohols were able to intercept the gold carbenoid species. This indicates that the competing steps of the gold-catalyzed phenol synthesis are much faster than the steps of the interception reaction. In the latter the barrier of activation is higher. At the same time this explains the high tolerance of this very efficient and general reaction towards functional groups.

Introduction

As documented in numerous reviews [1-10], over the last eleven years homogeneous gold catalysis has emerged from early examples [11,12] which documented its potential for organic synthesis of even complex molecules to an established tool in preparative organic chemistry [13,14]. One of these early examples is the gold-catalyzed phenol synthesis [12] in which the furan-ynes **1** used as substrates represent the first ene–yne-type compounds ever used in gold catalysis. While many investigations in the field focused on methodology, mechanistic research was much less widespread [2,3,15]. The gold-catalyzed ene–yne cycloisomerization reactions are, mechanistically, very complex reactions [16-18], and the furan–yne cycloisomerization is no exception. For the latter reaction arene oxides **D** [19] and oxepines **C** [20] could be detected as intermediates, and these could even be trapped by Diels–Alder reactions. In addition, labelling studies were carried out and the electronic influence of substituents was investigated [21]. Computational studies as well as side-products produced in the reaction pointed towards intermediates **A** and **B** (Scheme 1) [22-25]. Moreover, interesting new pathways were opened when ynamides and alkynyl ether substrates were employed: Here **A** is also a possible intermediate along these pathways [25].

Since direct experimental evidence existed only for **C** and **D**, we intended to intercept the postulated carbenoid intermediates



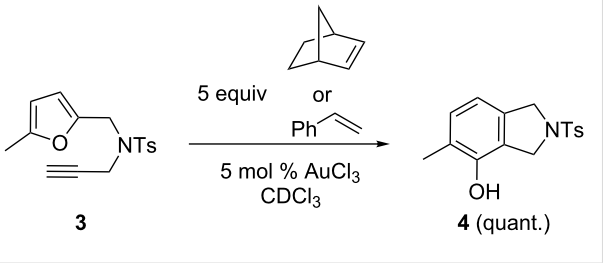
Scheme 1: Mechanism of the furan–yne reaction.

A or **B**. Apart from intermolecular trapping [26-33], intramolecular trapping of such carbenoids has also been reported [34]. One option would be to offer a competing carbonyl group, to produce a carbonyl ylide, which could then undergo a 1,3-dipolar cycloaddition [35]. The second option would be a classical cyclopropanation of an olefin. A third option would be trapping of intermediate **A** with an intramolecular hydroxy nucleophile [36]. Here we report our observations when trying to apply these principles to intermediates of type **A** or **B**.

Results and Discussion

Intermolecular olefinic trapping reagents

We started with the simplest experiments, namely the intermolecular trapping of the gold carbenoid intermediates. When **3** was reacted in the presence of an activated olefin, such as norbornene or styrene, phenol **4** was formed exclusively in essentially quantitative yield, no other products could be detected (Scheme 2).



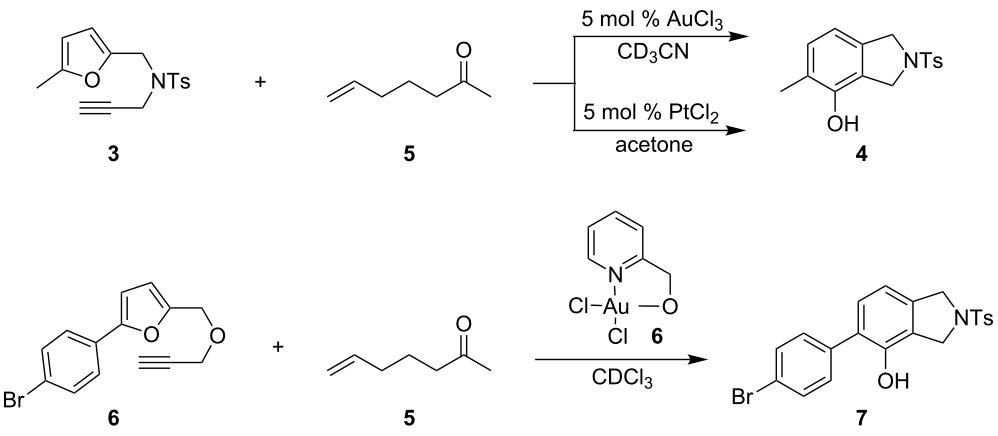
Scheme 2: Efforts for intermolecular trapping with olefins failed.

Experiments with a competing carbonyl group (competing with the carbonyl group in intermediate **B**) were also unsuccessful. Ketone **5** [37], prepared by the addition of methyllithium to commercially available hex-5-enoic acid, was used as an external carbonyl group. Reaction with both tosylamide **3** and ether **6** always delivered the phenolic products **4** or **7**, respectively (Scheme 3). The same result was obtained when $PtCl_2$ was used as the catalyst for the conversion of **3**.

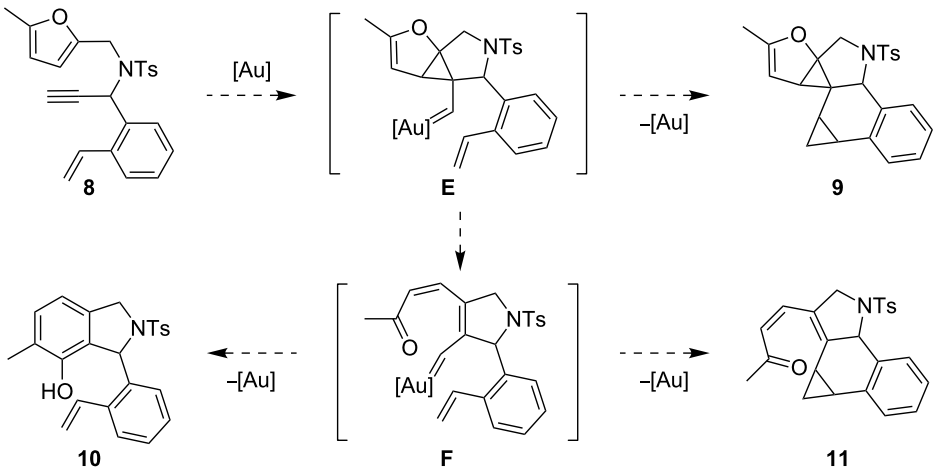
Intramolecular olefinic trapping reagents

The next step was to offer the styrene unit in an intramolecular manner. Substrate **8** could potentially undergo three different modes of reaction (Scheme 4). After the initial step, the intermediate **E** would be produced (analogous to **A**). Cyclopropanation of the styrene subunit by the cyclopropyl carbenoid would deliver **9**. If **E** rearranged to the vinylcarbenoid **F**, the two competing reactions would be the formation of the phenol **10** and cyclopropanation to form **11**.

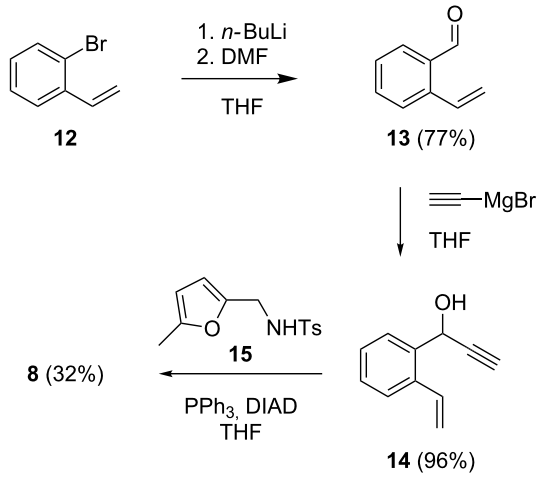
The synthesis of **8** was possible by a short route (Scheme 5). Starting from the commercially available 2-bromostyrene (**12**), a halogen–metal exchange and subsequent formylation according to a procedure of Fukumoto et al. [38] gave **13**. Add-



Scheme 3: Efforts for intermolecular trapping with ketones failed.



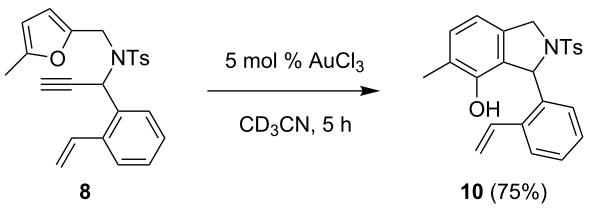
Scheme 4: Potential products of an intramolecular trapping experiment with substrate **8**.



Scheme 5: Synthesis of the substrate **8**.

ition of ethynylmagnesium bromide to **13** led to **14**, which reacted with furan **15** [40] under Mitsunobu conditions [39] to afford **8**. While the yields were good for the first two steps of the reaction sequence, the yield of the last step was only 32%.

With $AuCl_3$ the phenol **10** was formed exclusively (Scheme 6). The structure was unambiguously confirmed by X-ray crystal structure analysis (Figure 1). It shows an interesting hydrogen bond-like interaction of the phenolic hydroxy group and the alkene unit. After changing the solvent from acetonitrile to $CDCl_3$, and the gold(I) catalyst to $[Mes_3PAu]NTf_2$ [41], only **10** was again observed. Thus, neither of the two oxidation states of the gold catalyst gave any product derived from the intercepted intermediate (the solvent was changed to $CDCl_3$ since the activity of gold(I) is significantly reduced by MeCN).



Scheme 6: With substrate **8** the product of the phenol synthesis was exclusively obtained.

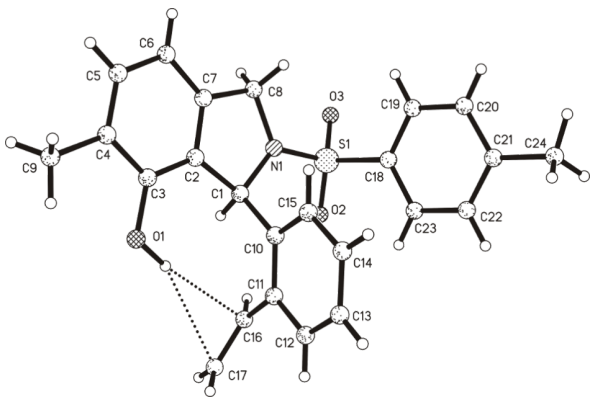
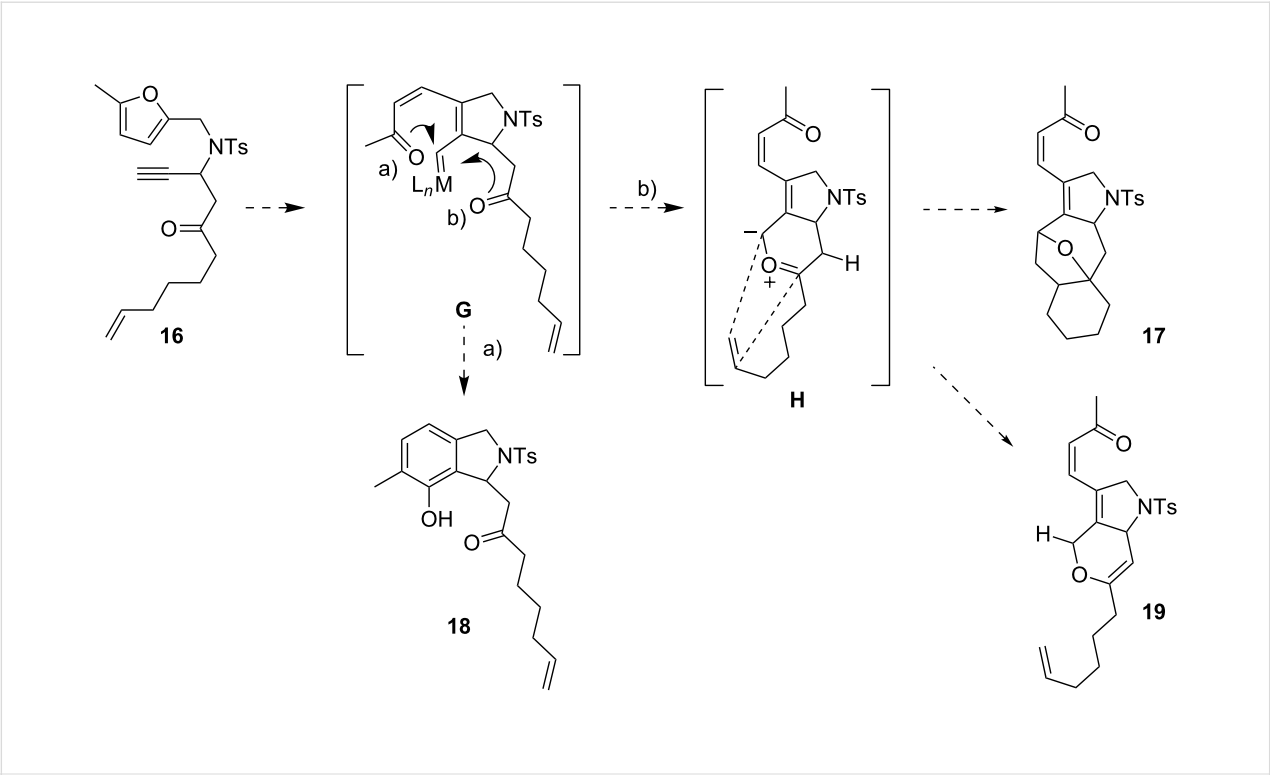


Figure 1: Solid-state molecular structure of **10**.

Intramolecular ketone as potential trapping reagent

Next we decided to use a carbonyl group as the competing unit. The intermediate **G**, formed from substrate **16**, would offer the option of competition of the phenol synthesis (Scheme 7, pathway a) to yield **18,** and reaction with the second carbonyl group (Scheme 7, pathway b). The latter would form intermedi-



Scheme 7: Potential products of an intramolecular trapping experiment with substrate **16**.

ate **H**, which could then either afford product **17** via intramolecular 1,3-dipolar cycloaddition with the olefin, or could form the diene **19** by proton migration.

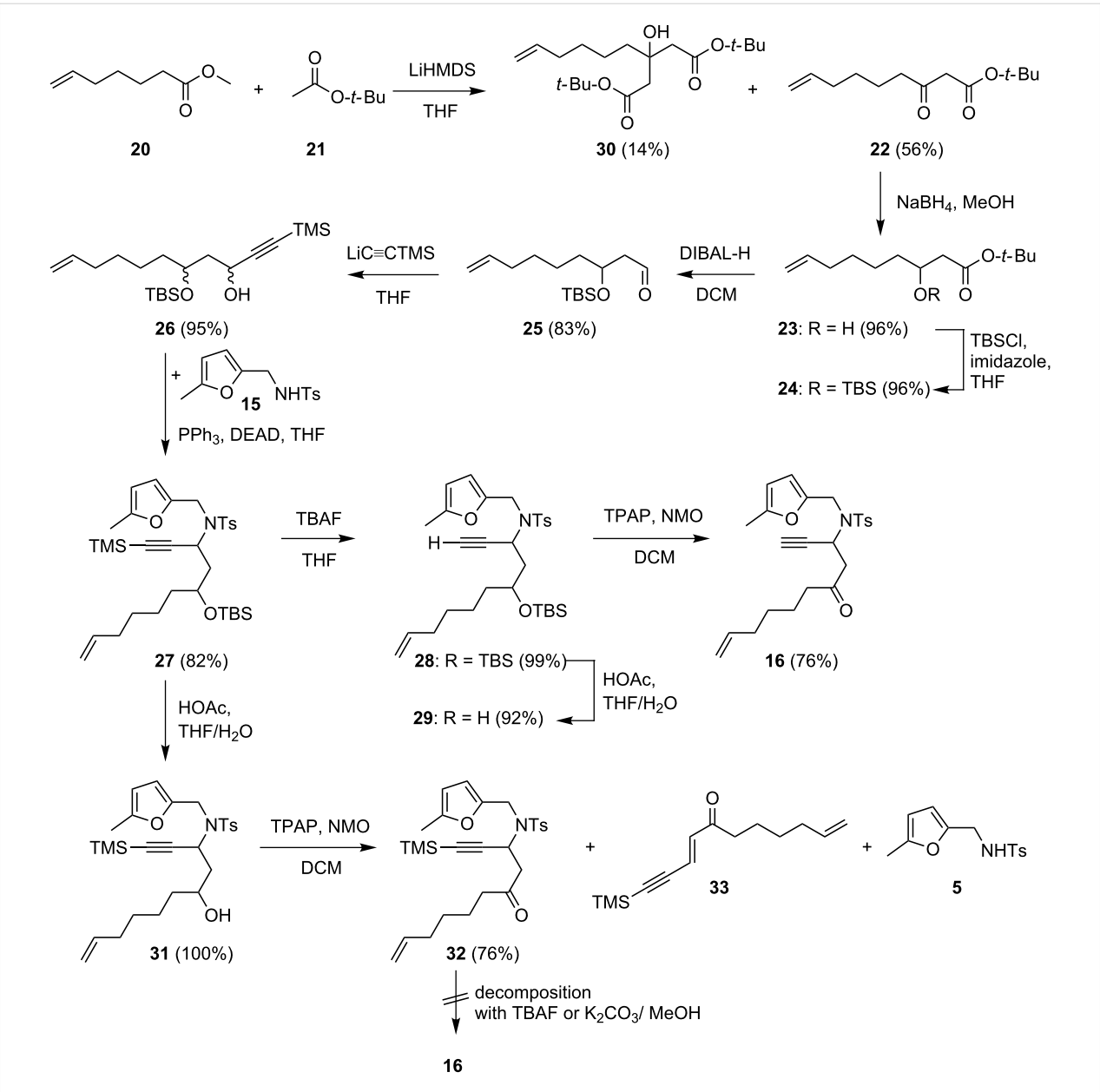
The synthesis of **16** was only possible by a 9-step sequence (Scheme 8). The starting point was a Claisen condensation of ester **20** and *tert*-butyl acetate (**21**) in the presence of lithium hexamethyldisilazide as the base. Ketoester **22** was obtained in 56% yield, however, the two-fold addition of **21** could not be suppressed completely and 14% of the corresponding tertiary alcohol **30** was also obtained. Reduction of the ketone **22** with sodium borohydride and protection of the alcohol **23** with *tert*-butyldimethylsilylchloride delivered **24** in excellent yield. Reduction of the ester group with diisobutylaluminiumhydride gave aldehyde **25**. The addition of lithiated trimethylsilylacetylene provided the propargylic alcohol **26** and reaction with **15** under Mitsunobu conditions yielded **27**. Deprotection of the alkyne **2**7 and the silyl ether **28**, followed by the oxidation of the resulting alcohol **29** finally led to **16**. It was not possible to remove both silyl groups simultaneously with TBAF, longer reaction times which would be necessary for the deprotection of the hydroxy group led to decomposition of the substrate. At 0 °C and with a very short reaction time, the alkyne was deprotected selectively. Selective deprotection of the alcohol was then possible with a mixture of acetic acid/water/THF. Another route, in which the alcohol function was deprotected first, then oxidized, followed by removal of the trimethylsilyl group from the alkyne also failed. Thus treatment of **27** with acetic acid in aqueous THF gave the desired alcohol **31**in quantitative yield. However, whilst Ley oxidation [42] on the small-scale delivered ketone **32** in yields of up to 80%, on a larger scale the yield of **32** dropped dramatically to 28% and was accompanied by two side-products, **33** and **5**. The latter are formed by an elimination reaction of the amide in **32**. Furthermore, it was not possible to deprotect ketone **32** due to rapid decomposition.

One of the diastereoisomers of **28** was identified as the *anti*-product **28a** by an X-ray crystal structure analysis (Figure 2).

The conversion of **16** with 5 mol % $AuCl_3$ proceeded fast and gave exclusively phenol **18**. No other products could be detected (Scheme 9).

The two gold(III) complexes **34** [43] and **35** [37] as well as the dinuclear gold(I) complex **36** [44] gave the same result (Figure 3). When the catalyst was changed to platinum(II) chloride in acetone, a complex mixture of inseparable products was obtained.

Since the two diastereoisomers **28a** and **28b** with the propargylic stereocenters were separable, we investigated the gold-catalyzed conversion of the pure isomers. From the NMR



Scheme 8: Synthesis of the substrate **16**.

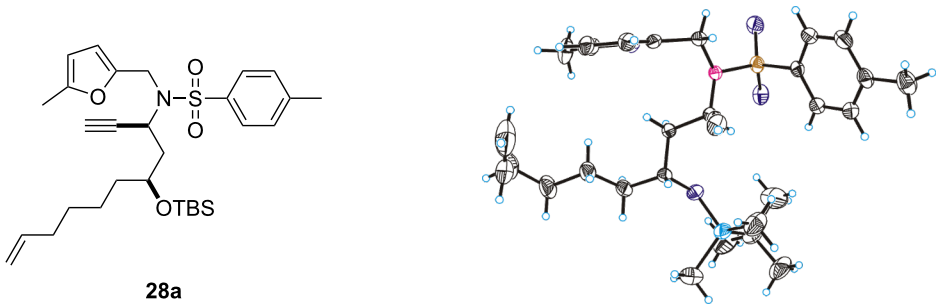
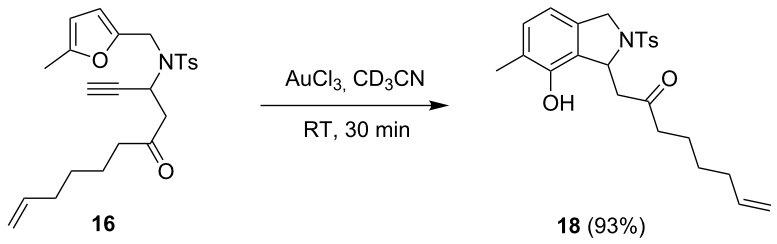


Figure 2: Solid-state molecular structure of **28a**.



Scheme 9: With substrate **16** the product of the phenol synthesis is obtained exclusively.

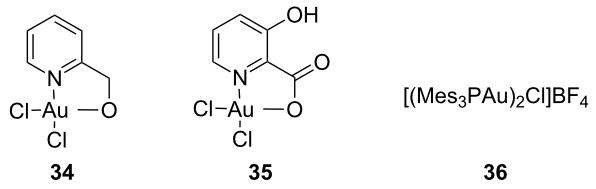


Figure 3: Catalysts **34**, **35** and **36**.

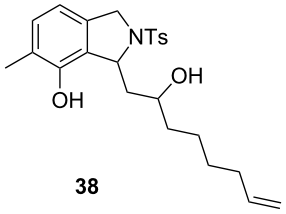


Figure 5: Structure of the desilylation product **38**.

spectra taken during the conversion (Figure 4), it could be clearly seen that no epimerization of the propargylic position occurred. In addition to the selective transformation to the phenols **37a** and **37b** as the main reaction products, partial removal of the TBS group was observed (**38**, Figure 5).

Intramolecular alcohol as potential trapping reagent

For the interception of intermediate **A** we also considered the option of an intramolecular hydroxy nucleophile, compound **39** (Scheme 10) would represent this type of substrate. The intermediate **I** would be an analogue of **A**. Instead of the phenol synthesis to yield **40**, an intramolecular nucleophilic attack at the activated three-membered ring could form intermediate **J**, which, after protodeauration, would provide ketal **41**.

The synthesis of **39** was readily accomplished by the addition of lithiated sylvan **42** to the PMB-protected aldehyde **43** (Scheme 11) [45]. The resulting furfuryl alcohol **44** was then propargylated to give **45**. The deprotection was however, problematic. Treatment of the latter with cerium ammonium nitrate led to decomposition. Only with DDQ was the desired alcohol **39** obtained in moderate yield.

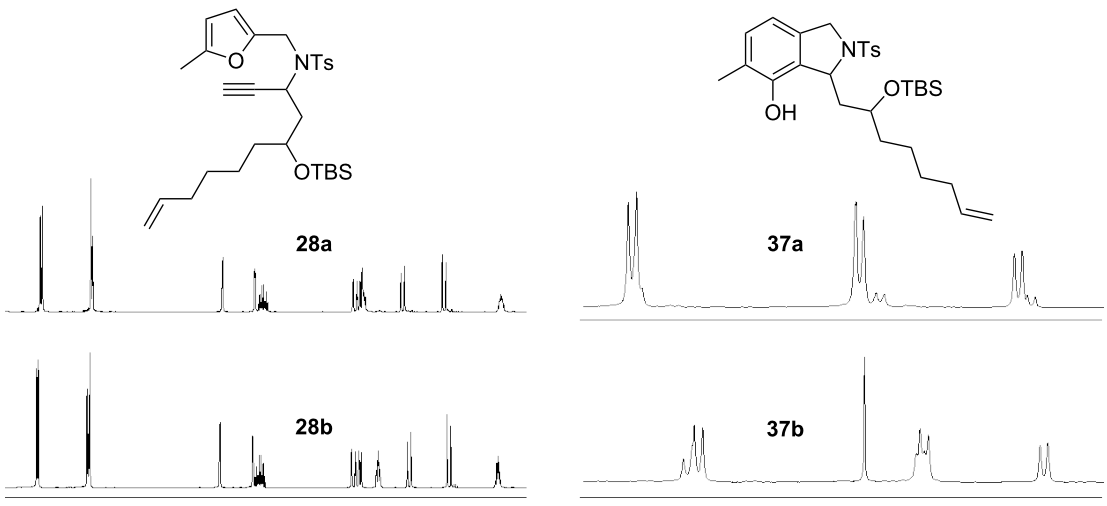
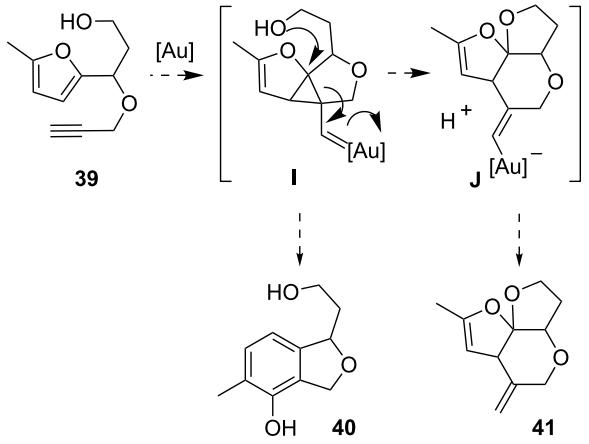
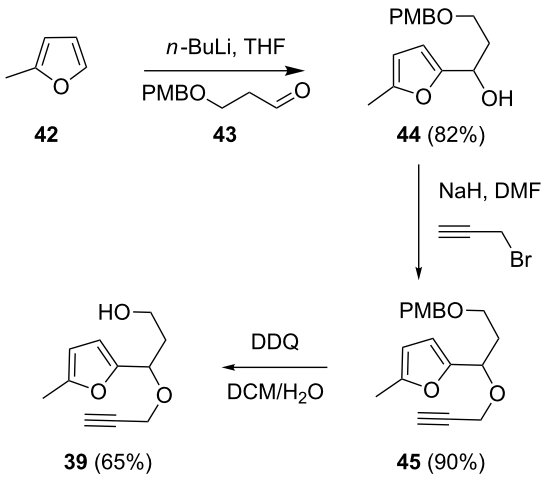


Figure 4: ^{1}H NMR spectra of the separated diastereoisomers of the substrates for catalysis **28** (left) and of the products **37** (right, the small signals are due to the deprotected compounds **38**).



Scheme 10: Potential products of an intramolecular trapping experiment with substrate **39**.

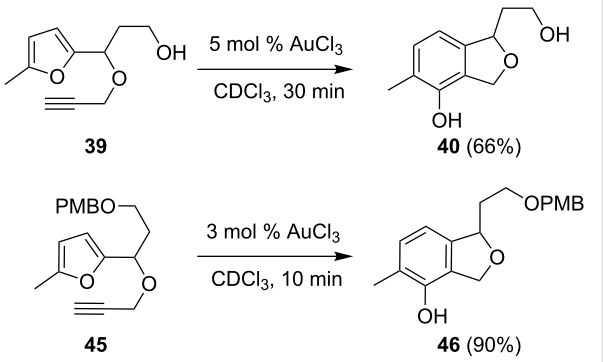


Scheme 11: Synthesis of the substrate **39**.

The conversion of **39**, catalyzed by $AuCl_3$ in $CDCl_3$, again only produced the expected phenol **40** (Scheme 12). Not unexpectedly, the PMB-protected alcohol **45** was similarly converted to **46**. $PtCl_2$ did not lead to a change in selectivity.

Conclusion

The complete failure of both the inter- and the intramolecular trapping experiments shows that the gold-catalyzed phenol synthesis follows a reaction pathway low in energy. These observations also nicely explain the high functional group tolerance, for example, towards olefins and alcohols.



Scheme 12: With substrate **39** and **45** exclusively the product of the phenol synthesis is obtained.

Supporting Information

Supporting Information File 1

Experimental details and characterization data of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-90-S1.pdf]

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A comparative study of the Au-catalyzed cyclization of hydroxy-substituted allylic alcohols and ethers

Berenger Biannic, Thomas Ghebreghiorgis and Aaron Aponick*

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Address:
Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, FL 32611, U.S.A

Email:
Aaron Aponick* - aponick@chem.ufl.edu

* Corresponding author

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Abstract

The Au(I)-catalyzed cyclization of hydroxyallylic ethers to form tetrahydropyrans is reported. Employing (acetonitrile)[(*o*-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate, the cyclization reactions were complete within minutes to hours, depending on the substrate. The reaction progress was monitored by GC, and comparisons between substrates demonstrate that reactions of allylic alcohols are faster than the corresponding ethers. Additionally, it is reported that Reaxa QuadraPure™ MPA is an efficient scavenging reagent that halts the reaction progress.

Introduction

Saturated oxygen heterocycles are found in a wide variety of biologically interesting and structurally complex natural products [1]. These compounds are typically densely functionalized and contain numerous stereogenic centers. Many challenges for the total synthesis of these molecules revolve around issues of selectivity and can be complicated by the presence of sensitive functional groups. While cyclization reactions of highly elaborated substrates are desirable, mild chemoselective methods are necessary for this endeavor.

Homogeneous gold-catalyzed reactions have emerged as a powerful new methodology for the construction of a diverse array of molecular architectures; for recent reviews on Au-catalysis, see [2-10]. Generally, only mild conditions are necessary and these processes are highly chemoselective. While the typical substrates employed in these reactions effect transformations on alkyne, allene, and alkene moieties, recent reports from our laboratory and others have demonstrated that unsaturated alcohols, such as allylic and propargylic alcohols, are reactive substrates that readily participate in dehydrative formal S_N2' reactions [11-25]. The formation of tetrahydropyrans is easily accomplished with monoallylic diol substrates, as illustrated in Scheme 1 [23-25]. The reactions are generally rapid and high yielding with low catalyst loading and can be carried out at low reaction temperatures. Additionally, they are stereospecific, as changing the olefin geometry provides enantiomeric products

(Scheme 1, reaction 1 versus reaction 2) [25], and they are also tolerant of highly substituted substrates (Scheme 1, reaction 3) [23].

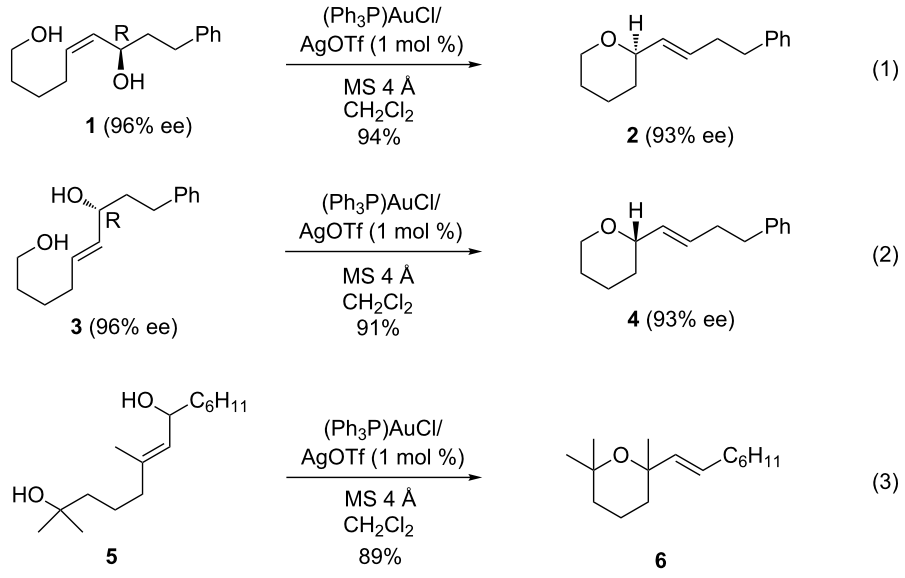
Although these features are attractive from a synthetic point of view, one potential disadvantage is that both the nucleophile and electrophile are alcohols that may require the introduction and cleavage of protecting groups in the preparation of more complex substrates. In the course of a synthetic project, we required a monoallylic diol but encountered difficulty due to an errant protecting group scheme. It was surmised that the problem would be solved if the allylic alcohol leaving group did not need to be revealed directly before the cyclization event. This led us to consider the use of alternative substrates where the allylic alcohol could be deprotected under the reaction conditions, or the use of other "protecting groups" that would also serve as leaving groups and obviate the need for a separate deprotection step. We reasoned that the best group to introduce would be one that was not susceptible to cleavage by standard deprotection conditions and therefore would only be removed after the desired cyclization reaction. Since alcohols are usually very poor leaving groups, but function extremely well in the present system, it seemed likely that a fairly robust group could perform satisfactorily here. Additionally, calculations suggest that in intermolecular hydroalkoxylation reactions of allenes the kinetic allylic ether products are isomerized by Au(I)-NHC complexes to the regioisomeric thermodynamic (and observed) products [26]. Successful implementation of such a strategy would offer an alternative to the use of the highly successful and well-established set of leaving groups employed in π-allyl-metal chemistry [27-32]. Herein we report a study of Au-catalyzed cyclizations with different leaving groups that do not require deprotection, and data on the reaction progress that allows comparison between leaving groups and *cis*- versus *trans*-olefins.

Results and Discussion

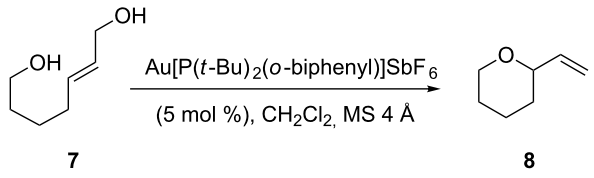
At the outset, one of the important goals was to be able to make comparisons between how well different substrates function in the reaction. Previous papers detail the results with diols and include a variety of substrates with yields and reaction times [23-25]. While the isolated yield is the ultimate measure of how well the system has performed, these data do not provide sufficient details to compare accurately between different classes of substrates. We also sought to gain more insight into how fast the reaction proceeds and to be able to comment on catalyst lifetime.

To be consistent, we chose to study the simple system shown in Scheme 2 and to vary the nature of the allylic leaving group and olefin geometry. These conditions are slightly different to those employed in the study of diols [23-25], differing in catalyst identity and loading (1 mol % $(Ph_3P)AuCl/AgOTf$ versus 5 mol % $Au[P(t\text{-}Bu)_2(o\text{-biphenyl})]SbF_6$).

As mentioned above, the ability to follow the reaction progress was desired but this presented several practical challenges. As the reactions are often complete within minutes, a continuous method of analysis would be necessary, or alternatively samples could be collected over the course of the reaction with analysis to follow. Initial experiments focused on using ^1H NMR, but this raised concerns due to the heterogeneous nature of the reac-



Scheme 1: Au-catalyzed cyclization reactions of monoallylic diols.



Scheme 2: Reaction conditions for the preparation of **8**.

tion mixture, which contained molecular sieves to absorb the water that was generated. Analysis by GC with decane as an internal standard was then explored. A standard curve was prepared with **8**, but, due to the fact that Au-complexes are fairly stable in air and moisture, a quenching method was needed to obtain accurate results. In a typical experiment, the reaction is generally filtered through a short plug of silica, but for small aliquots (25 μL) this was not practical. Instead the resin bound scavenging agent QuadraPure™ MPA **9** (Figure 1) was employed.

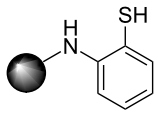


Figure 1: QuadraPure™ MPA.

To the best of our knowledge, scavenging reagents such as this have not previously been employed in homogeneous Au-catalysis and it was necessary to validate this method. In a typical reaction, the goal was to quench aliquots by injecting them into vials containing **9** suspended in CH_2Cl_2. For a detailed protocol see the Supporting Information File 1. As a test, samples were continually taken from the reaction illustrated in Scheme 2 and treated with **9** until TLC analysis indicated that the reaction was complete. GC analysis of the samples provided the data used to construct the black curve shown in Figure 2, which shows the expected behavior and was reproducible. As a control experiment, a sample taken after 3 minutes was diluted with CH_2Cl_2, but not exposed to the resin. After 16 h, the reaction had proceeded to 95% conversion demonstrating that **9** is necessary to halt the progress of the reaction. The precision of the analysis also warrants comment. At several points throughout the reaction, the same sample was analyzed 5 times. In each of these sample sets, the range of percent conversion spanned approximately 2%. The standard deviation from the mean was 0.92%.

Figure 2 also demonstrates that the reactions can be quenched with QuadraPure™ MPA. The curves in red, green, and blue show the results of reactions that were quenched after 1, 3, and

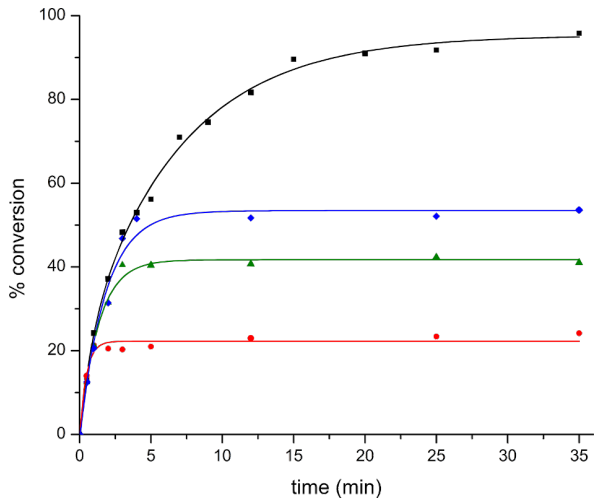


Figure 2: Quenching experiments using **9**. ● = quenched after 1 min; ▲ = quenched after 3 min; ◆ = quenched after 5 min.

5 minutes, respectively. The reaction conditions were otherwise identical to the reaction shown in black, which proceeded to 96% conversion, while the reactions quenched at 1, 3, and 5 minutes went to 23%, 41%, and 52% conversion, respectively.

Subsequently, a comparison between *cis*- and *trans*-diols **10** and **7** was made. As can be seen in Figure 3, both reactions were fairly rapid, with the *cis*-diol **10** being only slightly faster in the

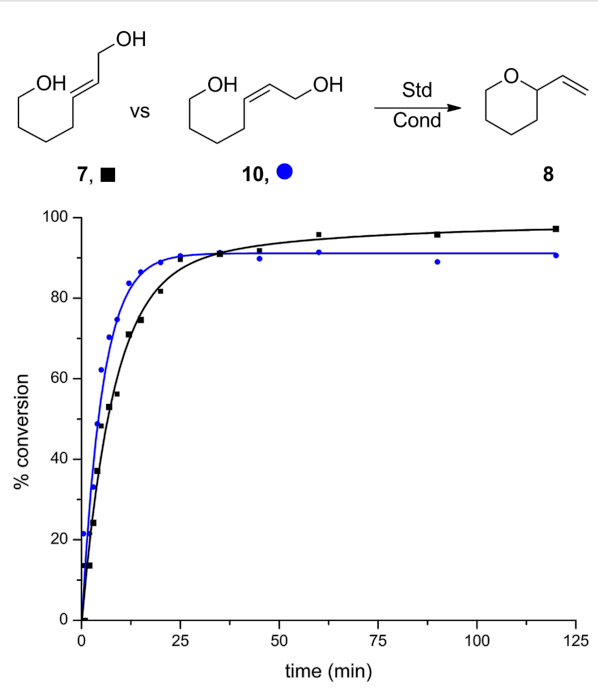


Figure 3: Reaction progress in *cis*- and *trans*-diols. Conditions: 5 mol % Au[P(*t*-Bu)$_2$(*o*-biphenyl)]SbF$_6$, CH_2Cl_2, MS 4 Å.

initial period than **7**. Interestingly, the reaction of **7** achieves higher conversion overall, but both substrates have >90% conversion after 25 minutes.

The methyl ethers **11** and **12** were explored and proved to be suitable substrates (Figure 4). While these reactions were slightly slower in the initial stages than the corresponding diols, excellent conversions were achieved. This demonstrates that methyl ethers fit the criteria described above. The methyl group efficiently shields this functional group under a variety of commonly used conditions and it can then act as a leaving group under Au-catalyzed cyclization conditions.

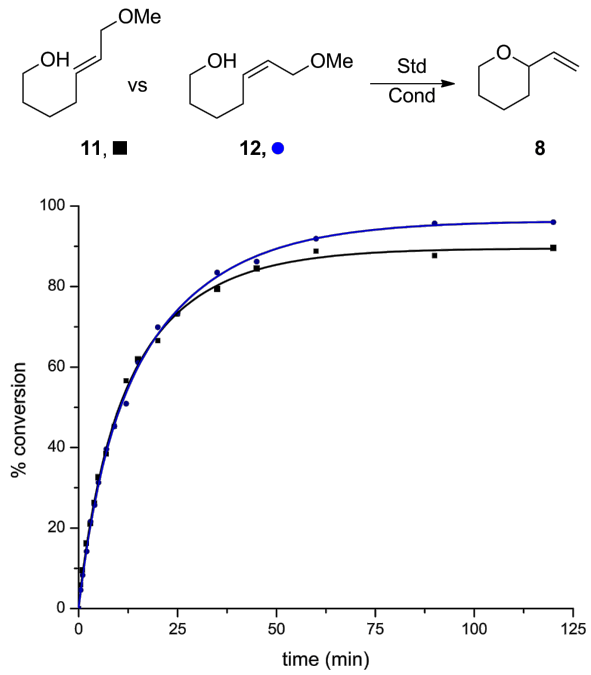


Figure 4: Reaction progress in *cis*- and *trans*-methyl ethers. Conditions: 5 mol % Au[P(*t*-Bu)$_2$(*o*-biphenyl)]SbF$_6$, CH_2Cl_2, MS 4 Å.

Several additional, commonly used, protecting groups were also screened under the reaction conditions (Figure 5). From the graph, it is apparent that benzyl (**13**), TBDPS (**14**), and THP [33] (**15**) could all be used, but esters such as benzoyl (**16**) were unsuitable. This may provide a basis for chemoselective transformations, as allyl esters are readily ionized by Pd^0 complexes and the resulting π-allylpalladium species are alkylated by a variety of nucleophiles [27,28].

Finally, 1° allylic and 2° allylic ether substrates were compared (Figure 6). Substitution at the allylic position drastically slows the reaction. Although the conversion of **17** and **18** is low on the timescale shown, the reactions continue and after 48 h provide acceptable, but moderate yields. The corresponding *trans*- and

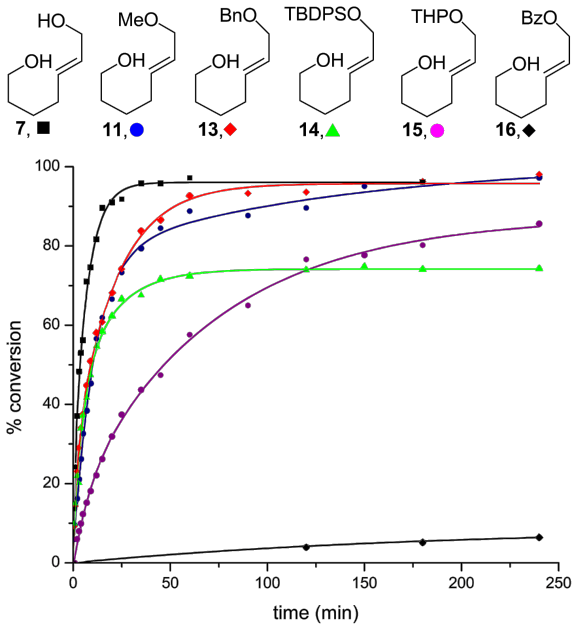


Figure 5: A comparison of commonly used protecting groups. Conditions: 5 mol % Au[P(*t*-Bu)$_2$(*o*-biphenyl)]SbF$_6$, CH_2Cl_2, MS 4 Å.

cis-cyclohexyl-substituted diols (not shown) provide the products in 96% and 92% isolated yields after 40 minutes, respectively [23-25]. While cyclohexyl substituents significantly slow the reaction, it is likely that other less sterically demanding substituents will be better tolerated. This is currently under investigation with more synthetically useful substrates.

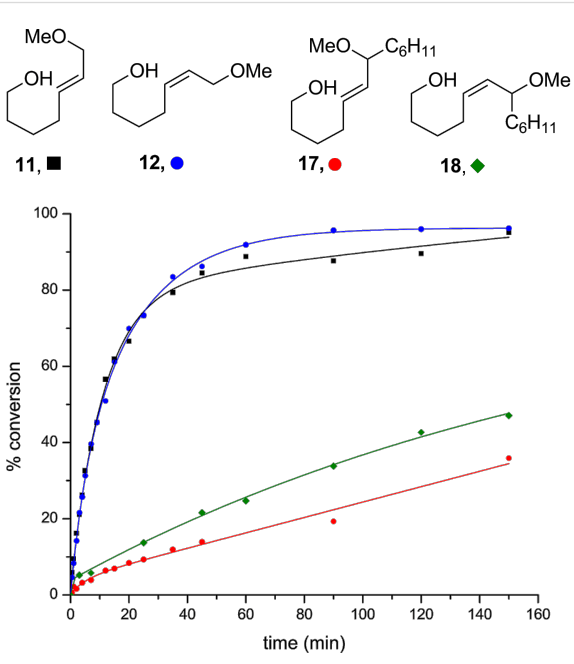


Figure 6: Comparison of 1° and 2° allylic ethers. Conditions: 5 mol % Au[P(*t*-Bu)$_2$(*o*-biphenyl)]SbF$_6$, CH_2Cl_2, MS 4 Å.

Conclusion

In conclusion, it has been demonstrated that a variety of allylic ethers undergo Au-catalyzed formal S_N2' reactions to form tetrahydropyrans. The reaction of allylic alcohols appears to be faster, although the leaving group is traditionally not considered to be as good. Reactions of *cis*-substrates appear to be slightly faster than the corresponding *trans*-allylic ethers. While the difference is small, it suggests that it is better to prepare the *cis*-substrates, and this is also very straightforward via a number of different routes. Further studies on secondary allylic ethers and on the application of the method in total synthesis are ongoing and will be reported in due course.

Supporting Information

Supporting Information File 1

General procedures and characterization data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-91-S1.pdf]

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Au(I)/Au(III)-catalyzed Sonogashira-type reactions of functionalized terminal alkynes with arylboronic acids under mild conditions

Deyun Qian[1] and Junliang Zhang[*1,2]

Full Research Paper

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Address:
[1]Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 N, Zhongshan Road, Shanghai 200062 (P. R. China) and [2]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Ling Ling Road 345 Shanghai 200032 (P. R. China)

Email:
Deyun Qian - 51100606057@ecnu.cn; Junliang Zhang[*] - jlzhang@chem.ecnu.edu.cn

* Corresponding author

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Abstract

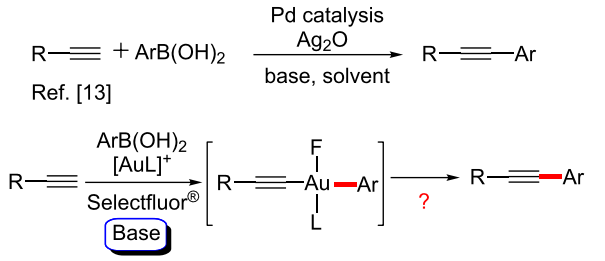
A straightforward, efficient, and reliable redox catalyst system for the Au(I)/Au(III)-catalyzed Sonogashira cross-coupling reaction of functionalized terminal alkynes with arylboronic acids under mild conditions has been developed.

Introduction

The Sonogashira reaction has become the most important and widely used method for the synthesis of arylalkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals and other materials [1-3]. In the past decade, considerable efforts have been made to enhance the efficiency and generality of this reaction. All kinds of palladium catalyst systems [4-10] and other metal catalyst systems [3] have been developed for facilitating the Sonogashira cross-coupling, as well as expanding the substrate scope [11-14]. Various examples have recently been reported for the palladium-catalyzed Sonagashira-type cross-coupling of terminal alkynes with arylboronic acids [13], and the Pd(0)/Pd(II) catalytic cycles have been well studied. Nevertheless, this transformation catalyzed by gold, involving Au(I)/Au(III) catalytic cycles has, as yet, been less explored [15-22]. In the few examples already documented some conditions, such as rather high reaction temperatures (130 °C), high catalysis loading or special reagents were required [23]. Herein, we report a straightforward, efficient and

robust catalyst system for the Sonogashira-type cross-coupling, in which Au(I)/Au(III) catalyzed C_{sp}^2–C_{sp} bond formation of terminal alkynes from arylboronic acids under mild conditions.

By analogy with other d^{10} species, Au(I) has the same electronic structure as Pd(0) and can easily interact with the acetylenic group, and has the ability to undergo the Au(I)/Au(III) redox cycles [24,25]. In addition, with an increasing interest in the chemistry of gold(I) and gold(III) compounds, more and more studies have provided strong evidence for the existence of Au(I)/Au(III) catalytic cycles [26-32]. For instance, Zhang and co-workers have developed a gold-catalyzed oxidative cross-coupling reaction of arylboronic acids with propargyl esters [27], and Selectfluor® – a source of electrophilic fluorine – was used to oxidize the resulting Au(I) intermediate to Au(III) species. Recently, Toste reported the first experimental evidence for alkylgold(III) fluorides undergoing C–C bond forming reactions with arylboronic acids [32]. Inspired by these results, we envisioned that terminal alkynes would react with arylboronic acids in the presence of oxidant (Selectfluor®) and base, and undergo a Au(I)/Au(III)-catalyzed Sonogashira-type cross-coupling reaction (Scheme 1).

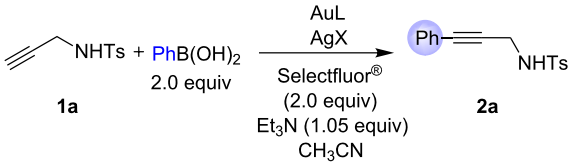


Scheme 1: Previous work and our projected gold-catalyzed Sonogashira-type cross-coupling.

Results and Discussion

We embarked on developing a general protocol for Sonogashira-type cross-coupling by using propargyl tosylamide (**1a**) and phenylboronic acid as the model substrates because of their stability, availability, and broad spectrum of nucleophilicity (Table 1). With commercially available Ph_3PAuCl as the catalyst, we treated **1a** and phenylboronic acid in CH_3CN at room temperature for 18 h (Table 1, entry 1). Disappointedly, only trace amounts of product was observed under the above conditions. Taking into account the counter ion effects in gold-catalyzed reactions [33-35], $Ph_3PAuOTf$, produced from a combination of Ph_3PAuCl and AgOTf in a 1:1 ratio, was investigated. To our delight, the expected product **2a** could be isolated in 56% yield (Table 1, entry 2). Moreover, a control experiment was carried out to determine whether AgOTf by itself could catalyze this transformation. However, no **2a** was

Table 1: Initial screenings of Au(I)/Au(III)-catalyzed Sonogashira coupling[a].



Entry	AuL (5 mol %)	AgX (mol %)	Time (h)	Yield (%)[b]
1	Ph_3PAuCl	—	18	trace
2	Ph_3PAuCl	AgOTf (5)	22	56
3	—	AgOTf (5)	24	0
4	AuCl	AgOTf (5)	24	21
5	$AuCl_3$	AgOTf (15)	24	37[c]
6[d]	Ph_3PAuCl	AgOTf (5)	22	0
7[e]	Ph_3PAuCl	AgOTf (5)	22	41
8	Ph_3PAuCl	$AgBF_4$ (5)	10	65
9	Ph_3PAuCl	$AgSbF_4$(5)	10	62
10	(XPhos)AuCl	AgOTf (5)	24	0
11[f]	dppm$(AuCl)_2$	AgOTf (5)	16	83[c]
12[f]	dppm$(AuBr)_2$	—	16	trace
13[f,g]	Ph_3PAuCl	AgOTf (5)	12	72 (73[c])
14[f]	Ph_3PAuCl	$AgBF_4$ (5)	12	75 (80[c])

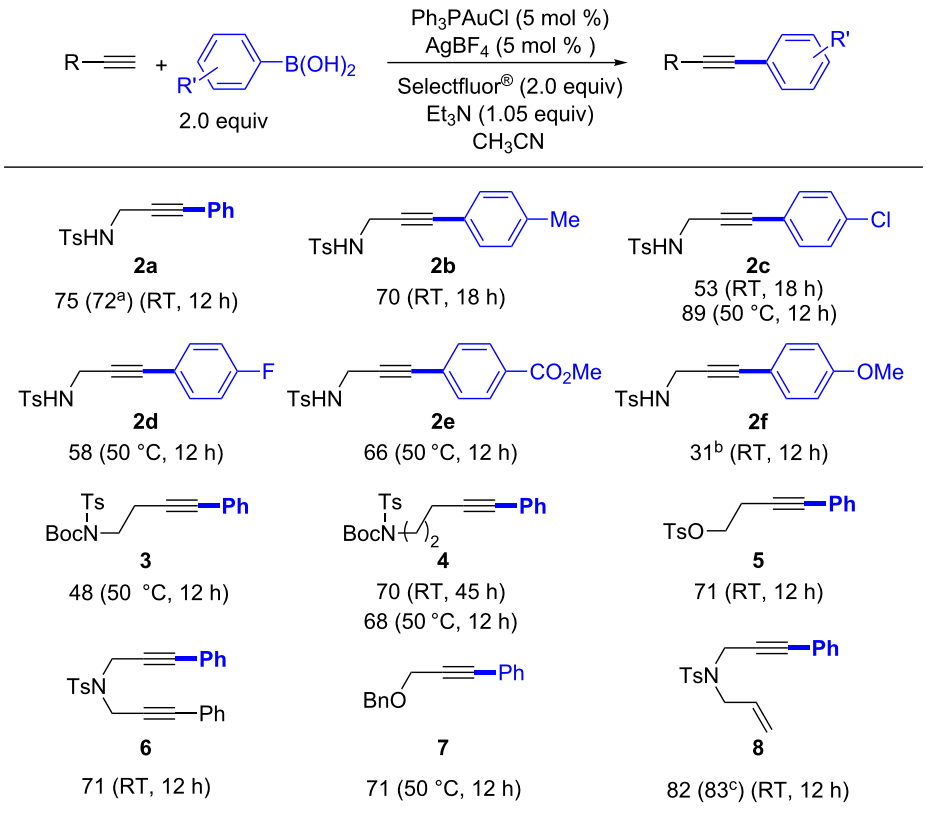
[a]Reaction conditions: The reaction was carried out by using **1a** (0.4 mmol) and phenylboronic acid (0.8 mmol, 2.0 equiv), and 1.05 equiv of Et_3N in 2 mL of CH_3CN stirred at room temperature. [b]Isolated yields. [c]Yield determined by ^1H NMR with dibromomethane as an internal standard. [d]Selectfluor® (0 equiv). [e]$PhB(OH)_2$ (1.5 equiv). [f]Under an atmosphere of nitrogen (N_2). [g]The reaction temperature was 50 °C.

produced in the absence of Ph_3PAuCl (Table 1, entry 3). Without the phosphine ligand, both AuCl/AgOTf or $AuCl_3$/AgOTf could catalyze this reaction, but the efficiency was quite low (Table 1, entries 4, 5). Without Selectfluor® as additive, the cross-coupling reaction did not occur (Table 1, entry 6), indicating that it was crucial for this transformation via oxidation of gold(I) to the gold(III) species [26-32]. Reducing the amount of phenylboronic acid resulted in a lower yield (Table 1, entry 7). The counter ion effect was then examined on cross-coupling reaction by variation of the silver salts. Alternative catalyst systems led to better yields (Table 1, entries 8, 9 and notably 11 vs entry 2). To optimize the reaction conditions, commonly employed well recognized and commercially available phosphine ligands [17,18], such as dppm, dppe, dppp, dppf, and XPhos, were screened to test the feasibility of this gold-catalyzed cross-coupling (Table 1, entries 10–12, see also Supporting Information File 1). In addition, a series of inorganic and organic bases was also investigated: K_2CO_3, K_3PO_4, $K_3PO_4{\cdot}3H_2O$, $NaHCO_3$, NaOAc were substantially less effective, whilst organic bases such as iPr_2NH, Et_2NH, TMEDA, Bu_3N, $PhNMe_2$ were not effective bases in this catalytic system (see Supporting Information File 1). These results indicated that Et_3N might also play an

important role in this process. Furthermore, it was also found that neither slow addition nor a significant excess of alkyne was required to obtain selective and almost quantitative conversion (see Supporting Information File 1). When the reaction was carried out under an atmosphere of nitrogen (N_2) there was a 10% increase in yield (Table 1, entry 8 vs 14). Although the conditions (Table 1, entry 11) seemed the best, this was not the general case for other substrates. Therefore, the optimum conditions were chosen as $Ph_3PAuCl/AgBF_4$ as the catalyst, Et_3N as the base and under an atmosphere of nitrogen (Table 1, entry 14) .

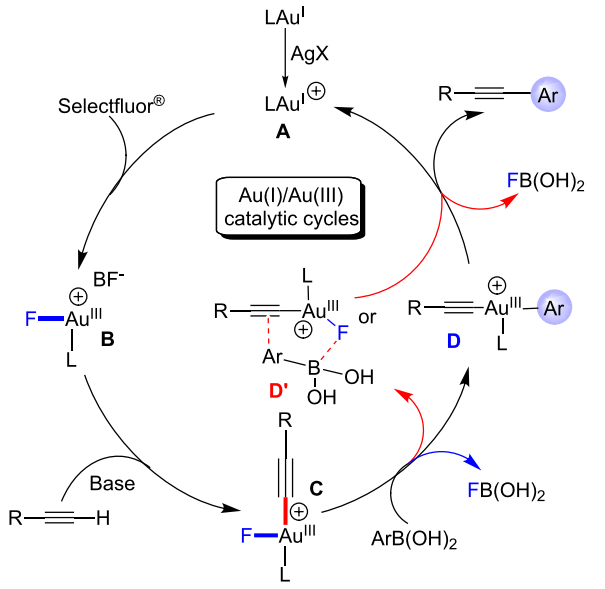
By using the above optimized conditions, the reaction scope was next studied by varying arylboronic acids. As shown in Scheme 2, functional groups including methyl, chloro, fluoro and ester in the para positions of the phenyl ring were tolerated. Reduced yields were observed with both electron-rich and electron-poor coupling partners (Scheme 2, **2a**–**f**). Arylboronic acids with electron-withdrawing groups afforded **2c**–**2e** in moderate to good yields. Notably, the slightly electron-deficient 4-chlorophenylboronic acid gave the best yield. On the other hand, the more electron-rich 4-methoxyphenylboronic acid produced the lowest yield, likely due to a competing oxidation of the boronic acid by Selectfluor® [27,30]. Gratifyingly, a number of potentially reactive functionalities, such as tertiary amine, 4-methylbenzenesulfonate, 1,6-enyne and 1,6-diyne, were compatible and remained unaffected, which illustrated the robustness of the catalyst system (Scheme 2, **3**–**8**).

On the basis of these results, a plausible mechanism is outlined in Scheme 3. Initially, unlike traditional C–X oxidative addition as shown by Pd in cross-coupling reactions, the active cationic gold(I) species **A** is oxidized by Selectfluor® to give a gold(III) species **B** [26-32,36]. With the aid of base, the reaction between **B** and alkyne affords intermediate **C**. The weak Au–F bond and the strong B–F bond drive the trans-metalation to produce intermediate **D** [29,36,37]. Finally, **D** undergoes reductive elimination to give the desired product and gold(I) species **A**. In addition, **C** also could experience a five-centered transition state **D'**, which leads to the C–C bond-forming reaction through a bimolecular reductive elimination [30-32]. Notably, we believed that the key step of this mechanism is the generation of cationic gold species **B** by Selectfluor®. In the absence of Selectfluor®, no coupling is possible (Table 1, entry



Scheme 2: Scope of the Sonogashira-type cross-coupling reaction (isolated yield). [a]AgOTf in place of $AgBF_4$. [b]Yield determined by ^1H NMR, the prouduct could not be separated from the unreacted starting material. [c]AgOTf in place of $AgBF_4$, RT, 36 h.

6). In a current study, Xu and co-workers have provided strong evidence for the oxidation of Au(I) to Au(III) by Selectfluor® in their XPS measurements [36].



Scheme 3: Proposed mechanism for the Au(I)/Au(III)-catalyzed Sonogashira-type cross-coupling.

Conclusion

In conclusion, we have developed an unprecedented Au(I)/Au(III)-catalyzed Sonogashira-type cross-coupling reaction of terminal alkynes and arylboronic acids under mild conditions. Selectfluor® and counter ion effects play a significant role in the development of an exceptionally mild catalyst system. This chemistry strongly suggests the feasibility of Au(I) and Au(III) catalytic redox cycles, which would substantially broaden the field of gold catalysis and offer more functionalized products. Furthermore, the good tolerance toward many functional groups of substrates considerably extends the scope of a number of organic transformations and performs modular $C_{sp}{}^2$–C_{sp} bond constructions at appropriate stages in the whole synthetic sequence.

Supporting Information

Supporting information features experimental procedure and spectroscopic data.

Supporting Information File 1

Experimental details and spectra of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-92-S1.pdf]

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Isotopic labelling studies for a gold-catalysed skeletal rearrangement of alkynyl aziridines

Paul W. Davies*, Nicolas Martin and Neil Spencer

Full Research Paper

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Address:
School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom

Email:
Paul W. Davies* - p.w.davies@bham.ac.uk

* Corresponding author

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Abstract

Isotopic labelling studies were performed to probe a proposed 1,2-aryl shift in the gold-catalysed cycloisomerisation of alkynyl aziridines into 2,4-disubstituted pyrroles. Two isotopomers of the expected skeletal rearrangement product were identified using ^{13}C-labelling and led to a revised mechanism featuring two distinct skeletal rearrangements. The mechanistic proposal has been rationalised against the reaction of a range of ^{13}C- and deuterium-labelled substrates.

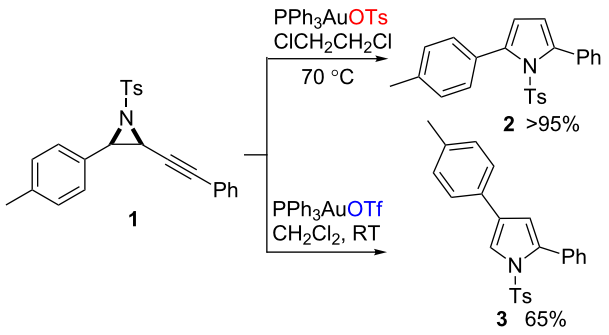
Introduction

Gold-catalysed cycloisomerisation reactions have emerged as powerful methods to construct a diverse array of hetero- and carbocyclic motifs under generally mild reaction conditions using straightforward preparative procedures [1-9]. Many such processes also incorporate a rearrangement of the hydrocarbon skeleton present in the starting material, which can lead to unexpected and synthetically interesting outcomes [10,11].

One of the most common fundamental steps in these skeletal rearrangements involves C–C bond fission through 1,2-migration. This step is triggered by the generation of carbocationic character, which is generally stabilised in some form, either by an adjacent gold atom or through extended delocalisation. While 1,2-alkyl migrations are well-established in gold-catalysed heterocyclic synthesis [12,13], 1,2-aryl shifts are much less common [14-17].

In relation to these processes, we recently reported the gold-catalysed reactions of aryl substituted alkynyl aziridines, such as **1**. Careful choice of reaction conditions resulted in selective cycloisomerisation to produce either the 2,5-disubstituted pyrrole **2** or the skeletally rearranged 2,4-disubstituted pyrrole **3** (Scheme 1) [18].

The nature of both the solvent, and the counter ion to the cationic gold catalyst, proved crucial to the reaction outcome:



Scheme 1: Gold-catalysed cycloisomerisations of aryl–alkynyl aziridine to pyrroles.

2,4-Disubstituted pyrroles were only observed in appreciable quantities when the reaction was performed with a non basic solvent and counter ion combination that allows for formation of a separated ion pair, such as dichloromethane and triflate (Scheme 1). This selectivity was switched and the 2,5-disubstituted products could be achieved in quantitative yields when the counter ion was the more basic tosylate [19]. Alternatively, the use of protic, ethereal or aromatic solvents favoured the formation of the 2,5-disubstituted products regardless of the counter ion. Similar solvent regimes were employed in other reports into π-acid promoted alkynyl aziridine cycloisomerisations without skeletal rearrangement [20-23].

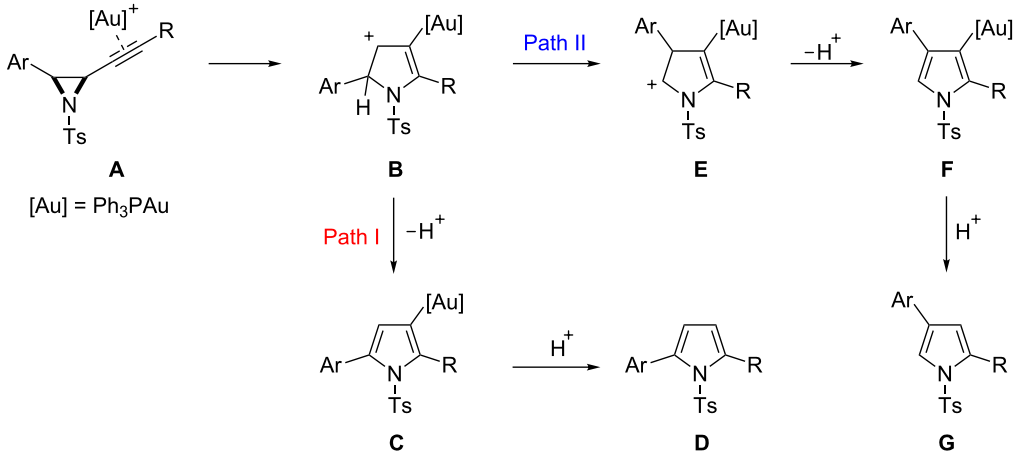
Our working mechanism to explain this reaction divergence centred on the electrophilic activation of the alkyne in **A** triggering a ring-expansion to a common intermediate **B** from which both isomeric products **D** and **G** evolved (Scheme 2). Path I follows proton elimination (**B**→**C**) and subsequent protodemetallation to give 2,5-disubstituted pyrrole **D**, in keeping with a previously reported furan synthesis [24,25]. The 2,4-disubstituted skeletal rearrangement product **G** was rationalised through Path II, where a 1,2-aryl shift (**B**→**E**) precedes proton elimination (**E**→**F**) and protodemetallation. The observed solvent and counter ion effects could be rationalised by considering that the 1,2-aryl shift at **B** is disfavoured relative to proton elimination as its cationic character is diminished, either by solvent stabilisation or the formation of a closer contact ion pair, and/or by more basic solvents/counter ions assisting proton elimination [18,26,27].

However, for the proposed skeletal rearrangement mechanism to be valid, gold bound carbocation **B** must be prone to undergo a relatively rare 1,2-aryl shift in preference to either proton elimination or a 1,2-hydride shift. We therefore sought to validate this proposal experimentally by isotopic labelling.

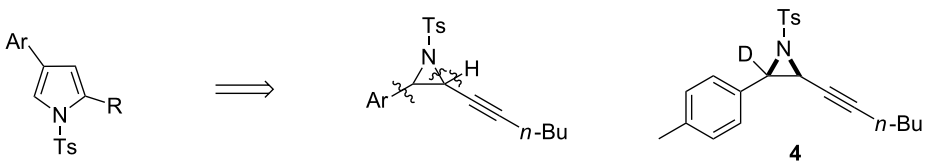
Results and Discussion

A deuterium labelled precursor

Alkynyl aziridine **4** was selected as the initial probe for the mechanism which requires fission of three bonds: The propargylic C–N bond in ring expansion; the aryl–aziridinyl C–C bond in the 1,2 shift and the propargylic C–H bond for aromatisation (Scheme 3). The positioning of a deuterium atom at the benzylic carbon in **4** enables the carbons of the aziridine ring to be distinguished and labels the carbon from which the aryl shift would occur. The tolyl and butyl groups were selected as substituents in place of other aromatic units to aid analysis by simplifying the key aromatic region in the resulting NMR spectra.



Scheme 2: Working mechanism to rationalise the formation of two regiosomeric pyrroles in the gold catalysed cycloisomerisation of alkynyl aziridines.



Scheme 3: Bond fissions featured in the proposed mechanistic hypothesis and the initial mechanism probe.

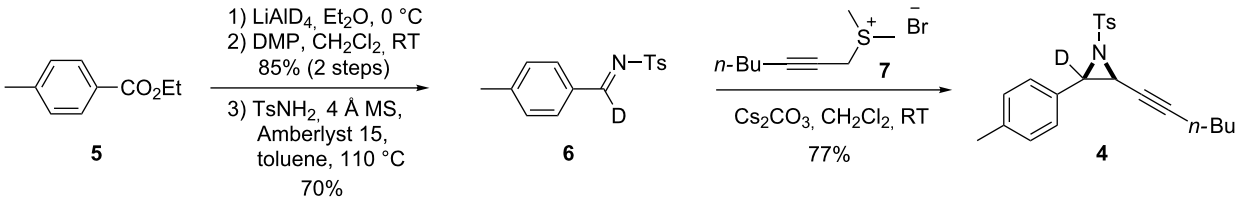
Deuterated aziridine **4** was prepared in four steps from ester **5** (Scheme 4). Reduction using lithium aluminium deuteride led to the insertion of the label at the benzylic position. Oxidation to the aldehyde followed by condensation with tosylamide afforded the deuterated imine **6**. Aziridination using the sulfonium ylide generated in situ from **7** proceeded smoothly to afford the desired cycloisomerisation precursor **4** [28]. The aziridines were formed as a mixture of diastereomers, with the *cis* diastereomer predominating, and were employed as such in the cycloisomerisation reactions.

Deuterated aziridine **4** was reacted under the standard conditions for skeletal rearrangement (5 mol % of $Ph_3PAuOTf$ generated in situ in CH_2Cl_2), to give a mixture of 2,4- and 2,5-pyrrole isomers **8c** and **9** alongside the main product, 3-deutero-2,4-disubstituted pyrrole **8b** (Scheme 5). Isomer **8a**, which was predicted as the major product under the proposed mechanism (Scheme 2), could not be indentified from the reaction mixture. Though H/D exchange in pyrroles has been noted in gold-catalysed reactions [13], control reactions had shown that no H/D exchange occurred in this specific system [18,19]. There was also no interconversion between 2,4- and 2,5-isomers under the same reaction conditions [18]. Surprisingly, despite several repetitions and the use of different batches of starting materials, the reaction of **4** was always less clean than its non-deuterated analogue, even when the substrates were tested side-by-side under identical conditions.

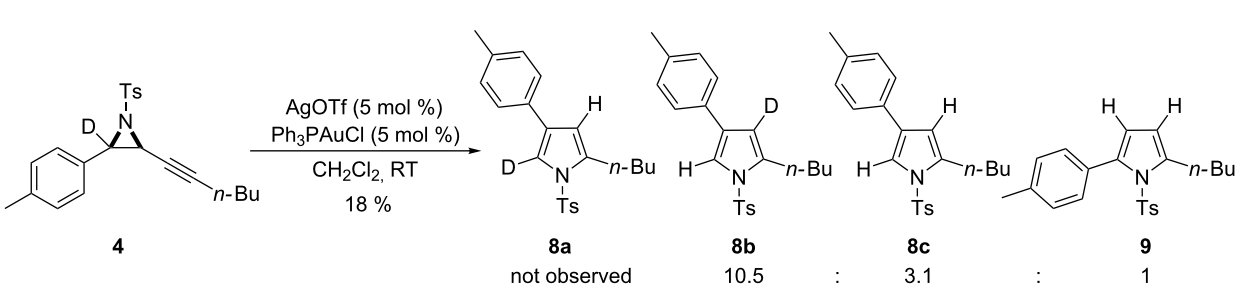
Despite this unexplained difference, the proposed mechanism does not account for the formation of 2,4-disubstituted pyrrole without deuterium incorporation at the C-5 position. More information on whether a 1,2-aryl shift occurs was therefore sought using a non-labile ^{13}C label at the aziridine carbon.

^{13}C labelling studies

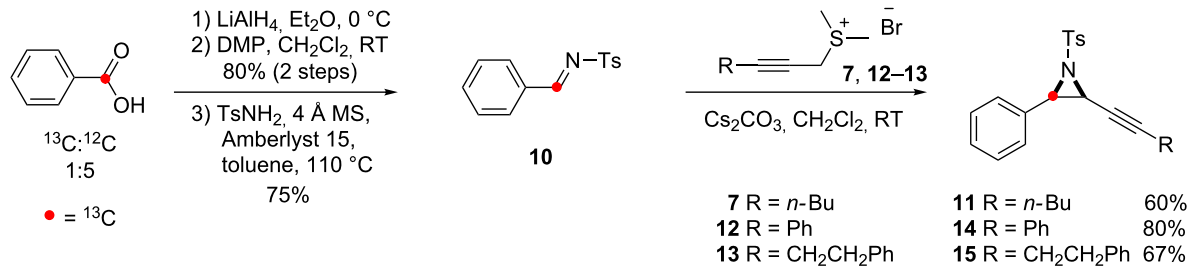
^{13}C-Enriched benzoic acid was converted into imine **10** and subsequently coupled with **7** to give the aziridine **11**, in four steps, as a 1:5 ^{13}C:^{12}C mixture (Scheme 6). Two further ^{13}C-



Scheme 4: Preparation of D-labelled alkynyl aziridine **4**. DMP = Dess–Martin periodinane.



Scheme 5: Reaction of deuterated alkynyl aziridine **4** in the skeletal rearrangement reaction.

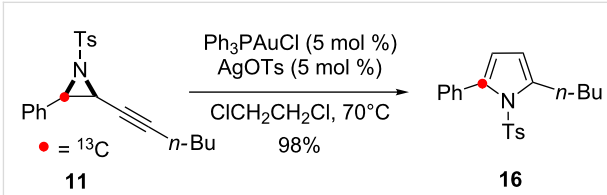


Scheme 6: Preparation of ^{13}C-enriched alkynyl aziridines.

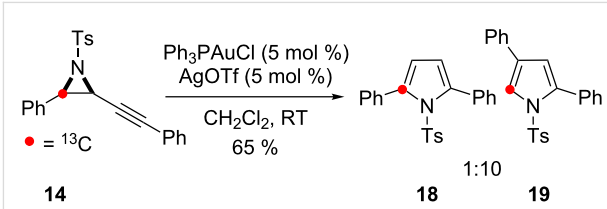
enriched alkynyl aziridines, **14** and **15**, with different substituents on the alkyne, were later prepared using the sulfonium salts **12** and **13**.

On subjecting **11** to the conditions for skeletal rearrangement (Scheme 7), three enhanced resonances were seen in the ^{13}C NMR spectra of the pyrrole products (Supporting Information File 1). One of the enhanced resonances was associated with the minor 2,5-disubstituted isomer **16** showing ^{13}C enrichment at the expected C-2 position (Scheme 2, Path I). This result was confirmed by carrying out the control cycloisomerisation of **11** under the conditions known to give solely 2,5-disubstituted products (Scheme 8) [19]. All other resonances were associated with the 2,4-disubstituted pyrrole **17** and the remaining enhancements were therefore assigned to the unexpected formation of two separate isotopomers of **17**. ^{13}C-enrichment at C-5 (117.7 ppm) corresponds to the isotopomer **17a** anticipated from the proposed 1,2-aryl shift mechanism. Isotopomer **17b** was identified by enrichment at the quaternary C-4 position (127.0 ppm). HMBC experiments confirmed this assignment showing clear ^{3}J coupling between the C-4 ^{13}C-enriched quaternary centre and the protons of the phenyl ring.

Cycloisomerisation of the alkynyl aziridine **14**, which bears a phenyl substituent on the alkyne, resulted in a different outcome under the same reaction conditions: Only a single isotopomer of the 2,4-disubstituted pyrrole **19** was formed with ^{13}C-enrichment at the C-5 position, alongside the 2,5-disubstituted isomer **18** (Scheme 9).



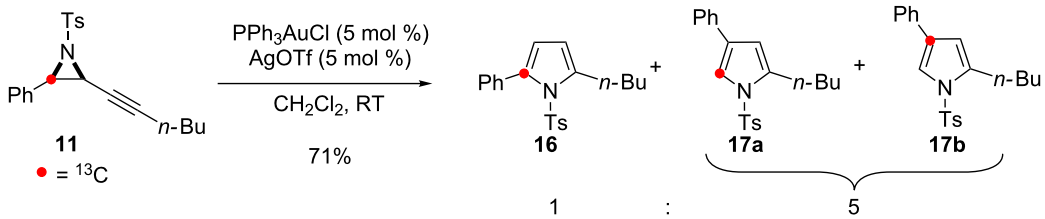
Scheme 8: Cycloisomerisation of **11** to give 2,5-disubstituted pyrrole.



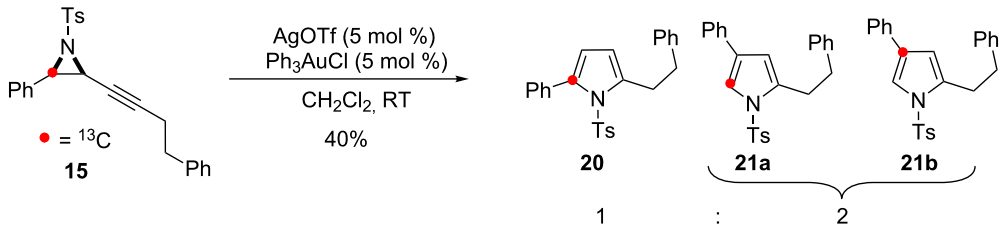
Scheme 9: Cycloisomerisation of **14** in the skeletal rearrangement reaction.

The observed inconsistency between the reactions of **11** and **14** was investigated using alkyl substituted alkynyl aziridine **15**. Cycloisomerisation of **15** once again afforded a mixture of isotopomers of the 2,4-disubstituted pyrrole **21a**/**b** alongside 2,5-disubstituted pyrrole **20** (Scheme 10).

The formation of the isotopomers **17a, 19** and **21a** with ^{13}C-enrichment at C-5 confirms C–C bond fission between the aryl group and the aziridine during the reaction. This outcome is consistent with an operative 1,2-aryl shift in the skeletal



Scheme 7: Cycloisomerisation of **11** in the skeletal rearrangement reaction.



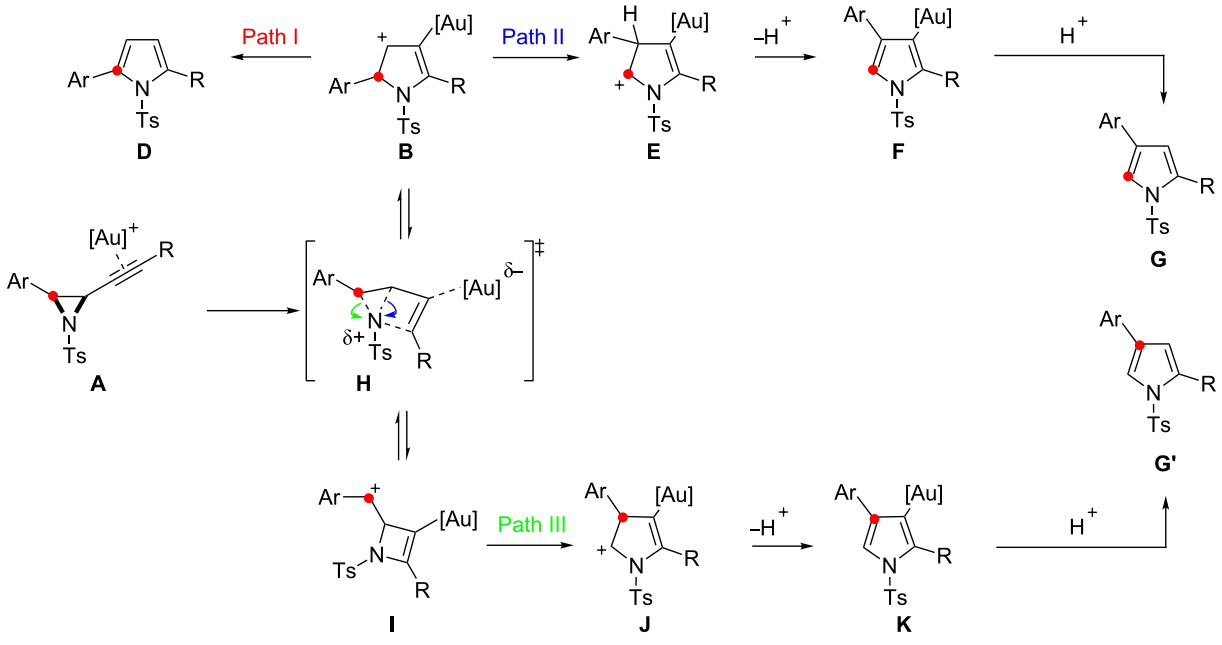
Scheme 10: Cycloisomerisation of **15** in the skeletal rearrangement reaction.

rearrangement of alkynyl aziridines to form 2,4-disubstituted pyrroles (Scheme 2, Path II).

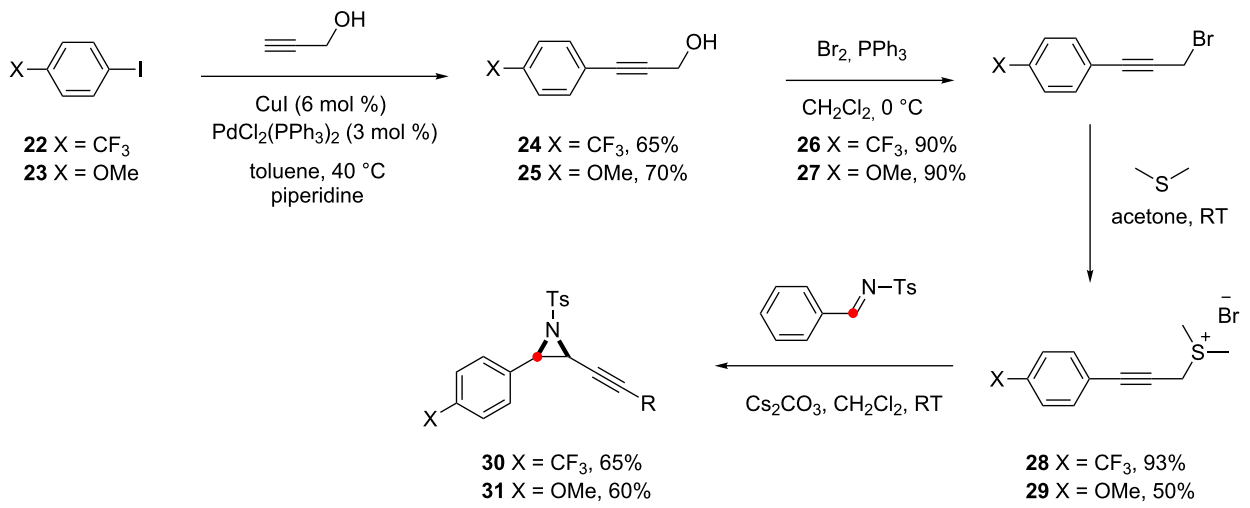
However, the initial use of the alkyl substituted aziridine **11** rather than the aryl-substituted aziridine **14** was fortuitous. A second accessible pathway must exist to account for the formation of the 2,4-disubstituted pyrrole isotopomers **17b**, and **21b** by an alternate skeletal rearrangement.

The mechanistic proposal for the skeletal rearrangement was therefore reappraised to explain these results (Scheme 11). Alongside the ring expansion of metal coordinated alkynyl aziridines to the 5-membered cyclic cation **B**, which leads to isotopomer **G** (Path II) and 2,5-disubstituted pyrroles **D** (Path I), a competing regioisomeric ring-expansion could afford 4-membered ring intermediate **I**. Evolution of **I** by a ring-expanding 1,2-shift of the metal stabilised vinyl unit onto the benzylic cation leads to a new 5-membered cyclic intermediate **J** [29]. Deprotonation and protodemetallation of **J** results in a 2,4-disubstituted isomer **G'** where the ^{13}C-enriched carbon maintains its connectivity to the aryl unit, and C–C bond fission occurs between the aziridine and the alkyne fragment.

The observed effects of the alkyne substituent can be rationalised if the pathway is dependent on the relative stabilisation of the developing positive charge at either carbon of the aziridine by the alkynyl aziridine intermediate **H** (Scheme 11). The formation of either benzylic cation **I** (Path III) or the enamide stabilised cation **B** (Path II), under a cationic ring-expansion manifold, is apparently closely balanced: Products from both pathways are observed for alkyl substituted systems such as **11** and **15**. However, when the alkyne substituent is a phenyl group Path II is favoured over Path III due to the additional stabilisation of **B** by delocalisation through an extended π-system.



Scheme 11: Revised mechanism for the formation of 2,4-isomers by skeletal rearrangement.



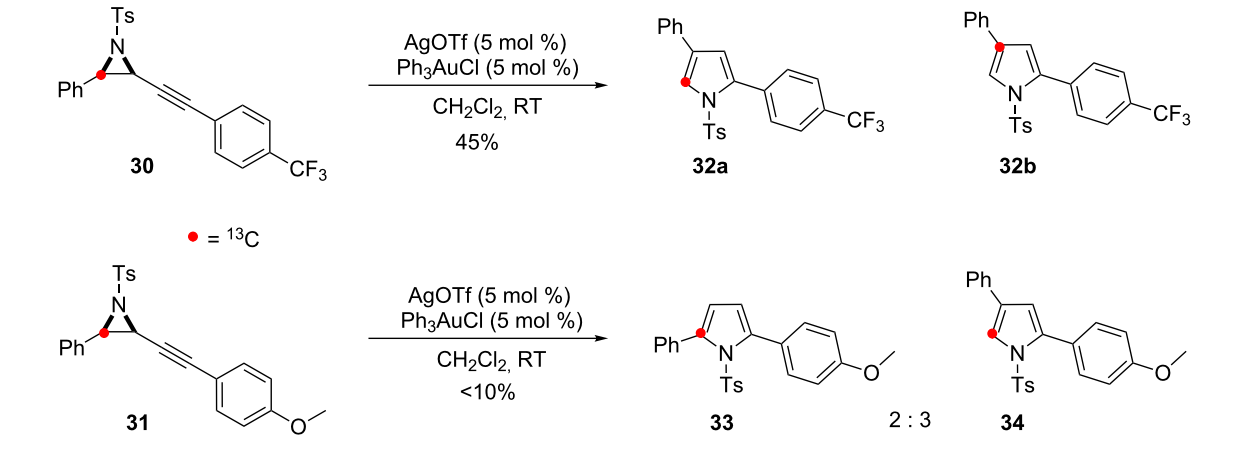
Scheme 12: Synthesis of alkynyl aziridines **30** and **31**.

The initial report showed how the ratio of 2,5- to 2,4-disubstituted pyrroles varied with the electronic properties of the aromatic unit substituent directly attached to the aziridine [18]. While the trend was consistent with that expected for a 1,2-aryl shift, the more complex mechanism also accounts for the observed outcomes. An increasingly electron-rich aryl group will favour both formation of benzylic cation **I** and 1,2-aryl migration from **B**, leading to the same products from each route. Electron-deficient aromatics would have a destabilising effect on the formation of **I** and also be less prone to undergo 1,2-aryl shift from **B** thus favouring Path I and formation of the 2,5-disubstituted pyrroles.

Two further ^{13}C labelled compounds were prepared to test this rationalisation by predictably affecting the relative stability of just one of the key intermediates: An electron-deficient aromatic substituent to the alkyne (R = *p*-$C_6H_4CF_3$) should disfavour Path II by destabilising **B** over **I**, whereas an electron-rich aromatic substituent on the alkyne (R = *p*-C_6H_4OMe) should favour Path II by further stabilising **B**.

The substrates were prepared by Sonogashira reaction between propargyl alcohol and the appropriately substituted iodobenzene substrate **22**, **23** (Scheme 12). Functional group interconversion of the alcohols by bromination and substitution results in the sulfonium salts **28**, **29** which were reacted with ^{13}C labelled imine **10** to yield the desired alkynyl aziridines **30** and **31**.

The anticipated outcomes of the catalysis were borne out under the standard conditions (Scheme 13). Two isotopomers of ^{13}C-enriched 2,4-disubstituted pyrrole **32** were produced from the



Scheme 13: Electronic effects on the outcome of the skeletal rearrangement processes.

reaction of **30**. Qualitative analysis of the two isotopomers showed that a greater proportion of the 2,4-isomer formed from Path III was observed than with the other cyclisation precursors (Supporting Information File 1). Additionally, none of the 2,5-disubstituted pyrrole isomer, which would also result from **B**, was formed.

In keeping with the previous observation that strongly electron-rich aromatic groups were poor substituents for this cycloisomerisation [19], only a low yield of the pyrrole products was obtained on reaction of **31**. However, this was sufficient to determine that Path II predominated over Path III, with no significant isotopomer identified from intermediate **I**. Isomer **34** was identified alongside a significant quantity of the 2,5-disubstituted pyrrole **33**. While solvents and/or counter ions that stabilise positive charge favour the formation of the 2,5-disubstituted pyrroles, likewise, reducing the localised cationic charge in the 5-ring intermediate **B** by conjugation appears to have the same effect.

Re-evaluation of the cycloisomerisation of the deuterium-labelled alkynyl aziridine **4** (Scheme 4) shows the results to be consistent with both the modified mechanistic scenario and the trends shown in the ^{13}C-labelling study. Relative to all the other substrates tested, excepting perhaps **30**, substrate **4** would be the most likely to favour Path III over Path II (Scheme 11). Whilst the butyl substituent does not lend any additional stabilisation to intermediate **B**, the tolyl group stabilises the benzylic cation **I** better than a phenyl group. Significant deuterium incorporation at C-5 in the product would therefore not be expected. Following Path III, the deuterium labelled carbon ends-up at C-4 (Scheme 14, **I-4**→**J-4**). Aromatisation results in C–D bond cleavage with deuterodemetallation of **K-4** affording the observed major product **8b** (Scheme 5). The intermolecular deuteron transfer allows for H/D exchange in the reaction media and hence the partial incorporation of a proton at C-3.

Conclusion

There are two operative skeletal rearrangement pathways for the formation of 2,4-disubstituted pyrroles by gold-catalysed cycloisomerisation of aryl-substituted *N*-tosyl alkynyl aziridines. The two competing pathways coincidentally give rise to the same isomer but with different absolute connectivities, as determined by the formation of two ^{13}C isotopomeric products.

A modified mechanistic scheme accounts for all of the results of the labelling studies. On activation by a cationic gold source and in the absence of coordinating solvents and/or counter ions, regioisomeric ring expansion of the alkynyl aziridine can lead to two different cationic cyclic intermediates, featuring either a 4-membered or a 5-membered ring. The regioselectivity, and hence the isotopomeric reaction selectivity, is controlled by the relative ability of the substituents to stabilise the respective cations in favour of a particular pathway. The observed skeletal rearrangements are consistent with either a 1,2-aryl shift or a 1,2-(metal-stabilised)-vinyl shift in the 5- or 4-membered cyclic intermediates, respectively. These studies highlight some of the complexities associated with gold-catalysed cycloisomerisation reactions and the continued relevance of labelling studies in this field.

Supporting Information

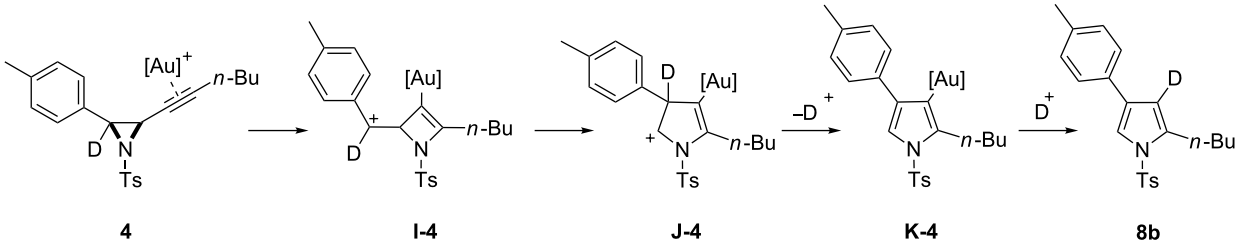
Supporting Information contains full experimental details for the preparation of the cyclisation precursors and their subsequent reactions. NMR spectra for the labelling studies are provided.

Supporting Information File 1

Full experimental details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-96-S1.pdf]

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Scheme 14: Mechanistic rationale for the deuterium labelling study using $Ph_3PAuCl/AgOTf$.

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When gold can do what iodine cannot do: A critical comparison

Sara Hummel and Stefan F. Kirsch*

Review

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Address:
Department Chemie and Catalysis Research Center, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany

Email:
Sara Hummel - sara_hummel@hotmail.co.uk; Stefan F. Kirsch* - stefan.kirsch@ch.tum.de

* Corresponding author

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Abstract

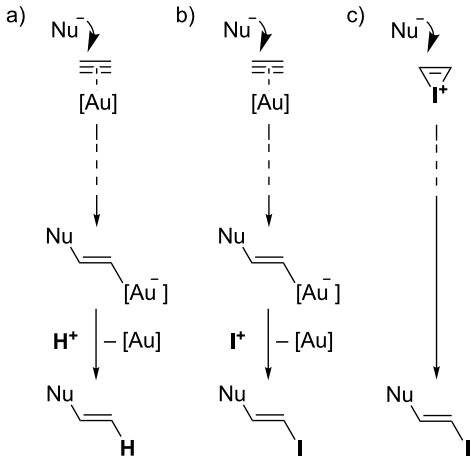
Gold catalysis has emerged as one of the most dynamic fields in organic synthesis. Only recently, more and more domino processes, for which gold pre-catalysts were found to be outstandingly effective, were paralleled by employing iodine electrophiles in place of gold compounds. This review highlights how, in certain cases, iodonium activation can match gold-catalyzed reactions to construct identical product scaffolds. Likewise, processes are discussed where mostly identical starting materials are transformed into diverse frameworks depending on whether gold or iodonium activation was used to trigger the reaction.

Introduction

Over the past decade, the diverse reactivity of carbophilic Lewis acids has attracted considerable interest in the development of domino reactions [1-5] that are initiated by the catalytic activation of π-systems [6-13]. In particular, the utilization of gold pre-catalysts has led to numerous elegant contributions in both heterocycle and carbocycle syntheses [14-20]. In general, these processes are easy to perform under simple reaction conditions: Significant redox chemistry is not involved. Since gold complexes show outstanding functional group tolerance, there has also been a considerable increase in the applications of such complexes in target-oriented synthesis [21-26].

A simplified mechanistic scenario for domino processes initiated by gold-catalyzed alkyne activation is depicted in Scheme 1a. After nucleophilic attack at the gold-activated alkyne and subsequent reorganization steps, the final step typically is a protodeauration [27-30] of the vinylgold intermediate to regenerate the catalytic species. In an analogous way, vinylgold intermediates can be successfully trapped by iodine electrophiles (and other electrophiles) to incorporate I rather than H in the final product (Scheme 1b) [27,31-40]. Even though both processes catalyzed by gold give rise to the same scaffolds, iodine incorporation allows for a further functionalization of the

scaffold by classical cross-coupling reactions [41,42]. As a logical extension, one might speculate about analogous processes triggered by direct iodonium activation in the absence of gold catalysts (Scheme 1c). Since Barluenga, Larock, and others have shown over the last decades that various cyclizations of carbon and heteroatom nucleophiles with tethered alkynes can be accomplished by using simple iodine electrophiles [43-54], it would be of great interest to know to what extent transition metal-free processes can be substituted for gold-catalyzed processes.



Scheme 1: Mechanistic scenarios for alkyne activation.

This review is intended to demonstrate that, in some cases, gold-catalyzed domino processes can be paralleled by employing iodine electrophiles. In particular, if classical cationic intermediates are assumed to explain the gold-catalyzed reactivity of a substrate, it is reasonable to expect analogous reactivity for this substrate in the presence of electrophilic iodine. The reader will also realize how gold-catalyzed processes, which mechanistically benefit from the carbenoid character [55-58] of the reactive intermediates, cannot be matched by electrophilic processes. As highlighted in the discussion, a starting substrate can be transformed into diverse product classes, depending on whether gold or iodonium activation was used to trigger the transformation.

Since a comprehensive discussion on gold catalysis is not intended, the following examples of gold-catalyzed reactions simply illustrate certain prototype reactivity that i) is matched by electrophilic activation modes, or ii) leads to different product frameworks on treatment with electrophiles. The focus is put on alkyne activation only, while related processes based on the activation of alkenes and allenes are not covered in this review.

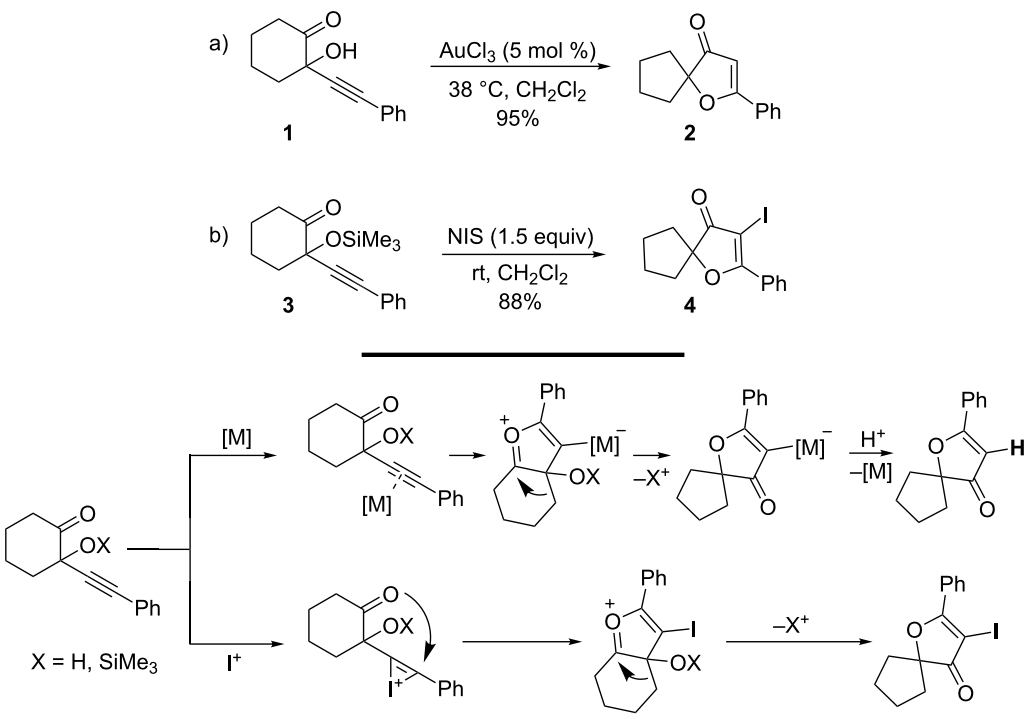
Review

Heterocyclization

The vast majority of gold-catalyzed cyclization modes have involved initial carbon-heteroatom bond formation [7,10]. As a general rule, the nucleophilic attack of a carbonyl (or imine) group onto an alkyne activated by gold-complexation generates first an oxonium (iminium) ion species, the cationic character of which then defines its follow-up chemistry [59-62]. Consequently, these reactions also have the potential to proceed in an analogous manner with classical iodine-based electrophiles. The same is true for intramolecular additions of simple heteroatom nucleophiles with protons attached. Nevertheless, heteroatom nucleophiles having no protons attached react in gold-catalyzed carboalkoxylations [63-66] and related processes where the analogous electrophilic processes are unknown. Catalyzed propargylic ester rearrangements [67,68] also remain the realm of gold-complexes since such reactions have not, so far, been achieved with classical electrophiles.

Analogous product formation

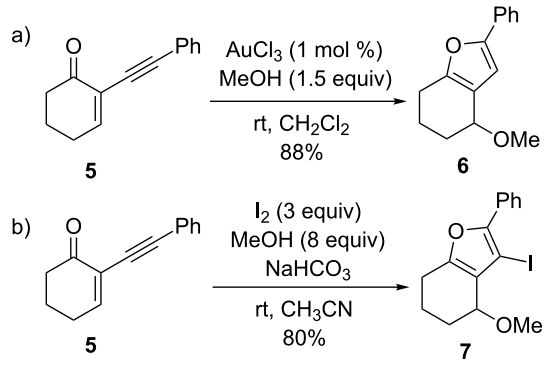
The synthesis of 3-furanones from 2-hydroxy-2-alkynyl carbonyl compounds is a striking example of how simple a gold-catalyzed pathway can be replaced with an iodonium-mediated one with both methods yielding the same core unit. In 2006, a substantial variation to the traditional synthesis of furanones was developed by Kirsch and co-workers from readily accessible 2-hydroxy-2-alkynylcarbonyl compounds by a gold-catalyzed cycloisomerization approach [69]. The gold-catalyzed cyclization of **1,** containing a hydroxy function at the propargylic position, was shown to undergo a cascade involving heterocyclization after activation of the alkyne π-system by the catalysts and a 1,2-alkyl shift (Scheme 2). It was found that this reaction was limited to aryl substituents on the alkyne when the reaction was catalyzed with $AuCl_3$ at 38 °C in CH_2Cl_2. With alkyl substituents on the alkyne, the same reaction led to low yields of products and decomposition. Significantly, the reaction also proceeds with cyclic carbonyl compounds with seven- and eight-membered rings to give six- and seven-membered spirocycles, respectively. Consequently, Kirsch and co-workers described a reaction process using *N*-iodosuccinimide (NIS) instead of $AuCl_3$ in an attempt to obtain 4-iodofuranones via an analogous iodonium-mediated cyclization [70]. With NIS as the electrophile at room temperature in CH_2Cl_2, the iodofuranone **4** was obtained in 88% yield. In contrast to the $AuCl_3$ catalyzed cyclization, the iodonium-induced cascade tolerates the presence of aryl, alkenyl and alkyl groups on the alkyne. Of particular significance, however, is the fact that the reaction with NIS did not proceed with acyclic substrates, since in these cases no product formation occurred. In contrast, $AuCl_3$ induced cyclization furnished acyclic products, albeit in low yields. Unlike gold-catalyzed heterocyclization, the NIS-mediated reaction



Scheme 2: Synthesis of 3(2*H*)-furanones.

allows access to C4-substituted products and therefore to fully substituted 3(2*H*)-furanones. It was deduced that a cyclic oxonium ion is produced in the first stage of the cascade via both gold- and iodonium-triggered cyclization. In both cases, the heterocyclization is followed by a 1,2-migration onto the oxonium ion, where the only difference is whether the final product bears a H or an I atom at the C4-position. It should be further noted that, in the case of the gold-catalyzed process, an external proton source (such as water) is required in the case of substrates with a silyl-protected tertiary hydroxyl group. Otherwise protodemetallation cannot occur to regenerate the catalytically active gold species. In the NIS-mediated pathway towards iodofuranones, the presence of a proton source is of no importance since both silyloxy and hydroxy substituents are reactive under the conditions.

Another example where the iodine-induced reaction nicely parallels the gold-catalyzed reaction pathway was reported by Larock and co-workers in 2005 [71,72]. Thus, the reaction of 2-(1-alkynyl)-2-alken-1-one **5** catalyzed by $AuCl_3$ affords the trisubstituted furan **6** in good yield (Scheme 3): A survey of other transition metal salts demonstrated that the optimum catalyst in CH_2Cl_2 at room temperature is $AuCl_3$ based on reaction time and yield. Iodine, NIS, and PhSeCl were all shown to be useful electrophiles in the analogous transition-metal-free process.

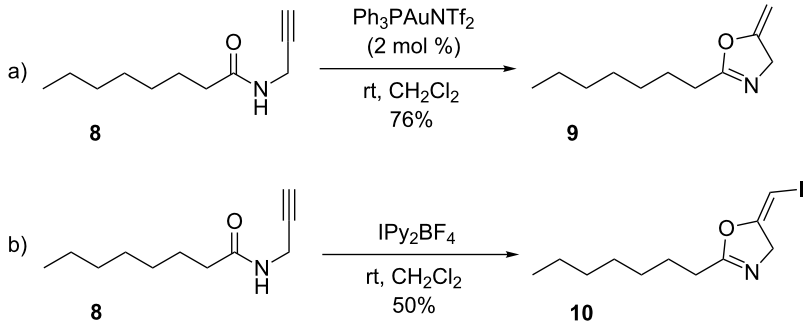


Scheme 3: Synthesis of furans.

Hashmi and co-workers demonstrated in 2010 that dihydrooxazole derivatives can be formed via both gold-catalyzed and iodonium-initiated pathways (Scheme 4) [34]. Interestingly, the bis(pyridine)iodonium tetrafluoroborate reagent [73] (IPy_2BF_4) developed by Barluenga proved to be the best reagent for the iodination pathway.

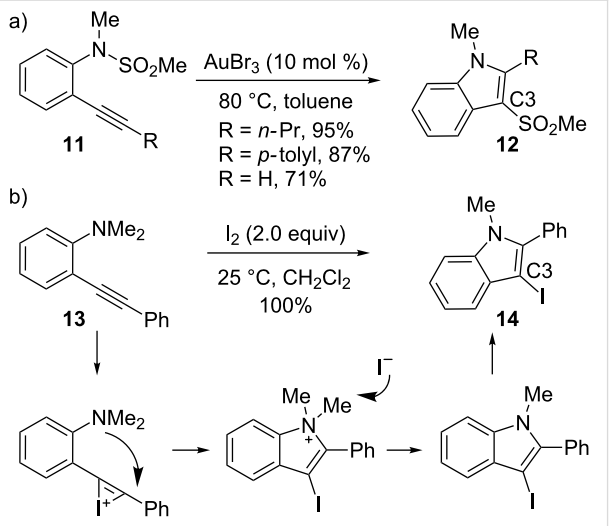
Diversity-creating transformations

In contrast to the examples discussed above, the heterocyclization onto activated alkynes can generate quite different product structures when there are no protons present on the nucleo-



Scheme 4: Formation of dihydrooxazoles.

philic group. A variety of gold-catalyzed transformations that proceed through heterocyclization have been described over the last few years. For example, in 2007, Yamamoto and co-workers reported that when the heteroatom is substituted with a sulfonyl group, migration of the sulfonyl group occurs in an intramolecular fashion (Scheme 5a) [74]. The migration step is now well understood: The heteroatom can effectively stabilize the positive charge that develops. The coordination of gold to the triple bond of **11** and subsequent nucleophilic attack of the nitrogen atom leads to an onium ion intermediate, from which the sulfonyl group migrates intramolecularly to the metallated C3-position, to generate the sulfonylindole product **12**.



Scheme 5: Variation on indole formation.

For this unique cyclization process, there has been no reported equivalent iodonium-mediated reaction. However, Larock and co-workers also investigated a cyclization process where the proton on the heteroatom is absent (e.g., **13**→**14**) [75]. After activation by the electrophile, the iodine substituent remains in the indole framework (Scheme 5b) since the 1,3-migration step observed in the gold-catalyzed reaction does not occur via electrophilic activation. Instead, due to the iodide ion still present in the reaction mixture, the ammonium ion intermediate undergoes S_N1 or S_N2 substitution, or even E2 elimination of an alkyl group. This system yields products in up to quantitative yields, and successfully displays the possibility of diverse product creation through the use of either gold- or iodonium-triggered heterocyclizations.

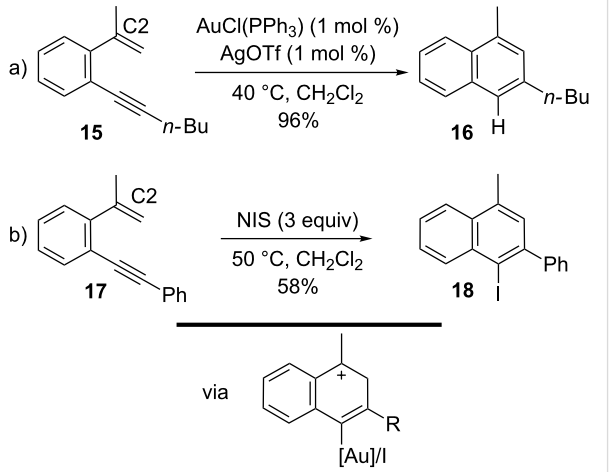
Carbocyclizations with 1,5-enynes

Within the rapidly developing area of gold-catalysis, enyne cycloisomerizations have been particularly well studied [76-83]. With an appropriate substitution pattern, both 1,5- and 1,6-enynes can be transformed into a broad array of product scaffolds. The corresponding electrophilic transformations are far less developed. With the exception of an early report by Barluenga and co-workers [84], iodonium-induced carbocyclizations have been mainly restricted to the intramolecular arylation of alkynes (i.e., arene nucleophiles) [85-88] whilst simple olefins have been rarely used in this way.

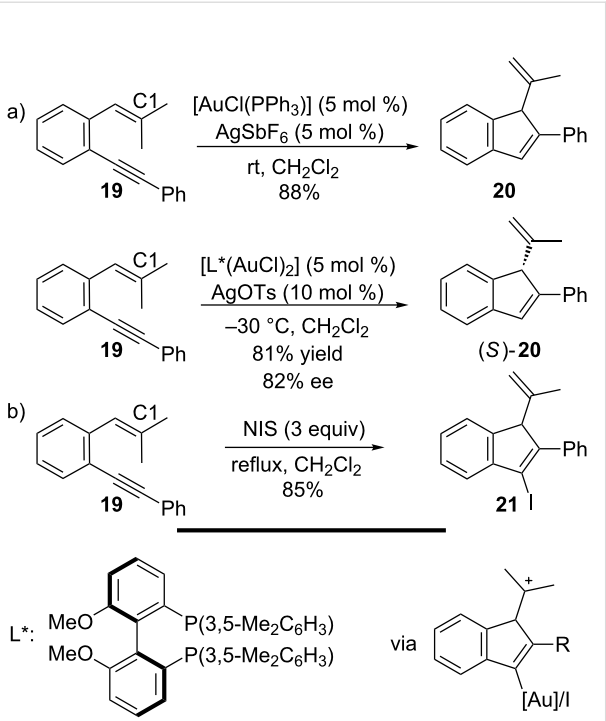
Analogous cyclization modes

Several processes involving the cycloisomerization of 1,5-enynes have been realized in an analogous manner either by using gold-catalysts or electrophilic iodine sources. Typically, these processes are easily understood by postulating stabilized cationic intermediates. For example, aromatic 1,5-enynes can be cyclized to the corresponding naphthalenes in the presence of gold(I) catalysts as demonstrated by Shibata and co-workers in 2006 [89]. By using 1 mol % of both $AuCl(PPh)_3$ and AgOTf at 40 °C in CH_2Cl_2, the 6-endo product was obtained exclusively, regardless of the nature of the counter ion of the Ag salt (Scheme 6). An analogous ring-closure was realized by Kirsch and co-workers in 2010, where NIS was used as the electrophilic agent [90]. Alkyne activation yields the iodonaphthalene as the sole product by an analogous 6-endo process. Both

methods, regardless of whether the cyclization is triggered by Au^+ or I^+, require an alkyl substituent at the C2-position for naphthalene formation to proceed over indene formation, since it is required to stabilize the intermediate carbocation. As before, the only difference in the product structure is whether H or I has been incorporated.



Scheme 6: Formation of naphthalenes.

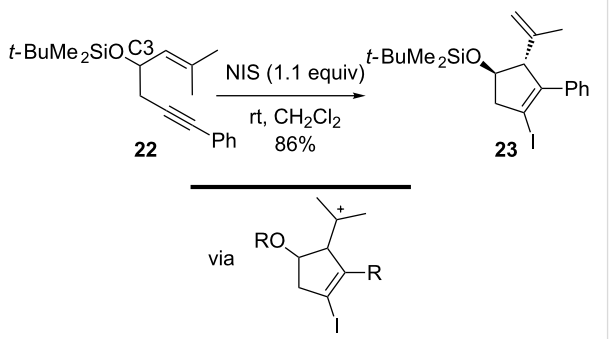


Scheme 7: Formation of indenes.

Sanz and co-workers reported in 2010 that indenes were formed from *o*-alkynylstyrenes in the presence of $AuCl(PPh_3)$ activated by $AgSbF_6$ (Scheme 7) [91]. A 1,5-enyne disubstituted at the terminal carbon of the alkene (e.g., **19**) leads to a very selective 5-endo carbocyclization where no side products resulting from 5-exo or 6-endo modes were observed. A mechanism was proposed involving a cationic intermediate after cyclization which, after loss of a proton and protodemetallation, afforded the product in 88% yield. The reaction can also be made to proceed enantioselectively by means of a gold complex with chiral ligands. The ligand *(S)*-3,5-xylyl-MeO-biphep (L*) gave the best results with respect to enantioselectivity, although all ligands tested with the gold complexes and silver salt $AgSbF_6$ allowed full conversion to the indene. From these results, Sanz and co-workers also reported the corresponding halocyclization of *o*-alkynylstyrenes to yield 3-halo-1*H*-indenes by employing NIS as the iodonium source (Scheme 7b) [92]. This reaction proceeds via an exceptional 5-endo halocyclization, which likely results from the stability of the tertiary carbocation, since only H at the C1-position rendered the enyne unreactive under the conditions used (excess NIS, CH_2Cl_2 at reflux). From a synthetic point of view, the development of an asymmetric halocyclization towards indenes remains an ongoing task [93-96].

Notably, 1,5-enynes that do not contain an aryl system react in quite a similar manner when disubstituted at C1. For example, Michelet and co-workers reported the diastereoselective cycloisomerization of 1,5-enynes via a 5-endo mechanism triggered by iodine electrophiles (Scheme 8) [97]. With 1.1 equiv of NIS at room temperature in dichloromethane, full conversion of **22** occurred to yield selectively only the 5-endo product **23** in 86%. However, when there was no substituent such as the silyloxy group on C3, the reaction yield was considerably reduced. Again in this case, product formation is best understood by assuming the intermediate formation of the most stabilized carbocation. Surprisingly, the analogous gold-catalyzed process has not been described up to now; instead, 3-silyloxy-1,5-enynes with a stabilizing substituent at C2 were found to undergo a cascade consisting of 6-endo cyclization and a subsequent pinacol-type shift [37,98].

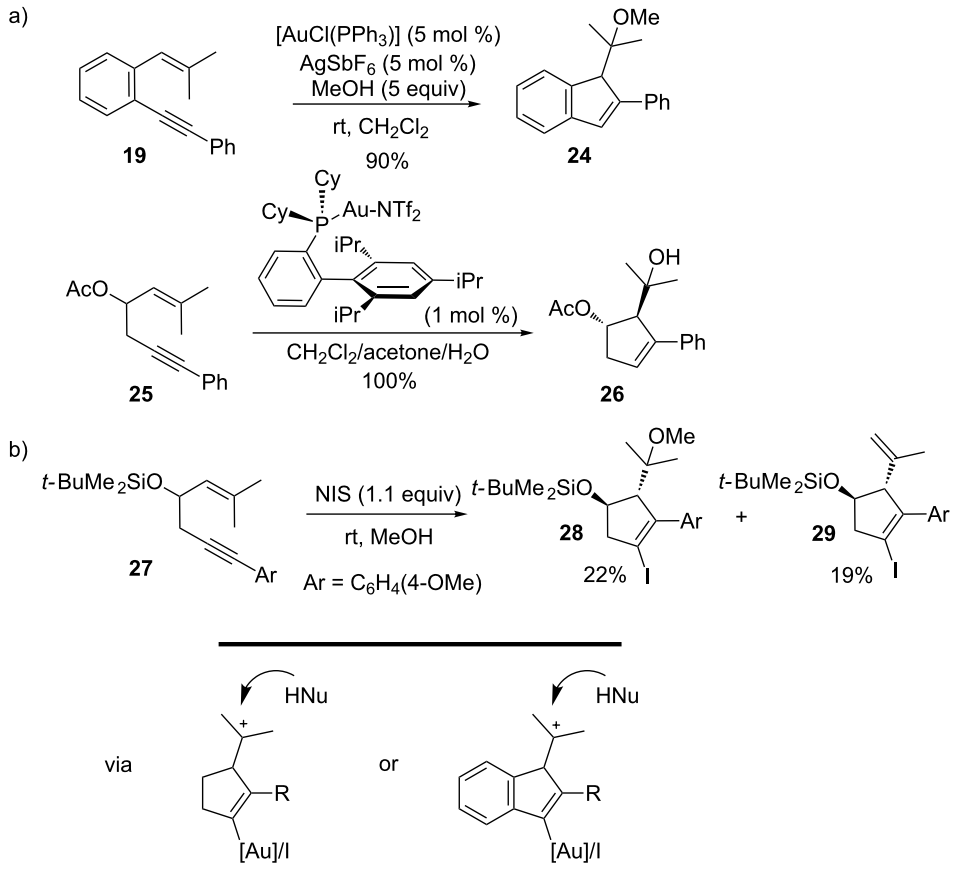
Since the 5-endo cyclizations discussed above most likely proceed through cationic intermediates, external nucleophiles were shown to trap these intermediates at C1 in both gold and iodonium-catalyzed reactions. Accordingly, Sanz and co-workers extended their investigations into 5-endo carbocyclizations of *o*-alkynylstyrenes by adding 5 equiv MeOH to their previous reaction conditions with Au-complexes and obtained the methoxy substituted product **24** at very high selectivity and 90% yield (Scheme 9a) [91]. Labeling experiments showed that the proposed mechanism where the cation is trapped by the nucleophile and subsequent loss of the proton



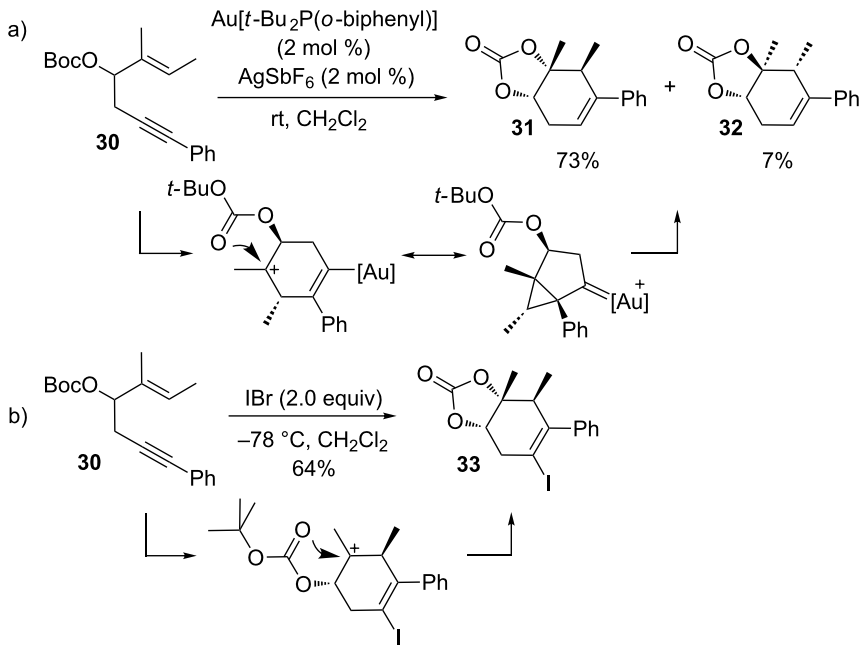
Scheme 8: Iodocyclization of 3-silyloxy-1,5-enynes.

and protodemetallation is viable. A more elaborate study of 5-endo hydroxy- and alkoxycyclizations of 1,5-enynes was described by Gagosz and co-workers as they examined a valuable route to functionalized cyclopentenes [99]. By the use of internal alkynes in substrates such as **25**, they were able to induce stereoselective cyclization followed by nuclophilic trapping. It was reported that by using water rather than methanol as the external nucleophile, excellent yields of the corresponding alcohol product **26** were obtained. Alcohols, for example methanol, and even acetic acid could also be employed as nucleophiles in the catalytic system. For this cascade, a gold carbene intermediate was postulated, although product formation can be explained well via a cationic intermediate as shown in Scheme 9. In an analogous way, Michelet and co-workers also showed that the NIS-mediated pathway can be combined with a nucleophilic trapping by using methanol (Scheme 9b) [97]. The reaction requires substituents at C1 and on the alkyne but, unlike in the case with gold-catalyzed cyclizations, the competing elimination through loss of a proton could not be entirely prevented. For example, a methoxyiodocarbocyclization of **27** occurred in 22% yield when the iodocyclization was run in methanol.

Additionally, the developing positive charge can be trapped with internal nucleophiles. For example, Shin and co-workers reported a valuable transformation using the *tert*-butoxycarbonyl (Boc) group to trap the cation following the activation of π-systems by gold in a route to cyclic carbonates (Scheme 10a) [100]. The Boc-group was considered to be very effective at undergoing intramolecular nucleophilic attack of the cationic



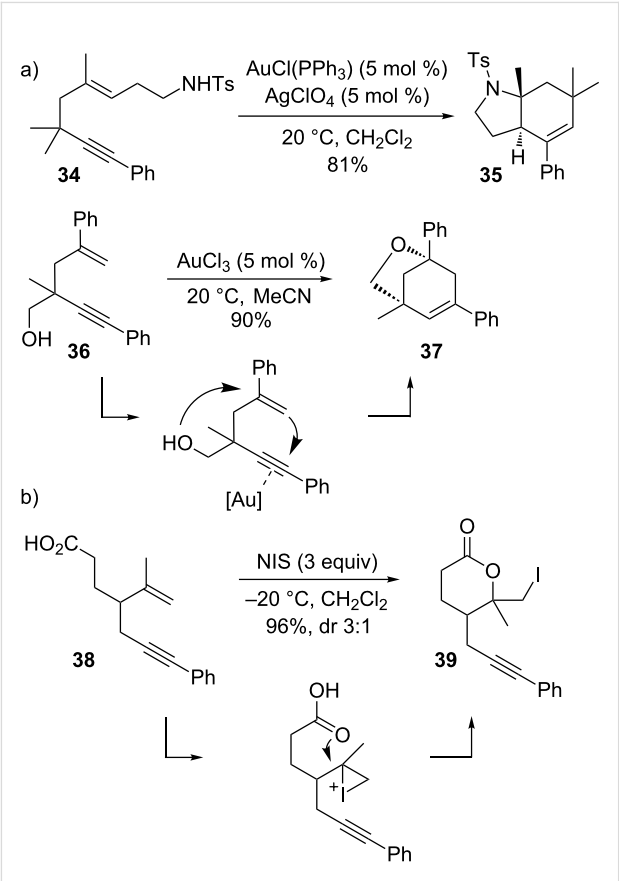
Scheme 9: 5-Endo cyclizations with concomitant nucleophilic trapping.



Scheme 10: Reactivity of 3-BocO-1,5-enynes.

intermediate to gain access to highly functionalized cyclohex-4-ene-1,2-diol derivatives from simple 3-BocO-1,5-enynes. A particular feature of this cyclization is that it developed good diastereoselective control over the adjacent stereocenters, including a quaternary carbon. As in the previous examples, the gold-catalyzed cyclization benefits strongly from a stabilizing substituent at C2 to direct the 6-endo mode of cyclization. Subsequent to the success of the gold-catalyzed cycloisomerization in trapping the developing carbocation with internal nucleophiles, Shin and co-workers expanded their work to feature iodonium-mediated cyclizations to produce highly functionalized iodocyclohexenes from substituted 1,5-enynes [101]. Substrates of the type shown in Scheme 10 reacted to form exclusively the iodocarbonate products, thus realizing a highly efficient domino reaction that creates two new stereogenic centers and three new bonds.

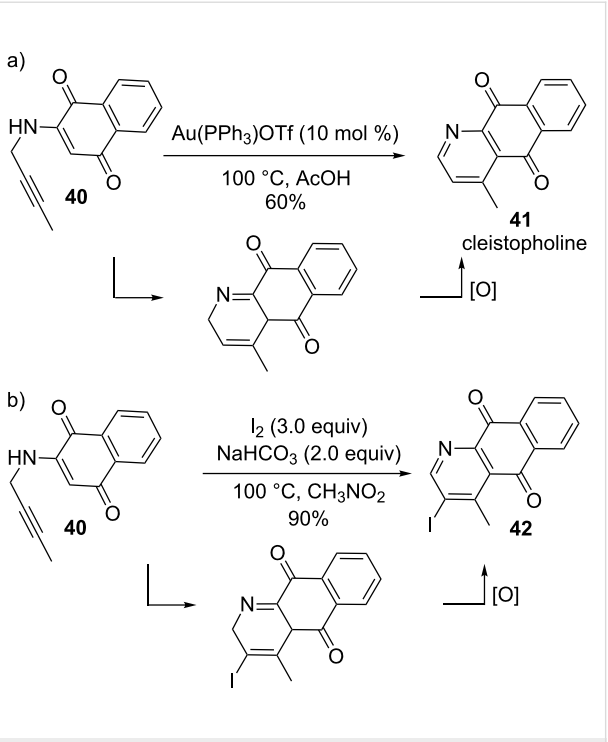
Other heteroatoms have also been successfully employed as internal nucleophiles for the trapping of positive charges. In gold-catalyzed cyclizations, Kozmin and co-workers reported the cycloisomerization of 1,5-enynes with nitrogen-tethered, as well as with oxygen-based nucleophiles (e.g., **34**→**35**; Scheme 11) [102]. It was postulated that the reaction proceeds in a concerted manner, as the double cyclization is highly diastereospecific due to the addition of the nucleophile and alkyne to the alkene being solely *anti.* This reaction is an excellent example that underlines the great potential of the alkynophilicity of the gold metal center. While gold-catalysts



Scheme 11: Intramolecular nucleophilic trapping.

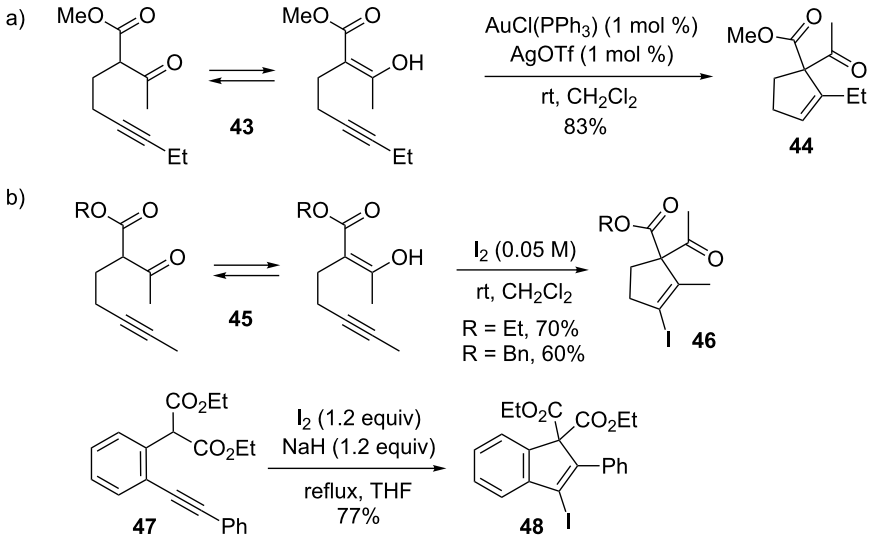
make both carbon–carbon and carbon–heteroatom bond formation possible, the analogous process with iodine electrophiles was not realized. Instead, a classical iodolactonization occurred in the reaction of acid **38** with NIS that left the alkyne moiety of the molecule completely untouched [90].

Other cyclizations of 1,5-enynes make use of highly nucleophilic enamine or enol moieties, as shown in Scheme 12 and Scheme 13. For example, Wang and co-workers achieved the synthesis of azaanthraquinones from *N*-propargylaminoquinones both by gold- and iodine-triggered processes via 6-endo cycloisomerization modes (Scheme 12) [103,104]. The gold-catalyzed process required a $Au(PPh_3)OTf$ loading of 10 mol % since an increased reaction time and decreased yield were observed with only 5 mol % of the pre-catalyst. It was found that electron-donating groups on the alkyne terminus facilitated the cyclization while electron-withdrawing substituents hindered it. Under the optimized conditions (10 mol % $Au(PPh_3)OTf$, 100 °C), successful synthesis of the alkaloid cleistopholine (**41**) from the aminoquinone **40** was easily achieved after in-situ aromatization of the intermediate to yield the desired compound in 60% yield. Furthermore, Wang and co-workers investigated a totally analogous cycloisomerization sequence using iodine as the electrophile to activate the alkyne, and induce nucleophilic attack by the alkene (Scheme 12b). In this variant, molecular iodine coordinates first with the alkyne **40** analogous to the activation using gold to form an iodonium ion, after which the cyclization proceeds as before to give the final product **42** containing iodine incorporated in the azaanthraquinone. The incorporation of iodine presents great possibilities for further modification and elaboration of the cleistopholine structure.



Scheme 12: Approach to azaanthraquinones.

The nucleophilic properties of enol moieties have also been exploited in the gold-catalyzed intramolecular addition of ß-keto esters to alkynes. For example, Toste and co-workers investigated the previously unreported 5-endo carbocyclization of **43** which involves the cyclization of ß-keto esters onto non-terminal alkynes by use of gold catalysts (Scheme 13) [105], where traditional transition metal-catalyzed Conia-ene type cyclizations are possible only with terminal alkynes [106]. It



Scheme 13: Carbocyclizations with enol derivatives.

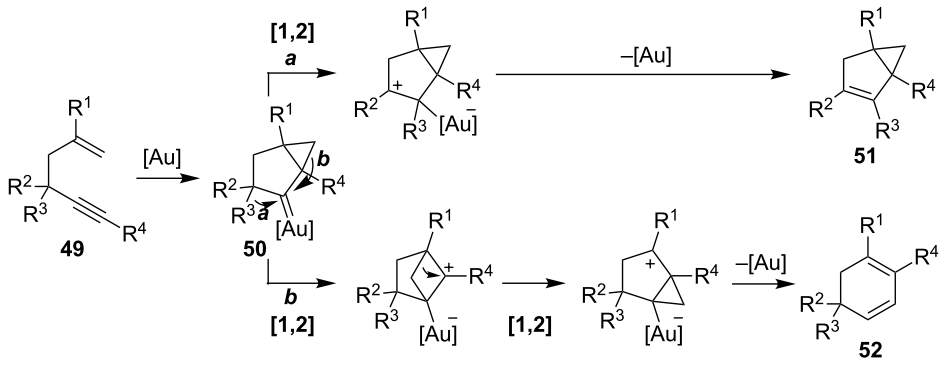
was proposed that the exclusive formation of the 5-endo product occurred with non-terminal alkynes because 5-exo cyclization, analogous to the traditional Conia-ene mechanism, results in too much strain in the transition state during gold-activation, and therefore 5-endo cyclization is favored in the conversion of acetylenic dicarbonyl compounds. Notably, Toste and co-workers also reported a valuable gold-catalyzed enantioselective variant of the Conia-ene reaction between ß-dicarbonyl compounds and alkynes [107]. Barluenga and co-workers successively developed a 5-endo approach to the iodocarbocyclization between ß-keto esters and non-terminal alkynes (Scheme 13b) [108]. Initially, 1,2-addition of iodine to alkynes such as **45** proved problematic, which was resolved by decreasing the molarity of the iodine in CH_2Cl_2 from 0.3 M to 0.05 M. This favored the cyclization process and eliminated competing reaction pathways. It was found that even haloalkynes could be employed in this type of cyclization to give doubly halogenated alkenes. The closely related synthesis of 3-iodo-1*H*-indenes such as **47** via electrophilic cyclization was examined by Wirth and co-workers in 2009 [109]. Following deprotonation by NaH, the iodine activates the alkyne and promotes nucleophilic attack of the stabilized enolate. With NIS as the iodonium source no cyclization was observed after deprotonation and only an α-iodomalonate and starting material were obtained.

Diversity-creating transformations

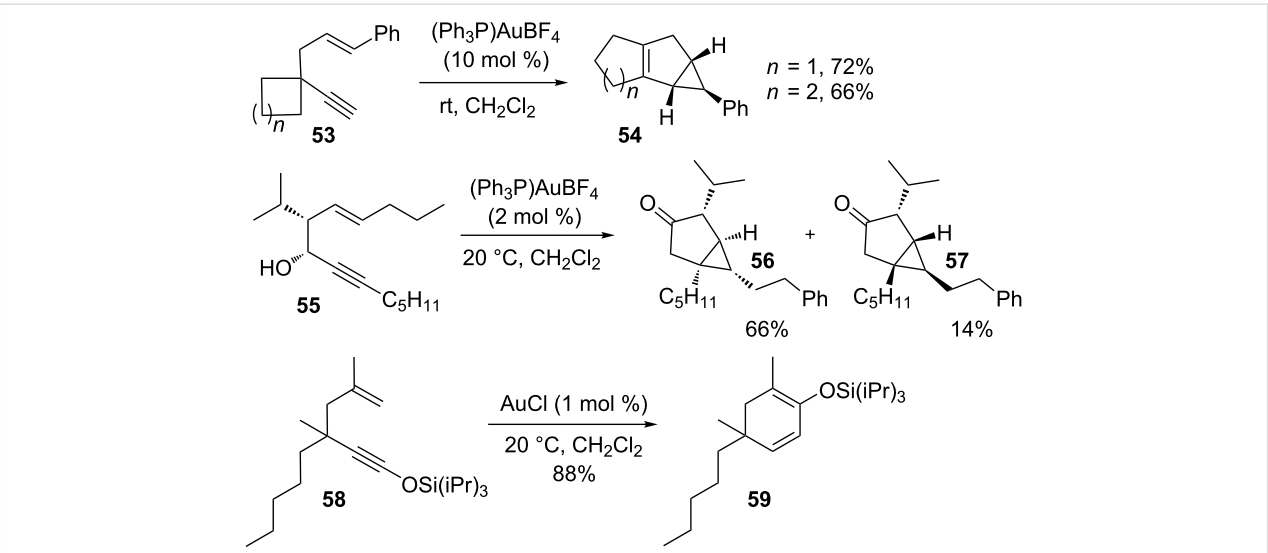
There are several gold-catalyzed processes for which there are no corresponding iodine counterparts. In general, most of the processes specific for gold are assumed to proceed via gold carbene intermediates. For example, 1,5-enynes **49** can react in gold-catalyzed domino reactions that include a 1,2-migration as an additional step (Scheme 14). Gold-induced activation of the alkyne followed by cyclization produces a cyclopropyl gold carbene **50** as the key intermediate. Depending on the substitution pattern, two alternative reaction outcomes are possible: The formation of bicyclo[3.1.0]hexane derivatives **51** (path a) or the formation of cyclohexadiene derivatives **52** (path b).

The catalytic isomerization of 1,5-enynes to bicyclo[3.1.0]-hexenes following path a was thoroughly investigated by Toste and co-workers (e.g., **53**→**54**; Scheme 15) [110]. Transformations of 1,5-enynes that involve 1,2-alkyl migration of R^3 are strictly limited to compounds that bear a quaternary center (R^3 = alkyl, $R^2 \neq H$). As shown for the gold(I)-catalyzed reaction of 1,5-enyne **53**, the formation of the bicyclo[3.1.0]hexene **54** is driven by the release of ring strain. Enynes with R^3 = H undergo exclusively a hydride shift to give the corresponding bicyclo[3.1.0]hexenes of type **51**. By contrast, Gagosz reported the gold-catalyzed cycloisomerization of 4-hydroxylated 1,5-enynes to yield a diverse range of products [111]. The syn-compound **55** reacted with $(PPh_3)AuBF_4$ to give a mixture of diastereomers **56** and **57** in 66 and 14% yield. Under the same reaction conditions, the anti-isomer exhibited reversed selectivity, indicating that the hydroxyl group functions as a possible stereodirecting component in this conversion. However, 1,5-enynes may participate in an alternative reaction pathway via path b (Scheme 14). This is dependent on the substitution pattern and configuration of the enyne and leds to variable product formation. For example, Kozmin and co-workers showed in 2006 that 1,5-enynes can also rearrange to 1,3-cyclohexadienes through a series of 1,2-alkyl shifts (Scheme 15) [112]. In particular, when silyloxy enynes such as **58** were treated with AuCl, the formation of cyclohexadienes was strongly favored, presumably due to the highly stabilized oxonium ion intermediates (path b).

Essentially, these transformations are not viable with an iodonium source as they do not possess the ability to proceed through simple cationic intermediates. As outlined in

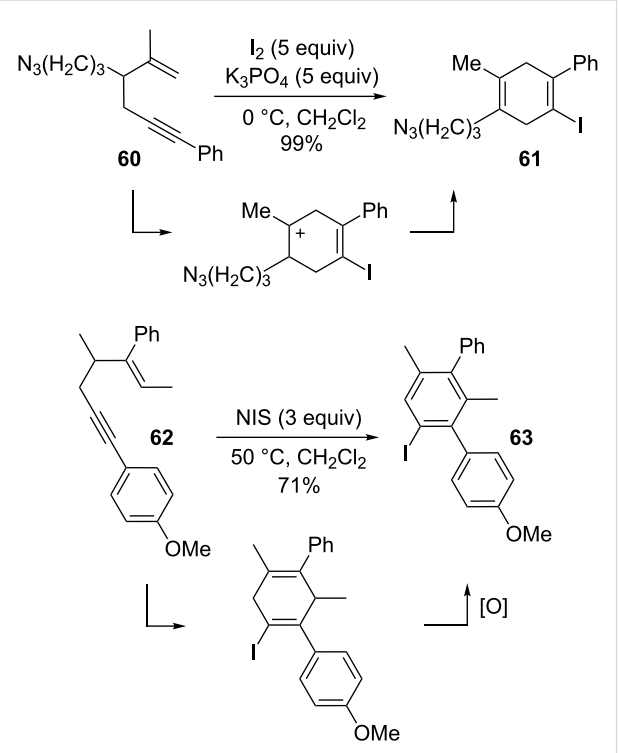


Scheme 14: Gold-catalyzed cyclization modes for 1,5-enynes.



Scheme 15: Iodine-induced cyclization of 1,5-enynes.

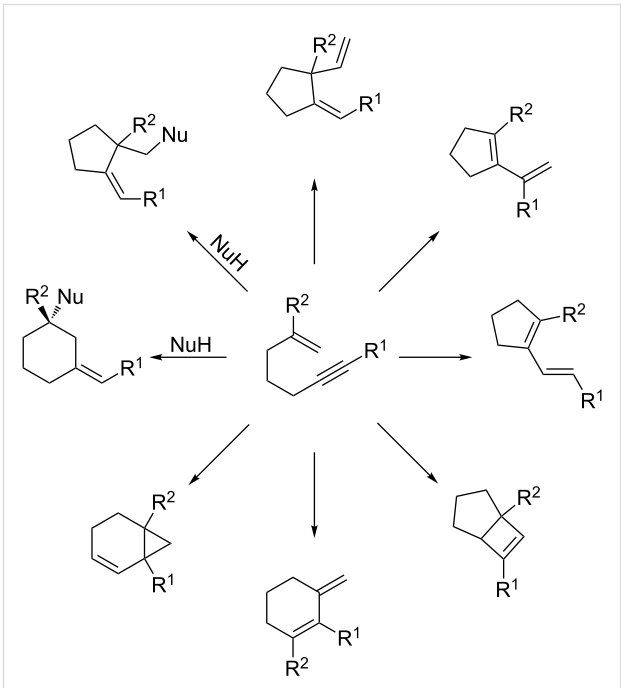
Scheme 16 [90,113], classical cationic intermediates and subsequent loss of a proton do lead to iodine-containing 1,4-cyclohexadienes, the formation of which does not include a 1,2-shift. Additionally, the oxidative power of NIS is able to oxidize cyclohexadienes further to aryl systems. It was found that a substituent at C2 was required in both cases to stabilize the carbocation in the cyclic intermediate.



Scheme 16: Diverse reactivity of 1,6-enynes.

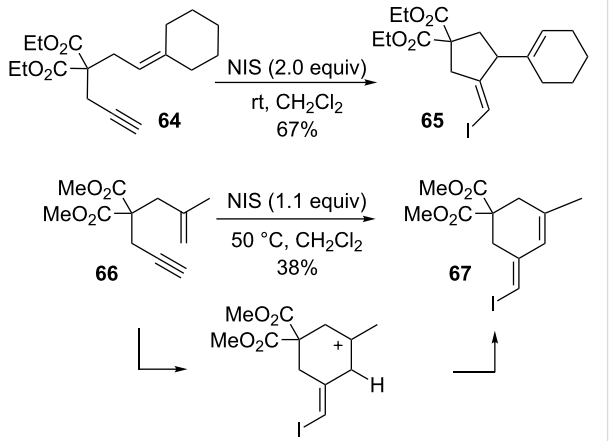
Carbocyclizations with 1,6-enynes

The gold-catalyzed carbocyclizations of 1,6-enynes have been extensively studied. Significant results have been reported by Echavarren and others in recent years and have been extensively reviewed [76-83]. As summarized in Scheme 17, the reactivity of 1,6-enynes displays great variability and a diverse range of product scaffolds are accessible (Scheme 17). From a mechanistic perspective, these cyclizations proceed through gold-carbene intermediates, and the gold in all cases activates



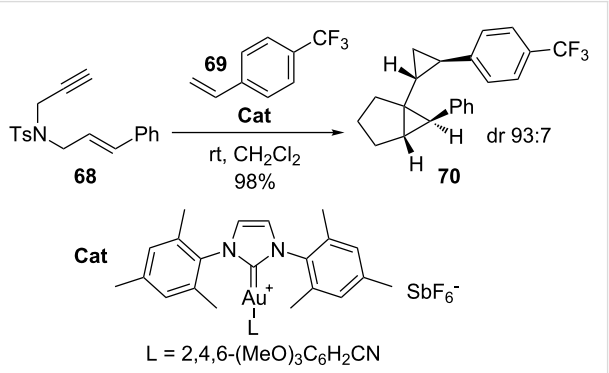
Scheme 17: Iodocyclization of 1,6-enynes.

the alkyne moiety exclusively. Consequently, most of the gold-catalyzed cyclization modes are not paralleled by iodine-mediated processes. Iodocyclization of 1,6-enynes is known only from very recent examples from Kirsch and co-workers [114]. As shown in Scheme 18, these processes give the cyclization products in only poor yields. With regard to the scope, a terminal alkyne was required for the 6-exo cyclization mode to occur. As with all of the iodine mediated cyclizations discussed above, the cyclization mode is determined by the stability of the intermediate upon carbon–carbon bond formation. It was found that the substitution pattern of the alkene moiety influenced the cyclization mode, whereby a substituent at C2 encourages 6-exo cyclization, and a disubstituted C1 favors 5-exo cyclization.



Scheme 18: Cyclopropanation of alkenes with 1,6-enynes.

On the other hand, gold-catalyzed domino processes with 1,6-enynes have been shown to proceed in high yields to provide access to carbon skeletons that are not easily synthesized by other approaches. A striking example of the latter is outlined in Scheme 19 [115]. The 1,6-enyne **68** reacts with substituted styrene **69** in the presence of an Au catalyst to afford the cyclopropanation product **70** with excellent diastereoselectivity. This is only one example where gold catalysts open the door to a realm of reactivity that traditional electrophiles can never reach.



Scheme 19: Cyclopropanation of alkenes with 1,6-enynes.

Conclusion

This review was intended to demonstrate that numerous domino processes can be carried out with either gold catalysts or iodine electrophiles to access the same core unit in an analogous manner. While electrophilic cyclization can incorporate iodine into the final product, gold catalysis typically results in hydrogen at the same position due to the protodeauration step required for catalyst regeneration. It is certain that many more reactions that have been described as gold-catalyzed will also be described as iodine mediated in the near future. Apparent in this small survey is also the fact that the electrophilic cyclization mode always proceeds through the most stable cationic intermediates. Therefore, the analogy between gold-catalyzed and iodine mediated reactions only holds true if the gold-catalyzed process makes use of the cationic character of the intermediate. The plethora of gold-catalyzed processes that are based on reactive carbene intermediates will most likely never be matched by electrophilic analogues and will be unique tools for the creation of valuable target compounds.

Acknowledgements

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Gold-catalyzed oxidation of arylallenes: Synthesis of quinoxalines and benzimidazoles

Dong-Mei Cui*[1], Dan-Wen Zhuang[1], Ying Chen[1] and Chen Zhang[2]

Full Research Paper

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Address:
[1]College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, PR China and [2]College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, PR China

Email:
Dong-Mei Cui* - cuidongmei@zjut.edu.cn

* Corresponding author

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Abstract

A gold-catalyzed oxidation of arylallenes to form α-diketones and aldehydes in good yields is presented. Further directed synthesis of quinoxalines and benzimidazoles, via the condensation of the resulting α-diketones and aldehydes with benzene-1,2-diamine, was achieved in high yields.

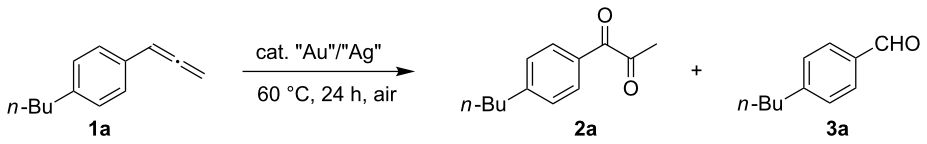
Introduction

Recently, several research groups have developed gold-catalyzed homogeneous catalytic reactions [1]. A variety of organic transformations have been shown to be mediated by gold(I) or gold(III) complexes in solution. In addition to its ability to activate unsaturated C–C bonds, the catalysis of nucleophilic addition by gold complexes for the formation of carbon–carbon and carbon–heteroatom bonds has been one of the most investigated reactions in recent organometallic catalysis [1-24]. In particular, water as a nucleophilic reagent has been used in the addition of alkynes and allenes [16-18]. In contrast, gold-catalyzed oxidation chemistry has been less well developed [25-36], although oxidative cleavage of carbon–carbon double bonds and carbon–carbon triple bonds by homogeneous gold catalysts was reported recently [28,29,33]. To the best of our knowledge, gold and other transition metal-catalyzed oxidations of allenes have not been reported [37,38]. In the context of ongoing studies on metal-catalyzed atom-economical reactions, we have been interested in the use of gold for simple and highly efficient transformations. Additionally, quinoxaline and benzimidazole skeletons are common building blocks for the preparation of substances with pronounced biological activities [39-44]. Herein, we report the gold(I)-catalyzed oxidation/hydration and oxidative cleavage of allenes to form α-diketones and aldehydes, and the synthesis of quinoxalines and benzimidazoles via the condensation of the resulting α-diketones and aldehydes with benzene-1,2-diamine [45-56].

Results and Discussion

Our initial explorations focused on the reaction of 4-butylphenylallene (**1a**) (0.5 mmol) in the presence of a catalytic mixture of $(Ph_3P)AuCl$ (2 mol %), $AgBF_4$ (8 mol %), and H_2SO_4 (0.5 mol %) in dioxane (1.0 mL) and water (10 mmol), at 60 °C for 24 h in air. This proceeded efficiently to form a 44:56 mixture of α-diketone **2a** and aldehyde **3a** in 70% combined yield (Scheme 1, Table 1, entry 1). The use of either the gold or silver pre-catalyst alone gave lower yields (Table 1, entries 18 and 19). These results indicate that both the Au source and $AgBF_4$ play a crucial role in this oxidation. The superior efficiency of the tetrafluoroborate anion was demonstrated by a comparison with other weakly or non-coordinating counter anions. In addition, a change of the counter anion to OTf^-, SbF_6^-, or NTf_2^- was also effective (Table 1, entries 2–4). The use of other gold catalysts, e.g., $(Ph_3P)AuNO_3$ and IMesAuCl, led to only to combined yields of **2a** and **3a** of 49% and 60%, respectively (Table 1, entries 16–17). Decreasing the amount of the sulfuric acid also resulted in a lower yield, although the addition of a large amount of the acid did not affect the reaction (Table 1, entries 8–9). Different acids were screened (Table 1, entries 1, 5–7) and sulfuric acid was found to be the most effective. The use of solvents such as THF, toluene, DCE or ether resulted in a lower conversion (Table 1, entries 10–13). Treatment of **1a** in an atmosphere of O_2 (1 atm) afforded **2a** and **3a** in a combined yield of 47% (Table 1, entry 20). When the reaction was conducted under a nitrogen atmosphere, only trace of products were observed (Table 1, entry 21).

In order to assess the scope of this process, we examined the oxidation of several aryallenes under the optimized conditions indicated in entry 1 of Table 1. The results are summarized in Table 2. Phenylallene gave a good isolated yield of 1-phenylpropan-1,2-dione (**2c**) and benzaldehyde (**3c**) in a ratio of 43:57



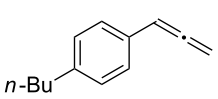
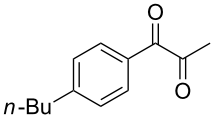
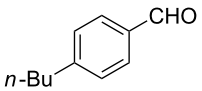
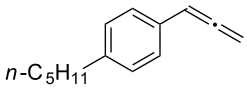
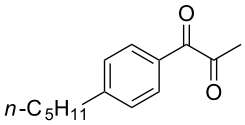
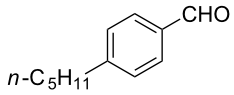
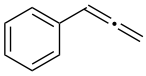
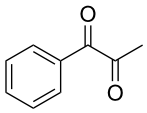
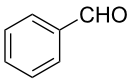
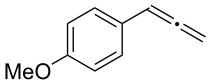
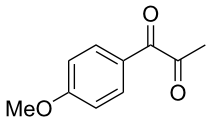
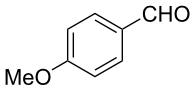
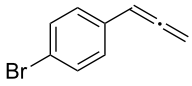
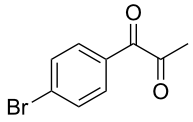
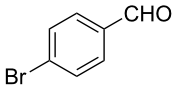
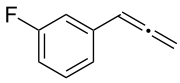
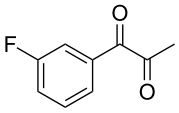
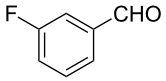
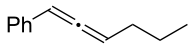
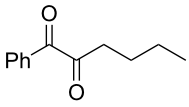
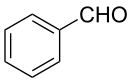
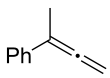
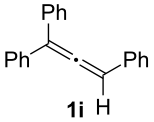
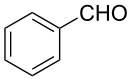
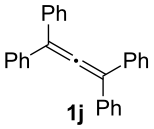
Scheme 1: Oxidation of 4-butylphenylallene.

Table 1: Oxidation of **1a** catalyzed by a mixture of $(PPh_3)AuCl$, $AgBF_4$, and H_2SO_4.[a]

Entry	Au (2 mol %)	Ag (8 mol %)	H_2O (equiv)	Acid (mol %)	Solvent	Ratio[b] **2a**:**3a**	Yield (%)[c] of **2a** and **3a**
1	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	dioxane	44:56	70
2	$(PPh_3)AuCl$	AgOTf	20	H_2SO_4 (0.5)	dioxane	38:62	63
3	$(PPh_3)AuCl$	$AgNTf_2$	20	H_2SO_4 (0.5)	dioxane	55:45	43
4	$(PPh_3)AuCl$	$AgSbF_6$	20	H_2SO_4 (0.5)	dioxane	49:51	47
5	$(PPh_3)AuCl$	$AgBF_4$	20	F_3CCO_2H (0.5)	dioxane	43:57	58
6	$(PPh_3)AuCl$	$AgBF_4$	20	MsOH (0.5)	dioxane	39:61	68
7	$(PPh_3)AuCl$	$AgBF_4$	20	TsOH (0.5)	dioxane	37:63	48
8	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.25)	dioxane	49:51	40
9	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (1.0)	dioxane	48:52	70
10	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	THF	47:53	19
11	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	toluene	39:61	49
12	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	DCE	43:57	60
13	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	ether	36:64	37
14	$(PPh_3)AuCl$	$AgBF_4$	10	H_2SO_4 (0.5)	dioxane	46:54	32
15	$(PPh_3)AuCl$	$AgBF_4$	40	H_2SO_4 (0.5)	dioxane	53:47	39
16	$(PPh_3)AuNO_3$	–	20	H_2SO_4 (0.5)	dioxane	49:51	49
17	IMeSAuCl	$AgBF_4$	20	H_2SO_4 (0.5)	dioxane	54:46	60
18	PPh_3AuCl	–	20	H_2SO_4 (0.5)	dioxane	38:62	15
19	–	$AgBF_4$	20	H_2SO_4 (0.5)	dioxane	47:53	28
20[d]	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	dioxane	50:50	47
21[e]	$(PPh_3)AuCl$	$AgBF_4$	20	H_2SO_4 (0.5)	dioxane	–	trace

[a]All reactions were carried out using **1a** (0.5 mmol), $(Ph_3P)AuCl$ (2 mol %), $AgBF_4$ (8 mol %), and acid (0.25–1.0 mol %) in solvent (1.0 mL) and water (0.5–1.0 mmol) at 60 °C for 24 h. [b]The ratio of **2a** and **3a** was determined by GC. [c]Isolated and combined yield of **2a** and **3a**. [d] Under an atmosphere of O_2 (1 atm). [e]Under an atmosphere of N_2.

Table 2: Oxidation of **1** catalyzed by a mixture of $(PPh_3)AuCl$, $AgBF_4$, and H_2SO_4.

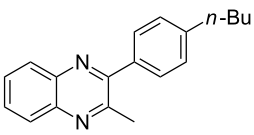
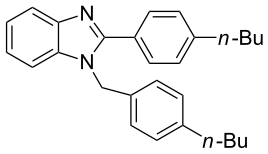
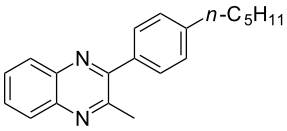
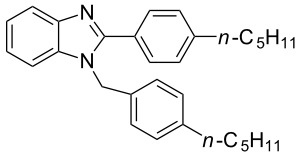
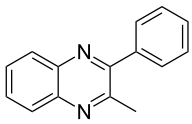
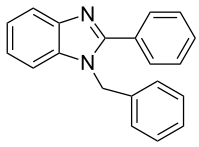
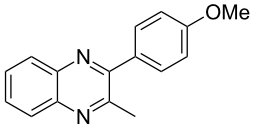
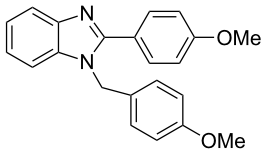
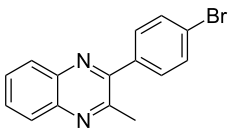
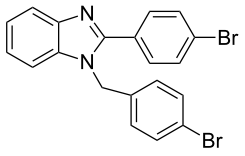
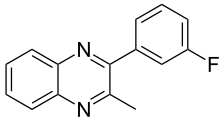
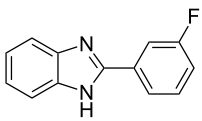
Entry	Allene **1**	Product **2**	Product **3**	Yield (**2** and **3**) (%)[a]
1	 **1a**	 **2a**	 **3a**	70 (48:52)
2	 **1b**	 **2b**	 **3b**	72 (46:57)
3	 **1c**	 **2c**	 **3c**	68 (43:57)
4	 **1d**	 **2d**	 **3d**	62 (35:65)
5	 **1e**	 **2e**	 **3e**	65 (52:48)
6	 **1f**	 **2f**	 **3f**	67 (43:57)
7	 **1g**	 **2g**	 **3c**	**2g**: 35 **3c**: 32
8	 **1h**	 **2h**		84
9	 **1i**	 **2i**	 **3c**	**2i**: 89 **3c**: 85
10	 **1j**	 **2i**		90

[a]Isolated yield. The ratio of **2** and **3** in the parentheses was determined by GC.

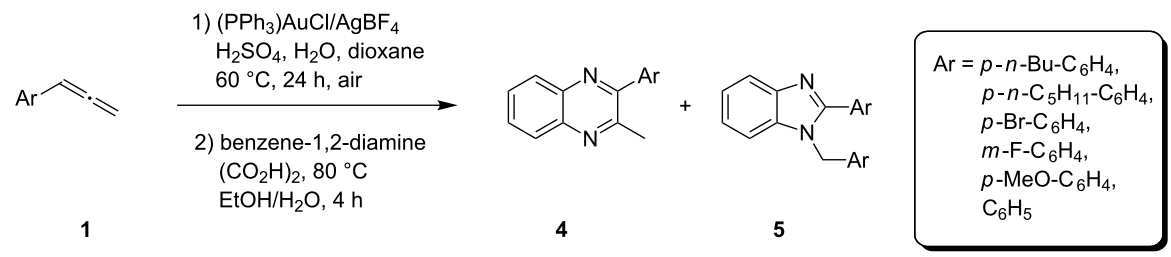
(Table 2, entry 3). With a more electron-donating alkoxy group, the expected products were again obtained in good yields (Table 2, entry 4). In addition, oxidation of arylallene with an electron-withdrawing fluoro or bromo substituent on the benzene ring also took place smoothly (Table 2, entries 5 and 6). Disubstituted allenes were also examined. Thus, the 1,3-disubstituted allene **1g**, was oxidized to afford α-diketone **2g** and aldehyde **3c** in 35% and 32% yields, respectively (Table 2, entry 7). Similarly, oxidation cleavage of 1,1-disubstituted, trisubstituted and tetrasubstituted allenes gave the expected products (Table 2, entries 8–10). In striking contrast to aromatic allenes, aliphatic allenes, such as hepta-1,2-diene and 1-(propa-1,2-dienyl)cyclohex-1-ene failed to undergo Au-catalyzed oxidative transformation under the same reaction conditions.

Having prepared a variety of α-diketones and aldehydes successfully, we then undertook the synthesis of quinoxalines and benzimidazoles (Scheme 2). Thus, the treatment of the corresponding mixture of α-diketone **2** and aldehyde **3** with benzene-1,2-diamine in the presence of 20 mol % oxalic acid afforded the desired quinoxalines **4** and benzimidazoles **5** in high yields (Table 3, entries 1–6).

Table 3: Preparation of quinoxalines and benzimidazoles.

Entry	Allene **1**	Ratio (**2**: **3**)[a]	Product **4**	Yield (%)[b]	Product **5**	Yield (%)[b]
1	**1a**	48:52	 **4a**	97	 **5a**	94
2	**1b**	46:57	 **4b**	95	 **5b**	90
3	**1c**	43:57	 **4c**	97	 **5c**	94
4	**1d**	35:65	 **4d**	90	 **5d**	92
5	**1e**	52:48	 **4e**	97	 **5e**	92
6	**1f**	43:57	 **4f**	97	 **5f**	94

[a]The ratio of **2** and **3** was determined by GC. [b]Isolated yield.



Scheme 2: Preparation of quinoxalines and benzimidazoles.

Conclusion

We have developed a new gold-catalyzed oxidation of arylallenes to give α-diketones and aldehydes in good yields. In addition, the directed synthesis of quinoxalines and benzimidazoles via the condensation of the resulting α-diketones and aldehydes with benzene-1,2-diamine was achieved in high yields. This reaction appears to proceed via oxidation/hydration and oxidative cleavage of the allene, and investigations into the mechanism of this reaction are underway in our laboratory.

Experimental

General methods: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} and visualized with UV light. Column chromatography was performed with silica gel (mesh 300–400). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer in $CDCl_3$ with Me_4Si as internal standard. Data are reported as follows: Chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet), coupling constant in Hertz (Hz) and signal integration. Infrared spectra (IR) were obtained on 370 FT-IR spectrometer; absorptions are reported in cm^{-1}. Mass spectra were obtained under electron impact mode (EI) and high resolution mass spectra were measured on a high resolution mass spectrometer (GCT Premier).

General procedure

Step A (a typical procedure): Sulfuric acid (0.5 mol %) was added to a mixture of 4-butylphenylallene (0.5 mmol), water (10 mmol), $(PPh_3)AuCl$ (2 mol %), $AgBF_4$ (8 mol %), and dioxane (1 mL). The mixture was stirred at 60 °C for 24 , the reaction quenched with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the desired products **2a** and **3a** (48:52, 63.75 mg, 70%).

Step B (a typical procedure): A mixture of **2a** and **3a** (63.75 mg), benzene-1,2-diamine (28 mg, 0.259 mmol), oxalic acid (6.3 mg, 0.07 mmol, 20 mol %), water (1 mL) was dissolved in ethanol (1 mL). The mixture was heated under reflux for 4 h. The reaction was quenched with a saturated solution of $NaHCO_3$ and then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give the desired products **4a** (45.0 mg, 97%) and **5a** (33.9 mg, 94%).

Supporting Information

Supporting Information File 1

Analytical and spectroscopic data for new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-98-S1.pdf]

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Gold-catalyzed propargylic substitutions: Scope and synthetic developments

Olivier Debleds, Eric Gayon, Emmanuel Vrancken and Jean-Marc Campagne*

Review

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Address:
Institut Charles Gerhardt, UMR 5253, Equipe AM2N, ENSCM 8 rue de l'Ecole Normale, 34296 Montpellier Cédex, France

Email:
Emmanuel Vrancken - Emmanuel.Vrancken@enscm.fr;
Jean-Marc Campagne* - jean-marc.campagne@enscm.fr

* Corresponding author

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Abstract

This personal account summarizes our recent developments in gold-catalyzed direct substitutions on propargylic (allylic, benzylic) alcohols, with various nucleophiles (and bi-nucleophiles) based on the σ- and/or π-acidity of gold(III) complexes. Synthetic developments are also briefly described.

Introduction

In the field of nucleophilic substitution reactions, leaving groups are mostly often obtained from alcohols but initially require their transformation to better leaving groups such as sulfonates or acetates. For economic, environmental and practical reasons it is therefore of interest to develop new experimental conditions for the direct substitution of activated alcohols such as tertiary, allylic, benzylic or propargylic ones [1-4]. Since some pioneering work using stoichiometric amounts of Lewis acid catalysts [3-5], much effort has been devoted to this goal. In this context, we have been particularly interested in the direct substitution of propargylic alcohols, because i) the presence of the alkyne function in the substitution product allows many further synthetic modifications, ii) the challenge of controlling the possible competition between substitutions at the propargylic and/or the allenic positions [6], and iii) compared to allylic and benzylic substitutions these reactions have been studied to a far lesser extent. Direct propargylic substitutions have traditionally and efficiently been carried out using the Nicholas [7] conditions but this implies the use of stoichiometric amounts of a cobalt complex. In 1994, Murahashi [8] described in a seminal paper the propargylic substitution of monosubstituted alkynes bearing a good leaving group on the propargylic alcohol moiety, where a mechanism through a copper-allenylidene intermediate was postulated. Subsequently,

asymmetric versions have been described [9,10]. Thus, Hidai, Nishibayashi and Uemura developed a diruthenium complex catalyst for the direct substitution of monosubstituted propargylic alcohols (R^3 = H), by a large number of heteroatomic and carbon centered nucleophiles [11-15]. Enantiomerically pure ruthenium catalysts for asymmetric propargylic substitutions were next developed using acetone, hydrides and electron rich aromatics as nucleophiles [16-18]. In 2003, oxo-rhenium catalysts were introduced by Toste [19-21]. Substitution products were obtained in high yields with alcohols, allylsilanes, aromatic compounds and nitrogen nucleophiles. Interestingly, these reactions were not limited to monosubstituted propargylic alcohols [19-22].

In 2005, we described the direct Au(III)-catalyzed substitution of propargylic alcohols in the presence of various nucleophiles (allylsilanes, alcohols, thiols, electron rich aromatic compounds), and showed that gold probably acts as a Lewis acid to promote the formation of a stabilized propargylic carbocation intermediate [23,24]. A related reaction was subsequently reported by Dyker [25] in 2006, using azulene and 1,3-dimethoxybenzene in Friedel–Crafts type reactions with benzylic and propargylic alcohols. Shortly after, Sanz and Zhan discovered, that these reactions could also be carried out under Brønsted acid and $FeCl_3$ catalysis, respectively [26-29]. Later, the use of copper, indium, bismuth, scandium, ytterbium, phosphomolybdic acid and iodine catalysts were reported by several groups worldwide [30-39]. These aspects have been recently reviewed [40-43]. Among all these various Lewis acid catalysts, gold stands out since it possesses a unique hard/soft Lewis acid dichotomy allowing the activation of both alcohols and π-bonds. We therefore assumed that we could take advantage of this ambivalence in order to perform new domino processes [44,45]. Moreover, due to these ambivalent properties, the control of the chemo- and regioselectivity is challenging and raises interesting mechanistic considerations.

In this special issue dedicated to "Gold catalysis for organic synthesis", we would like to give a personal account on our work related to this topic: Scope, limitations and synthetic utilization of the gold(III)-catalyzed direct substitution of alcohols and the development of domino reactions.

Review

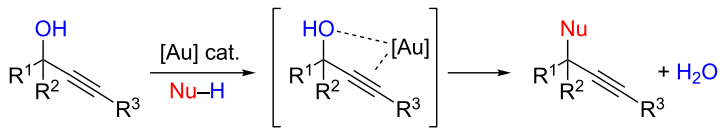
Gold-catalyzed alcohol substitution

Scope and limitations

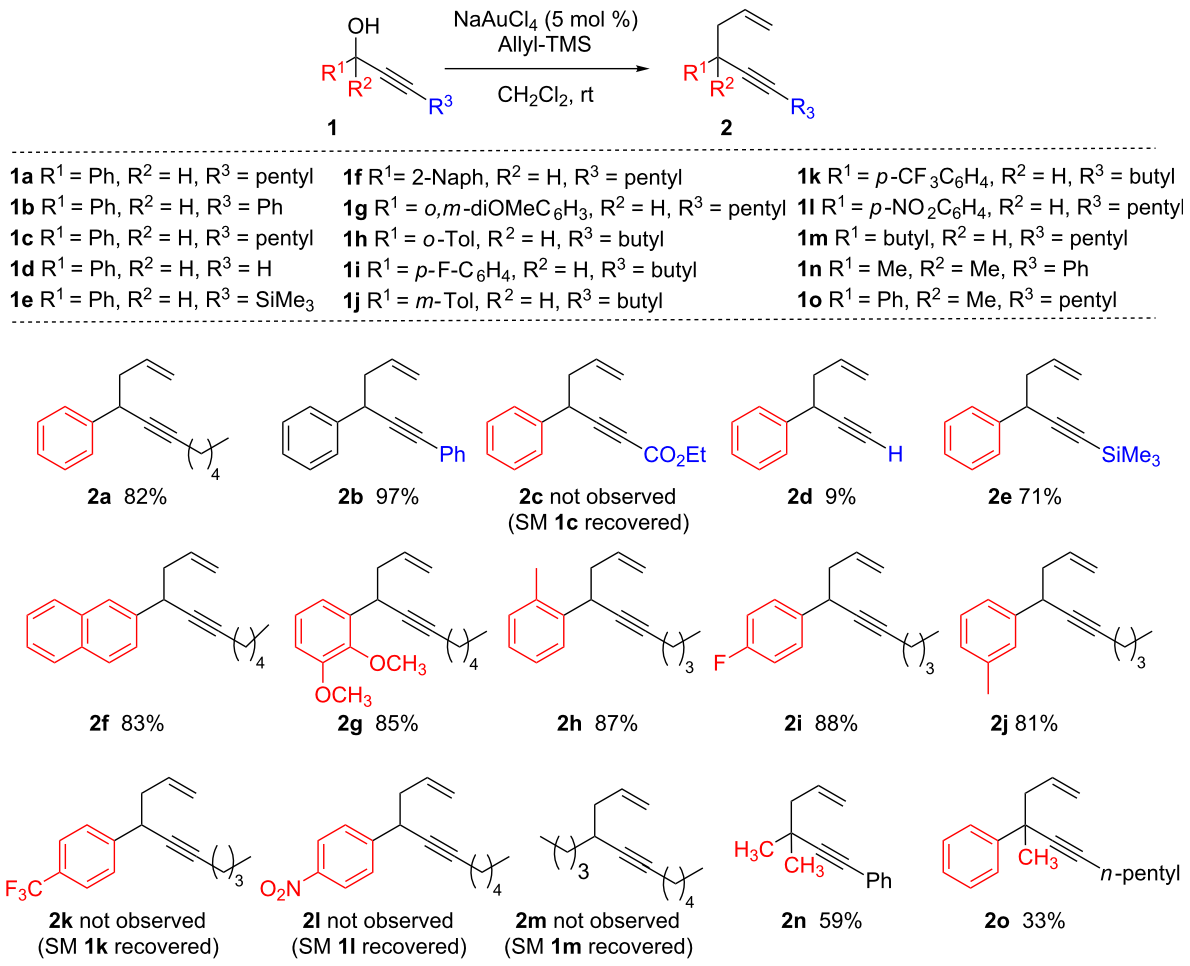
In the past few years, homogeneous gold catalysis has emerged as an efficient tool to activate triple bonds for the addition of various nucleophiles to alkynes. We initially anticipated that, through coordination to π-bond [46-48], gold catalysts may also act as propargylic alcohol-activating agents in propargylic substitutions (Scheme 1).

To validate this hypothesis, the reactivity of 1-phenyloct-2-yn-1-ol (**1a**, R^1 = Ph, R^2 = H, R^3 = *n*-pentyl) with allyltrimethylsilane in the presence of various gold catalysts at room temperature was investigated (Scheme 2, Table 1). Gratifyingly, the reaction proved to be efficient with various Au(III) reagents (at 5% catalyst loading) (Table 1, entries 1–4). The best results were observed with $NaAuCl_4{\cdot}2H_2O$ (Table 1, entry 1). In the presence of Au(I) catalysts (Table 1, entries 5 and 6), the results were more disappointing. Under the same reaction conditions (dichloromethane at room temperature), no reaction occurred in the presence of $PtCl_2$ and $PdCl_2(PhCN)_2$ catalysts.

Based on the results of these initial experiments, we set out to define the scope of these reactions by first examining variations on propargylic alcohols **1a**–**o**. As illustrated in Scheme 2, the effect of the nature of the substituent on the acetylenic position (R^3 group, Scheme 2) was examined. The following trend was observed: Ph > alkyl > SiR_3 > H >> CO_2Et. Indeed, the best yield (**2b,** 97%) was obtained with propargylic alcohol **1b** bearing a phenyl group and no reaction was observed when an electron-withdrawing group such as ester was present on the propargylic alcohol **1c**. It is worth noting that with terminal alkynes, the product **2d** was obtained in low yield (9%). The presence of various substituted aromatic groups on the propargylic position (R^1, R^2 groups), i.e., compounds **1f**–**1j** (for other examples, see reference [24]) gave good product yields, whilst aryl groups with strong electron-withdrawing groups such as *p*-NO_2 **1l** and *p*-CF_3 **1k** were unreactive. When the aryl group was replaced by an alkyl chain, no reaction occurred (as illustrated with **1m**) whereas when two alkyl substituents were present, as in **1n**, the reactivity was restored to give **2n** in 59% yield. When both an alkyl and an aromatic group were both

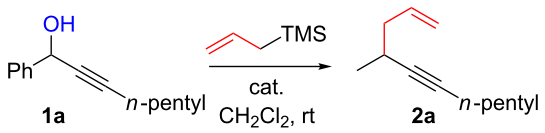


Scheme 1: Gold-catalyzed propargylic substitutions.



Scheme 2: Propargylic substitution: scope of substrates.

Table 1: Catalyst screening.



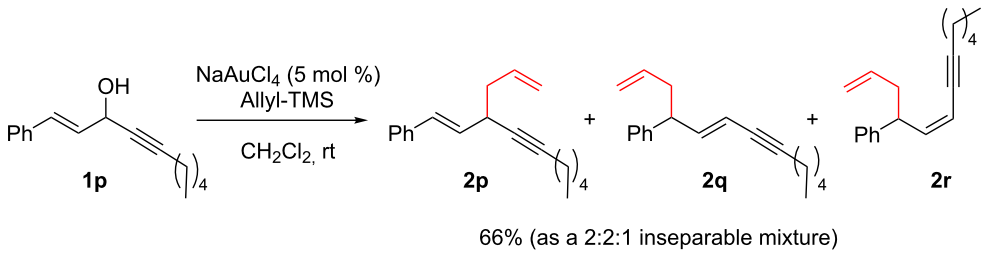
Entry	Gold cat (%)	Time (h)	**2a** Isolated yield (%)
1	$NaAuCl_4 \cdot 2H_2O$ (5)	12	82
2	$AuBr_3$ (5)	12	68
3	$AuCl_3$ (5)	12	65
4	$HAuCl_4 \cdot 3H_2O$ (5)	12	60
5	AuCl (10)	12	30
6	Ph_3PAuCl (10)	12	NR[a]
7	$PdCl_2(PhCN)_2$ (5)	12	NR[a]
8	$PtCl_2$(5)	12	NR[a]

[a]NR = no reaction.

present, as in **1o**, a lower yield was obtained due to rapid decomposition of the product **2o** at room temperature. It should be emphasized that all the allyl substituted products **2a**–**2o** have, in general, low stabilities and decompose within a few days at room temperature. Two general conclusions can be drawn from these experiments using allylsilanes as nucleophiles: A stabilization of a positive charge (+ or δ+) on the propargylic position by electron-donating groups on the propargylic and/or acetylenic positions favors the reaction, and no product resulting from attack at the acetylenic position could be observed.

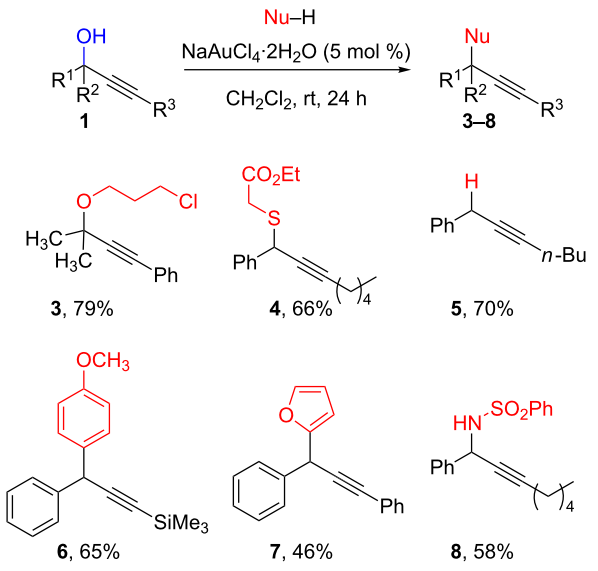
To explore further regioselectivity issues, compound **1p**, which is both an allylic and a propargylic alcohol, was submitted to the same reaction conditions. A 2:2:1 inseparable mixture of S_N **2p** and S_N' **2q** and **2r** products was obtained (Scheme 3).

The Au(III)-catalyzed reaction was next investigated for diverse series of nucleophiles. A large number of nucleophiles are very



Scheme 3: Propargylic substitutions on allylic/propargylic substrates.

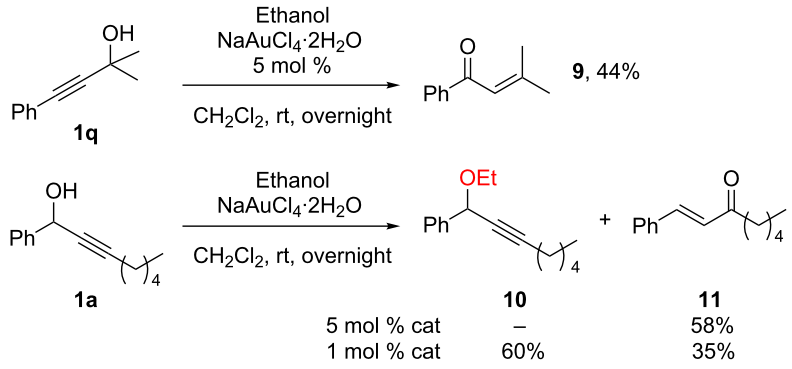
effective in these reactions including alcohols, thiols, hydrides (from Et_3SiH or PMHS), electron-rich aromatic and heteroaromatic derivatives such as anisole or furan, and deactivated nitrogen nucleophiles such as phenylsulfonamide (compounds **3**–**8**, Scheme 4).



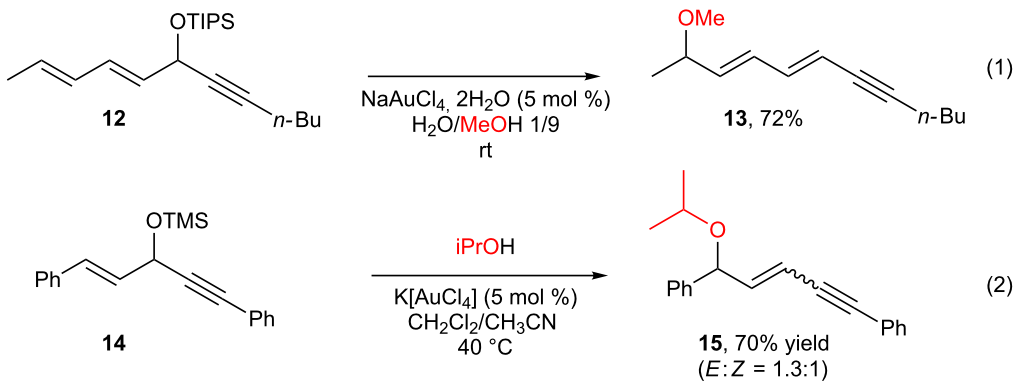
Scheme 4: Direct propargylic substitutions: Scope of nucleophiles.

In some instances unexpected selectivities and further transformations were observed. When ethanol was used as the nucleophile, the corresponding Meyer–Schuster products [49-54], first observed by Utimoto [49], were selectively obtained as illustrated with the formation of compounds **9** and **11** (Scheme 5).

Interestingly, lowering the catalyst loading to 1 mol %, the substitution product **10** could be isolated in 60% yield (along with 35% of the Meyer–Schuster product **11**). This result could be explained by considering that **11** is derived from **10** through the conjugated addition of water (residual or produced during the substitution reaction) and a lower amount of gold catalyst should slow down the Meyer–Schuster process. It also suggests that, not only the OH group but also the OEt group can act as a good leaving group in these reactions. Indeed, when isolated compound **10** was subjected to Au(III) catalyst in the presence of water, **11** was obtained as the major product along with some unidentified by-products. Two consequences from these results are i) the use of an alcohol as nucleophile gives a product that can act as a substrate for further transformations (such as a Meyer–Schuster reaction), and ii) other ether (O–Si, O–C) functions can be used in these reactions. Indeed, the use of silyl protected OH groups is possible as illustrated by our group (Scheme 6, reaction 1) and by the Kirsch group (Scheme 6, reaction 2) [24,55]. In both cases selective S_N' reactions were observed, not only with oxygen nucleophiles but also with



Scheme 5: Meyer–Schuster rearrangements.



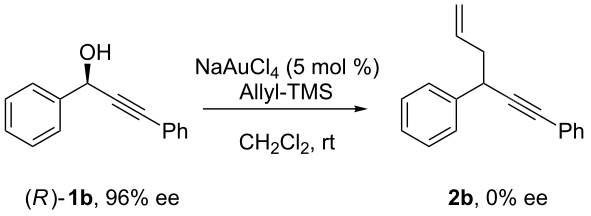
Scheme 6: Silyl-protected propargyl alcohols in propargylic substitutions.

nitrogen and electron-rich aromatic nucleophiles [55]. It is worth noting that a mixture of S_N and S_N' products was obtained when allylsilane was used as the nucleophile with related substrates (Scheme 3).

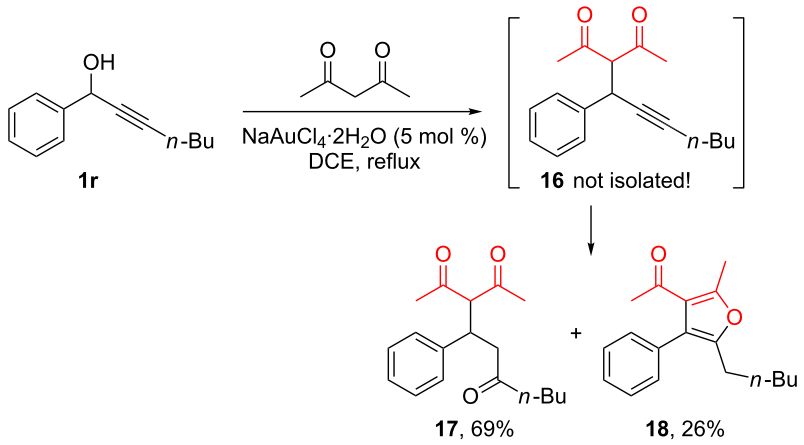
When acetylacetone was used as the nucleophile, no reaction occurred with **1r** at room temperature, whereas in refluxing dichloroethane the substitution product **16** led to a mixture of products via triple bond hydration to give **17** [49,50,56] and furan formation to afford **18** (Scheme 7). The furan may possibly result from intramolecular addition of the enol form of acetylacetone. Related experiments have been independently reported by Arcadi [57].

The main limitations of the methodology appeared when azido ($TMSN_3$), amides and phosphorus centered nucleophiles were used as nucleophiles: In these cases, either decomposition products or dimerization to the ether product were observed [58].

As previously noted, the lack of reactivity when aryl substituents bearing electron-withdrawing groups are present either at the propargylic or acetylenic positions, or when the propargylic position is only substituted by one alkyl group, suggests that an S_N1-type reaction is involved. To confirm this hypothesis, the reaction starting from enantiomerically pure **1b** was carried out and the resulting substitution product **2b** was shown to be the racemate (Scheme 8).

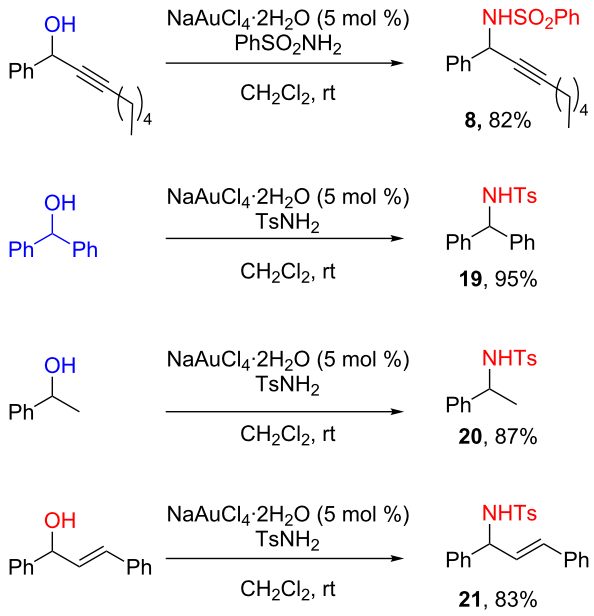


Scheme 8: Enantiomerically enriched propargylic alcohols.



Scheme 7: Acetylacetone as nucleophile in direct propargylic substitution.

This result showed that the presence of triple bond may be not necessary and prompted us to extend the methodology to other activated alcohols such as diarylmethanol, benzylic and allylic alcohols (Scheme 9) [24,59-61]. This reaction was further extended to tertiary alcohols by Asensio [62].



Scheme 9: Scope of 'activated' alcohols in direct substitution reactions.

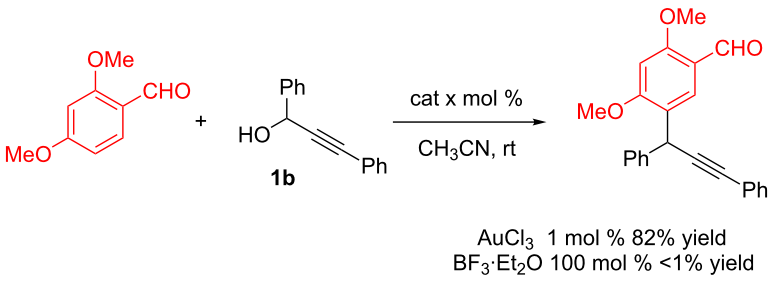
Shortly after the publication of our seminal results [23], the direct substitution of activated (propargylic, benzylic and allylic) alcohols became of increasing interest and many efficient alternative methods were proposed [40-43]. Among these, great interest has been shown in the use of APTS or iron(III) catalysts due to their low cost and toxicity [26-29]. Despite its high cost, gold catalysis has some intrinsic benefits compared to other reported methodologies. Firstly, these Au(III)-catalyzed substitutions are clean and efficient processes and are usually carried out at room temperature. This point was very nicely illustrated by Dyker: In the reaction of 2,4-dimethoxybenzaldehyde with propargylic alcohol **1b** (Scheme 10), no substitution occurred at room temperature with a stoichiometric amount of $BF_3{\cdot}Et_2O$ but was complete with only 1 mol % of $AuCl_3$ as catalyst [25].

Secondly, gold(III) possesses π-acidic properties and is able to activate triple bonds towards the addition of nucleophiles. Thus different reactivities and selectivities might be expected under gold catalysis conditions. For example, it could be interesting to combine both Lewis and π-acidities to promote domino reactions [44,45].

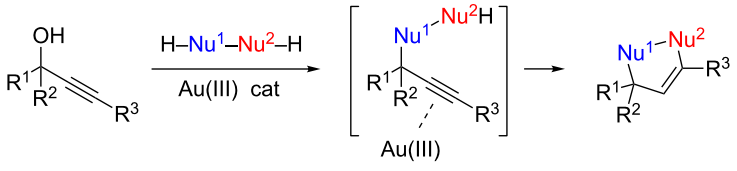
Domino reactions in the presence of bi-nucleophiles

We anticipated that by using bi-nucleophiles $HNu^1–Nu^2H$, the first nucleophilic substitution would be followed by activation of the triple bond and addition of the remaining nucleophilic group to the alkyne (Scheme 11) [63].

Whereas no reaction occurred with bis-protected hydrazines, unexpected reactions occurred with protected (P = Cbz, $PhSO_2$) hydroxylamines (Scheme 12). In model reactions of propar-

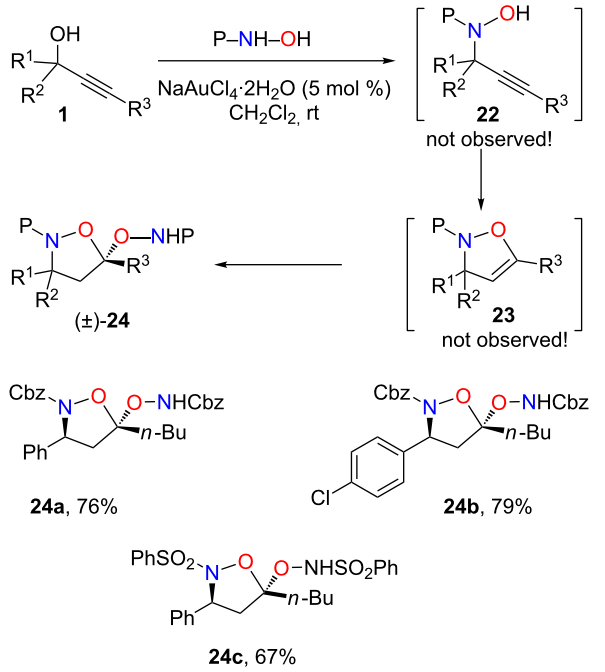


Scheme 10: BF_3 vs $AuCl_3$ in propargylic substitutions [25].



Scheme 11: The use of bis-nucleophiles in direct propargylic substitutions.

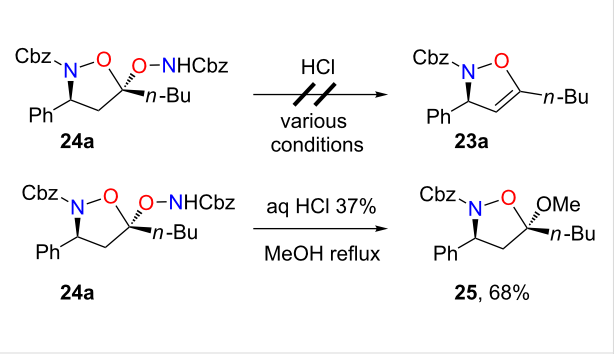
gylic alcohol **1** with $PhSO_2NHOH$ in the presence of $NaAuCl_4$ neither the propargylic substitution product **22** nor the expected isoxazoline **23** could be observed in the crude product. Instead a 1:1 mixture of unreacted alcohol **1** and compound **24** formally resulting from the addition of a second equivalent of hydroxylamine was obtained. By using 2.1 equivalents of the Cbz- or $PhSO_2$-protected hydroxylamines, compounds **24a–c** were isolated in 67–79% yields as single diastereomers. Determination of the structures of **24** was a challenging task and could only be determined by an X-ray crystal structure determination on compound **24b** [63].



Scheme 12: Tandem reactions from protected hydroxylamines and propargylic alcohols. P = Cbz, $PhSO_2$.

Efforts to regenerate isoxazolines **23a** from **24a** by acidic treatment, under various conditions, were unsuccessful in our hands. Notably, in the presence of 37% aqueous HCl in refluxing methanol, the transacetalized product **25** was isolated in 68% yield (Scheme 13).

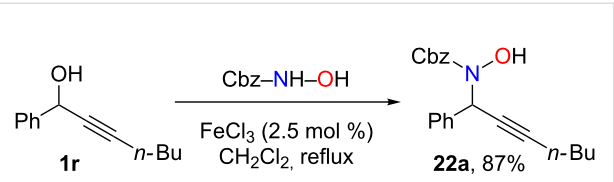
The desired isoxazolines cannot be directly obtained from propargylic alcohols **1** in the presence of gold(III) catalysts. From these preliminary experiments, it appears that the addition of hydroxylamine to the isoxazoline double bond is much faster than propargylic substitution. Consequently, the only possibility to obtain these isoxazolines would be to realize the propargylic substitution first of all (and consume all of the hydroxylamine) and subsequently perform the cyclization. Since iron(III) was known to be inefficient in the hydration of



Scheme 13: Tentative hydrolysis of bis-adduct **24a**.

triple bonds [64,65], we anticipated that its use would lead only to the propargylic substitution product [28,29], and then, by adding a gold(III) catalyst, the cyclization could occur to yield the isoxazolines.

Indeed, in the presence of iron(III) chloride [66-69], the substitution product **22a** was obtained in 87% yield, with no trace of the cyclized product even after prolonged reaction at reflux (Scheme 14). Very recently, Darcel described the iron(III) hydration of terminal alkynes [65]. These conditions were attempted to cyclize **22a** but in our hands only extensive decomposition was observed. We thus turned our attention to gold-catalyzed cyclization of **22a** which proved more difficult than initially expected (Table 2). As shown in Table 2, different metal salts were tried, and it was found that the best conditions were obtained when gold(III) was used in the presence of a catalytic amount (30 mol %) of DMAP [70].

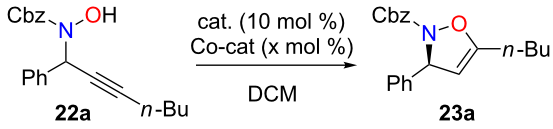


Scheme 14: Iron-catalyzed propargylic substitutions.

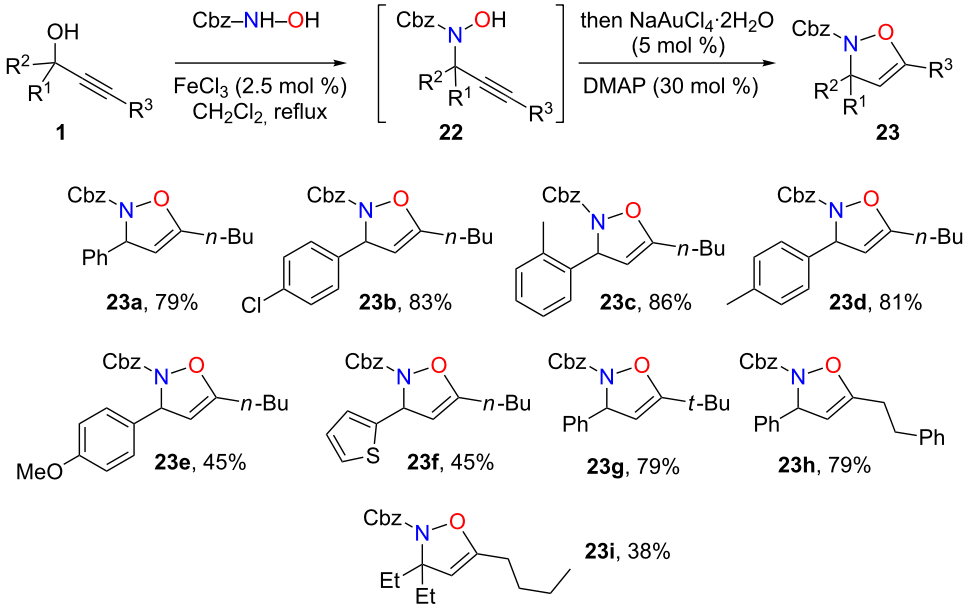
We next tried to develop one-pot conditions for the direct transformation of propargylic alcohols **1** to isoxazolines **23**. Thus, treatment of the propargylic alcohol first of all with $FeCl_3$ to promote the propargylic substitution followed by reaction with $NaAuCl_4$, in the presence of DMAP 30 mol %, for the cyclization step as outlined in Scheme 15 proved to be efficient and compounds **23a–i** were obtained in 38–86% yield (Scheme 15).

Prompted by the apparently simplicity of the addition of hydroxylamine to the isoxazoline double bond (Scheme 12), we next tried to promote the gold-catalyzed addition of various

Table 2: Propargylic *N*-hydroxylamine cyclization.



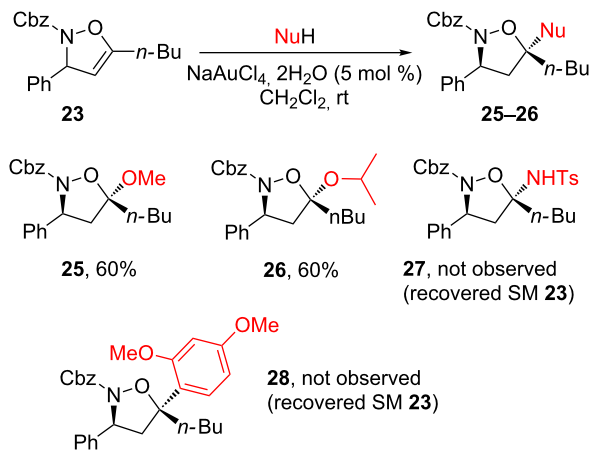
Entry	Cat. (10 mol %)	Co-Cat mol %	*T*	Yield (%)
1	$NaAuCl_4·2H_2O$	—	rt or reflux	<20%
2	Ph_3PAuCl	—	rt or reflux	—
3	$Ph_3PAuCl/AgOTf$	—	reflux	8
4	ZnI_2	DMAP 30	rt or reflux	15–20
5	$FeCl_3$	DMAP 30	reflux	—
6	$NaAuCl_4·2H_2O$	DMAP 30	reflux	84



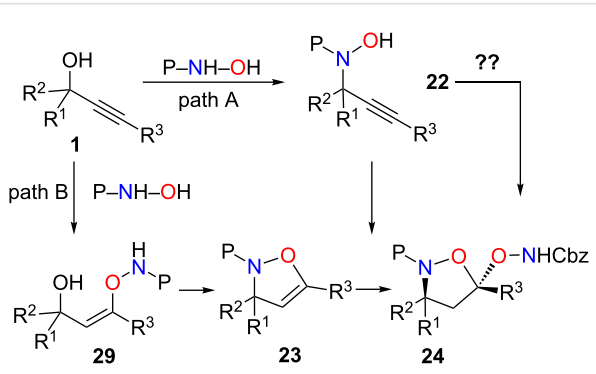
Scheme 15: Isoxazolines formation.

nucleophiles. As illustrated in Scheme 16, the reaction proved restricted to alcohols and no reaction occurred with $TsNH_2$ or electron-rich aromatic compounds such as 1,3-dimethoxybenzene.

Some contradictions arose from these experiments. On one hand, when propargylic alcohols **1** and protected hydroxylamines were treated with gold catalyst at room temperature (Scheme 12), the reactions were rapid and led to the formation of **24**. On the other hand, when trying to perform gold-catalyzed cyclization of the isolated propargylic substitution product **22**, the reaction appeared to be difficult and required the addition of a co-catalytic amount of DMAP, under reflux conditions, to be effective. Moreover, it has been shown that oxygen nucleophiles are prone to attack at the acetylenic site. Thus the reaction pathway could proceed in one of two ways: First, propargylic substitution by the nitrogen of the nucleophile followed by the cyclization (Scheme 17, path A) or attack on the acetylenic position by the oxygen of the nucleophile followed by intramolecular propargylic substitution (Scheme 17, path B).

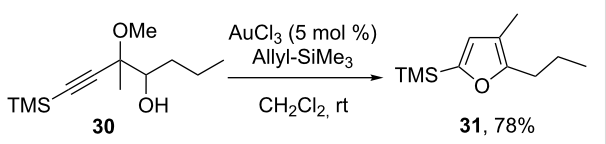


Scheme 16: Addition of nucleophiles to isoxazolines.



Scheme 17: Potential mechanistic pathways.

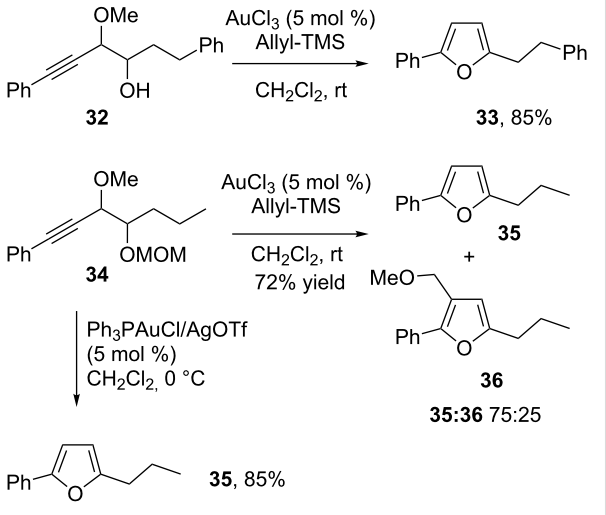
The determination of the reaction pathway is a challenging task and to gain more insight we designed a model substrate **30** bearing a methoxy group in a quaternary substituted propargylic position and a (nucleophilic) alcohol function in the homopropargylic position. In order to deactivate the triple bond toward nucleophilic addition, a TMS group was placed in the acetylenic position. This substrate, obtained from the addition of an allenyl(cyano)cuprate on butyraldehyde [71-73], was reacted with allyltrimethylsilane. The reaction was totally regioselective for the propargylic site. Different reaction paths can be expected: i) The formation of a propargylic carbocation that can be attacked by allyltrimethylsilane or vicinal hydroxy group and ii) homopropargylic alcohol attack on the triple bond. The only product that could be isolated was the furan **31** which was obtained in 78% yield, with no trace of any product arising from an allylsilane attack (Scheme 18). The formation of the furan might be explained by a direct attack of the homopropargylic alcohol on the triple bond or a gold-catalyzed rearrangement of a transient epoxide as recently described by Blanc and Pale [74-76].



Scheme 18: Synthesis of furans from homoproargylic alcohols.

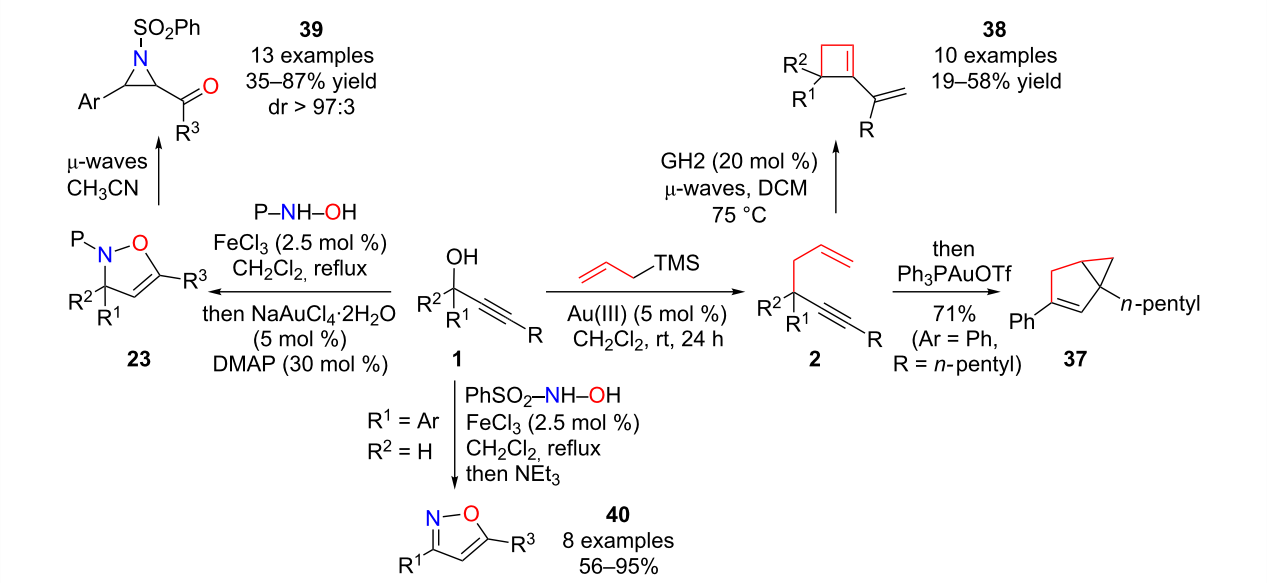
Synthetic developments

This result prompted us to explore the synthesis of functionalized furans from various homopropargylic alcohols obtained on a multi-gram scale, by our recently described allenylcuprate chemistry [71-73]. In the meantime, Aponick [77] and Akai [78] described very similar results using Au(I)/Ag(I) catalysts. Some of our gold(III)-catalyzed reactions are illustrated in Scheme 19. Interestingly, when the homopropargylic alcohol is protected as a MOM ether, a mixture of furans resulting from proto-demetallation **35** and MOM transfer **36** was obtained in a 75:25 ratio, respectively, whereas in the presence of gold(I) catalyst the proto-demetallation product **35** was the sole product. For related cyclization with subsequent migration of the ether substituent, see [79] and references therein. This experiment further highlights the strong propensity of oxygen nucleophiles for the addition to gold activated triple bonds.



Scheme 19: Synthesis of furans.

From allylated substitution products **2**, we were also able to develop two synthetic applications. In an one-pot, sequential, reaction with first a gold(III)-catalyzed propargylic substitution followed by a gold(I)-catalyzed cycloisomerization, the bicyclic compound **37** was obtained in 71% yield [24,80-82]. Very recently, a remarkable one-pot reaction using an original gold(III) catalyst has been described by Fairlamb [82]. We were



Scheme 20: Propargylic substitutions: Synthetic applications. GH2 = Grubbs–Hoveyda 2nd generation catalyst.

also able, from compound **2**, to develop a 1,5-enyne metathesis that leads to functionalized cyclobutenes **38** (Scheme 20) [83], which was subsequently nicely illustrated by Goess in a total synthesis of grandisol [84].

From isoxazolines **23**, we were also able to promote, under micro-waves irradiation, a Baldwin rearrangement to yield the *cis*-acylaziridines **39**, with high diastereoselectivity [85]. Finally, from propargylic alcohols **1**, a sequential iron(III)-catalyzed propargylic substitution [28,29] followed by a NEt_3-mediated elimination of the sulfonyl group and oxime cyclization gave, in a *one-pot* sequence, the corresponding isoxazoles **40** in good yields (Scheme 20) [86].

Conclusion

In conclusion, we have developed gold(III)-catalyzed direct propargylic (allylic, benzylic) substitutions which have proved efficient with a great number of nucleophiles under mild conditions (dichloromethane, room temperature). A notable limitation of this methodology is since a stabilized positive charge is involved the scope of the reaction is limited to the use of tertiary or benzylic (allylic) propargylic alcohols. On the other hand, such a mechanism also implies that in the presence of chiral gold catalyst, through coordination to the triple bond (Scheme 1), enantioselective transformations could be obtained. We also found that with chiral gold(III) complexes very deceiving results can be obtained. It is worth noting that, recently, Bandini described very impressive enantioselective intramolecular direct allylic substitutions using chiral gold(I) complexes [87,88]. We also took advantage of the π- and σ-(Lewis) acidities of gold(III) complexes to promote domino reactions with bi-nucleophiles such as protected hydroxylamines. In the presence of gold(III), the expected isoxazolines **23** could not be directly obtained but required a dual iron(III)/gold(III) catalysis to be effective. Nevertheless, gold catalysts exert interesting π- and σ-Lewis properties, allowing direct nucleophilic substitution of various di or tri-substituted alcohols and cyclization reactions under mild conditions. This methodology gives easy access to various elaborated molecules with varied functionalities, as illustrated in this account.

Acknowledgements

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Gold(I)-catalyzed formation of furans by a Claisen-type rearrangement of ynenyl allyl ethers

Florin M. Istrate and Fabien Gagosz*

Letter

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Address:
Département de Chimie, UMR 7652, CNRS/Ecole Polytechnique, 91128 Palaiseau, France

Email:
Fabien Gagosz* - gagosz@dcso.polytechnique.fr

* Corresponding author

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Abstract

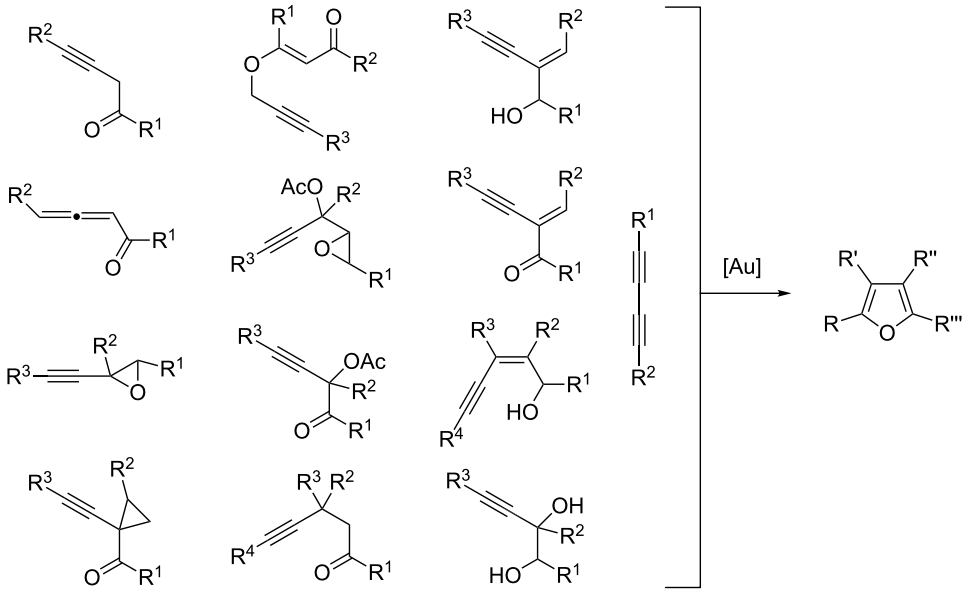
A series of ynenyl allyl ethers were rearranged into polysubstituted furans in the presence of a gold(I) catalyst. It is proposed that the transformation involves a Claisen-type rearrangement that allows the efficient creation of quaternary centers under mild experimental conditions.

Findings

Furans represent an important class of heteroaromatic compounds, which are found in a large number of natural products, in synthetic biologically active substances and also in flavor chemicals [1,2]. Consequently, many efforts have been devoted to the development of synthetic methods which allow a rapid, efficient, and selective access to the furan motif [3-6]. Recently, several new strategies that involve a metal-mediated cyclization of an allene or an alkyne derivative with an oxygen functionality have appeared in the literature [7]. Among the transition metals that are commonly employed in these transformations (viz. Cu, Ag, Pd and Au), gold has proven to be particularly suitable given the strong π Lewis acidic property of cationic gold species and their ability to activate alkynes and allenes towards the addition of oxygen functionalities [8-16]. The various alkynyl and allenyl compounds presented in Scheme 1 have thus proved to be suitable precursors for the formation of polysubstituted furans in the presence of a gold(I) or a gold(III) catalyst [17-44].

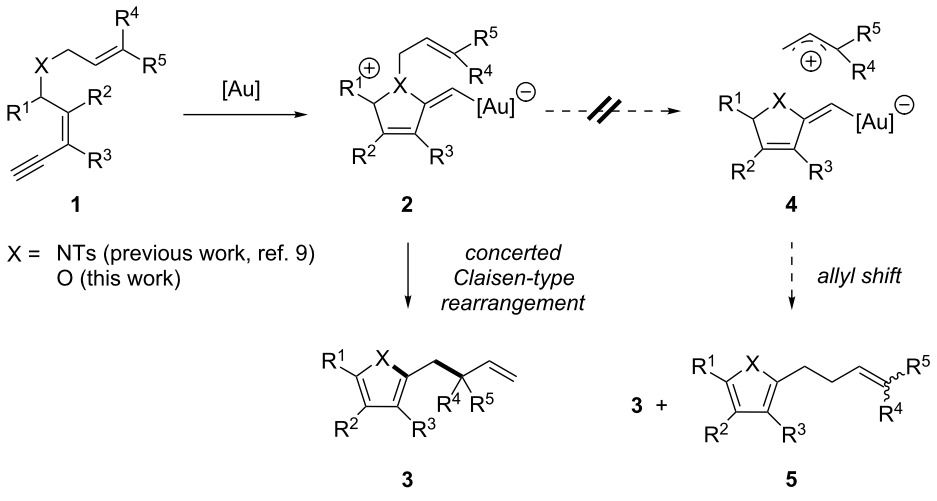
We report herein our own investigations in this field which have led to the development of a new procedure for the synthesis of polysubstituted furans by a gold-catalyzed cycloisomerization of ynenyl allyl ethers [45-48].

In the course of our work on the development of new gold-catalyzed transformations [49-51], we recently found that a series of ynenyl allyl tosylamides **1** (X = NTs) could be converted under mild experimental conditions into functional-



Scheme 1: Alkynyl and allenyl substrates in gold-catalyzed formation of furans.

ized pyrroles **3** (X = NTs) in the presence of a gold(I) catalyst (Scheme 2) [52]. In contrast to Fürstners observations for the rearrangement of allyl pent-4-ynyl ethers [53,54], the results obtained during this study strongly suggested that no allyl cation was formed during the reaction. The substitution pattern of the pyrroles thus obtained point toward the involvement of a more concerted aza-Claisen-type rearrangement mechanism (**2** → **3**) and tend to exclude the possibility of a simple N to C allyl shift (**2** → **4** → **5**). Based on these initial findings, we envisaged that an analogous transformation could be employed for the synthesis of substituted furans **3** (X = O) from ynenyl allyl ethers **1** (X = O) (Scheme 2). The proof that a similar reaction can take place via an analogous pathway using oxygen- instead of nitrogen-derivatives would therefore support our initial mechanistic proposal and would broaden the scope of this new gold-catalyzed Claisen-type rearrangement [55-62].



Scheme 2: Synthetic approach to functionalized furans.

Moreover this synthetic approach to furans would be particularly interesting for several reasons:

• The required ynenyl allyl ether substrates are easily accessible via various methods (see Supporting Information File 1 for more details),

• the Claisen-type rearrangement would allow the formation of two new C–O and C–C bonds in a single step,

• the reaction would allow the easy formation of quaternary centers and the introduction of a variety of other substituents on the side chain (when $R^4 \neq H$ and $R^5 \neq H$),

• and the reaction could be particularly useful for the preparation of 2-butenylfurans, whose motif can be found in a variety of natural products, such as rubifolide [63], curzerene [64] or pumiloxide [65] (Figure 1).

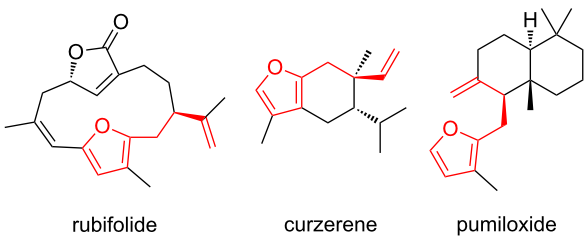
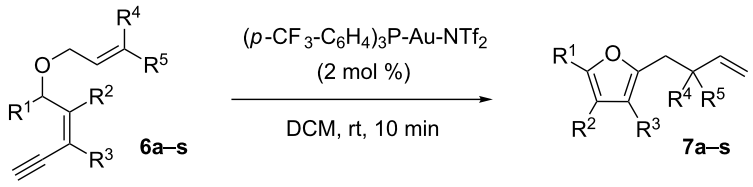


Figure 1: Natural products possessing a 2-butenylfuran motif.

Thus, a wide range of ynenyl allyl ethers **6a–s** was synthesized (see Supporting Information File 1) and reacted under the conditions that were found to be optimal for the analogous formation of pyrroles from ynenyl allyl tosylamides, that is, 2 mol % of the gold catalyst {[(*p*-CF_3-C_6H_4)$_3$P]-Au-NTf_2} [66] in dichloromethane at room temperature (Table 1).

Table 1: Scope of the gold(I)-catalyzed formation of furans.[a]



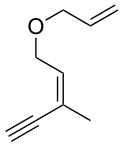
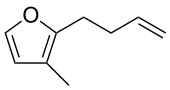
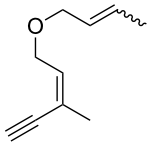
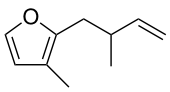
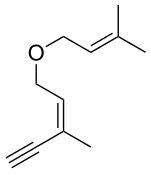
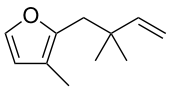
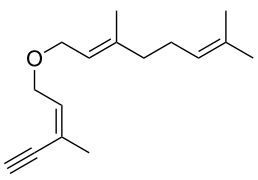
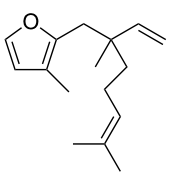
entry	substrate		product		conversion[b]	yield[c]
1		**6a**		**7a**	100%	18% (75%[d])
2		**6b**[e]		**7b**	100%	39% (86%[d])
3		**6c**		**7c**	100%	59% (82%[d])
4		**6d**		**7d**	100%	81% (92%[d])

Table 1: Scope of the gold(I)-catalyzed formation of furans.[a] (continued)

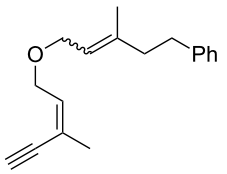
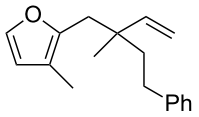
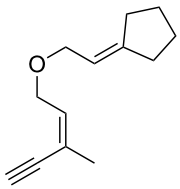
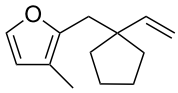
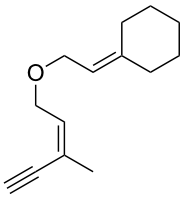
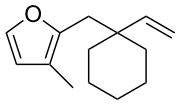
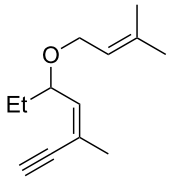
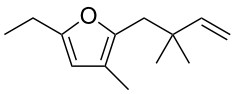
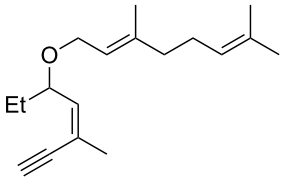
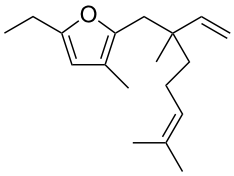
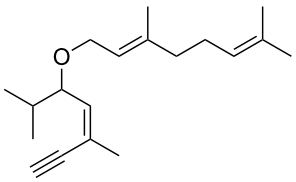
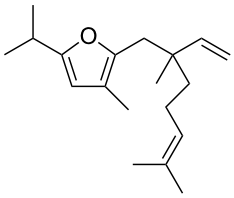
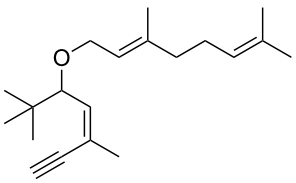
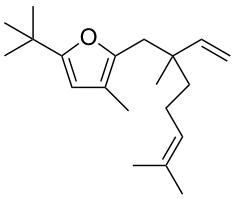
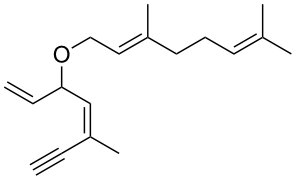
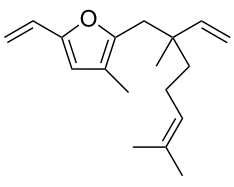
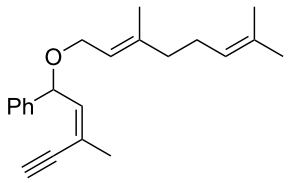
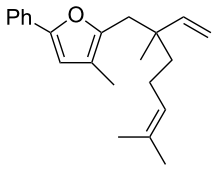
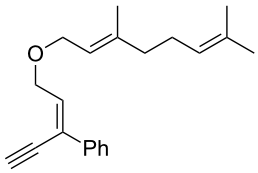
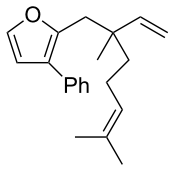
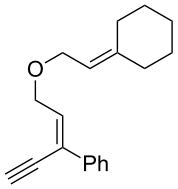
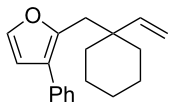
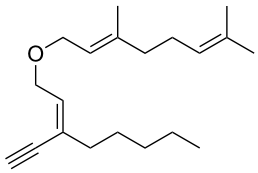
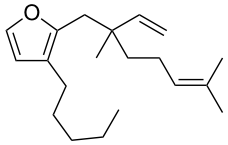
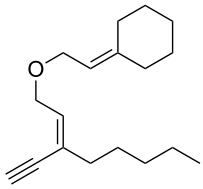
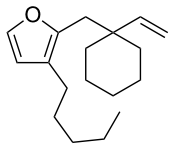
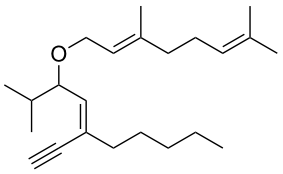
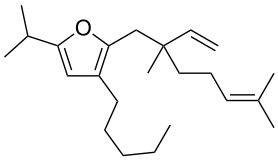
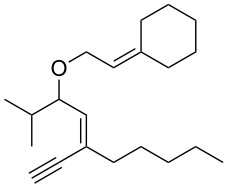
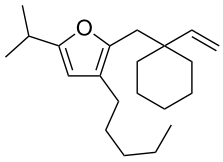
5		**6e**[f]		**7e**	100%	66%
6		**6f**		**7f**	100%	71%
7		**6g**		**7g**	100%	63%
8		**6h**		**7h**	100%	quant.
9		**6i**		**7i**	100%	quant.
10		**6j**		**7j**	100%	78%
11		**6k**		**7k**	100%	78%
12		**6l**		**7l**	100%	17%

Table 1: Scope of the gold(I)-catalyzed formation of furans.[a] (continued)

13		**6m**		**7m**	100%	77%
14		**6n**		**7n**	100%	80%
15		**6o**		**7o**	100%	90%
16		**6p**		**7p**	100%	82%
17		**6q**		**7q**	100%	86%
18		**6r**		**7r**	>84%[g]	73%
19		**6s**		**7s**	>62%[g]	36%

[a]Reaction conditions: 0.1 M of substrate in DCM with 2 mol % of (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 at rt for 10 minutes. [b]Conversion of the substrate determined by ^{1}H NMR of the crude mixture. [c]Isolated yields. [d]Yields determined by ^{1}H NMR of the crude mixture (with 1,3,5-trimethoxybenzene as an internal reference). [e]*Z*/*E* ratio ≈ 1/3. [f]Z/E ratio ≈ 1/2.6. [g]Reaction time: 40 minutes.

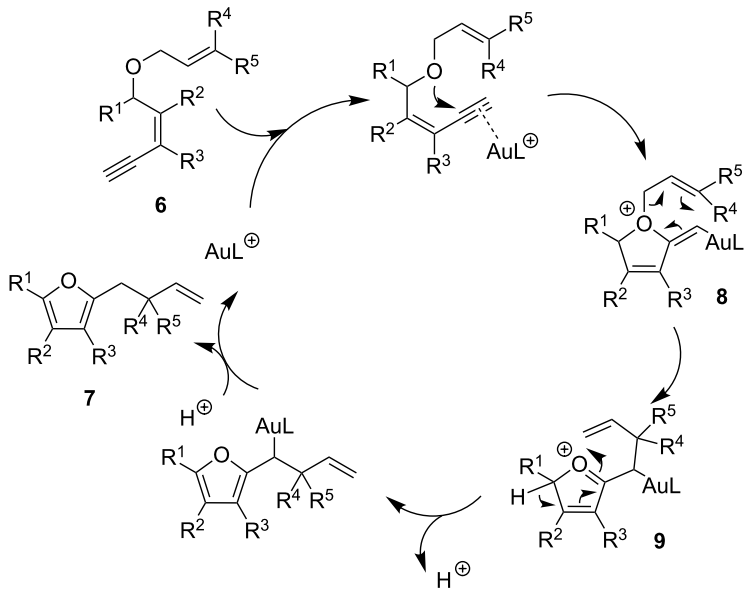
Under these conditions, we observed the rapid formation (usually less than 10 minutes) of the expected furans. The allyl (**6a**), crotyl (**6b**), prenyl (**6c**) and geranyl (**6d**) derivatives were readily cycloisomerized in the presence of the gold catalyst, but the isolation of the corresponding furans **7a**–**d** proved to be quite challenging due to their high volatility (entries 1–4). These reactions were therefore performed in deuterated dichloromethane and their yields assessed by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal reference (75–92%). All the examples presented in entries 2–19 are in

agreement with the postulated Claisen-type rearrangement since only the exclusive formation of branched products of type **3** was observed. Indeed, a linear product of type **5** resulting from an O to C shift of the allylic moiety could not be detected, whatever substrate was used [67]. Substrates **6b** and **6e**, which were used as a mixture of *Z*/*E* isomers, each afforded a single product, i.e., the furans **7b** and **7e**, respectively (entries 2 and 5). The cycloisomerization of compounds **6f**, **6g**, **6o, 6q** and **6s**, which possess an exocyclic allyl moiety, furnished the corresponding furans **7f**, **7g**, **7o, 7q** and **7s** in moderate to quantitative yields (entries 6, 7, 15, 17 and 19). It is also worth noting that an increase in the substitution at the terminus of the allylic moieties of the substrates (monosubstitution in the case of **6b**, disubstitution for **6c**–**s**) did not notably influence the conversion, the rate or the yield of the reaction, even though the steric hindrance of the postulated Claisen intermediate **2** would have increased. This behavior strongly contrasts with the generally less efficient Claisen reactions of similarly substituted substrates and consequently allows the easy creation of a new quaternary center for the disubstituted substrates **6c**–**s** (entries 3–19). Interestingly substrates **6h**–**m**, which possess an extra substituent at the allylic position of the ynenyl fragment, also easily rearranged to afford the expected furans **7h**–**m** in good to quantitative yields (entries 8–13). A large variety of substituents were tolerated including primary, secondary or tertiary alkyl groups and even a vinyl or a phenyl group. However, a poor yield (17%) was obtained when compound **6l** was used as the substrate, due to the facile polymerization of the corresponding vinylfuran **7l** (entry 12). Substituents other than a simple methyl group could be introduced at position C(3) of the furans. Substrates **6n**–**q**, which possess either a phenyl or a longer alkyl chain, were indeed efficiently converted into compounds **7n**–**q** (80–90%, entries 14–17). However, limited reactivity was observed with ethers **6r**–**s**, which could not be completely converted into the corresponding furans **7r**–**s** (entries 18–19).

A mechanistic proposal for the formation of furans **7a**–**s** is presented in Scheme 3. It is based on the results shown in entries 2–19 (Table 1), which support the involvement of a gold-catalyzed Claisen-type rearrangement as the key step of the transformation.

The gold(I) activation of the alkyne moiety in substrate **6** could promote the nucleophilic addition of the oxygen atom, and lead to the formation of the cationic vinyl gold intermediate **8**. A subsequent Claisen-type rearrangement would furnish the intermediate **9**. The loss of a proton to allow aromatization of the system, followed by a protodemetalation step would finally give furan **7**.

In summary, we have developed a new gold(I)-catalyzed formation of polysubstituted furans, which is characterized by its efficiency, the mild conditions employed and the easy formation of quaternary centers. The selectivity observed in the structure of the final product is in agreement with the postulated Claisen-type rearrangement. Further studies related to the development of an asymmetric version of this new gold(I)-catalyzed process and its application to the synthesis of natural products are underway.



Scheme 3: Mechanistic proposal.

Supporting Information

Supporting Information File 1

Detailed experimental procedures.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-100-S1.pdf]

Supporting Information File 2

NMR spectral data for substrates **6a**–**s**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-100-S2.pdf]

Supporting Information File 3

NMR spectral data for products **7a**–**s**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-100-S3.pdf]

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The role of silver additives in gold-mediated C–H functionalisation

Scott R. Patrick, Ine I. F. Boogaerts, Sylvain Gaillard, Alexandra M. Z. Slawin and Steven P. Nolan*

Full Research Paper

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Address:
EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK

Email:
Scott R. Patrick - srp3@st-andrews.ac.uk; Ine I. F. Boogaerts - ib51@st-andrews.ac.uk; Sylvain Gaillard - sg210@st-andrews.ac.uk; Alexandra M. Z. Slawin - amzs@st-andrews.ac.uk; Steven P. Nolan* - snolan@st-andrews.ac.uk

* Corresponding author

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C–H functionalisation; gold catalyst; halide abstraction; *N*-heterocyclic carbene; silver salt; substrate activation

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Abstract

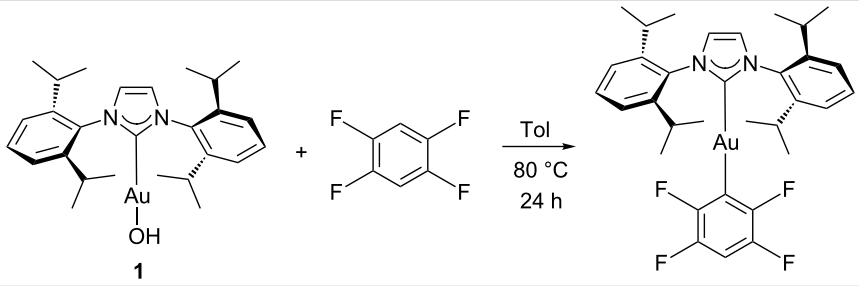
The role of silver additives is examined in the context of gold-mediated functionalisation of aromatic C–H bonds. Doubt is cast on the commonly cited route of halide abstraction from gold and evidence of substrate activation is given.

Introduction

The use of gold in homogeneous catalysis is an area where fascinating advances have been realised in the last few years [1-4]. One of these discoveries has focused on the possibility of using gold in metalation reactions [5-8] directly leading to organogold complexes. The further use of organogold complexes bearing *N*-heterocyclic carbenes (NHC) [9,10] as supporting ligands has enabled the isolation of a "golden synthon", [Au(OH)(IPr)] **1** (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), that is able to participate in metalation reactions with aromatic C–H bonds (Scheme 1) [11].

The reactivity profile of **1** appears linked to bond acidity, and was found to functionalise selectively the most electron-deficient C–H bond in a substrate. Unfortunately, the reactivity of **1** was limited to bonds with a pK_a value below 30.4 [12].

Current gold research has shown that silver salts can not only improve reaction times and yields [13,14], but also allow the C–H functionalisation of previously unreactive substrates. Larrosa has recently disclosed a mild methodology for the Au(I)-mediated C–H functionalisation of 1,3,5-trifluoroben-



Scheme 1: Silver-free C–H functionalisation using [Au(OH)(IPr)].

zene (**2**, p$K_{a\ DMSO}$ 31.5 [15]) using a mixture of reagents and additives (Scheme 2) [16]. The observation of a high kinetic isotope effect is suggestive of a concerted metalation–deprotonation mechanism, as first suggested for Pd(II) complexes, in which a pivalate ligand behaves as a proton acceptor via a six-membered transition state [17]. However, addition via a transient Au(III) hydride would also be consistent with these observations.

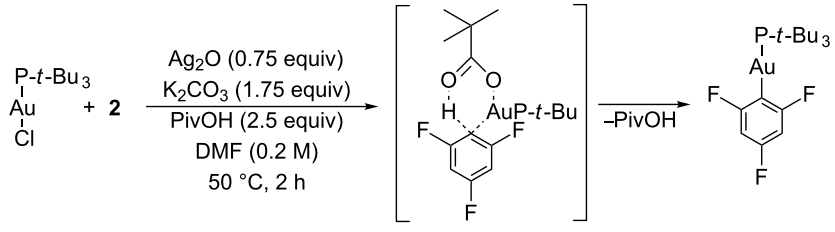
Results and Discussion

We became interested in understanding the mechanistic details of this transformation by identifying the role of the individual components. Reactions were performed between individual reagents and the formation of products was observed by ^{1}H NMR spectroscopy. Silver(I) oxide and potassium carbonate both reacted with pivalic acid to form metal pivalates after stirring in toluene at 50 °C for 20 h. Potassium carbonate did not interact directly with the aryl substrate after stirring in DMF at 50 °C for 24 h. A stoichiometric reaction between Ag_2O and the substrate displayed substitution of one of the protons. However, deuterium incorporation experiments were unsuccessful and mass spectrometry on the product was inconclusive.

The reaction depicted in Scheme 2 was performed using a neutral gold(I)-NHC complex. The reaction time was extended to 20 h in order to obtain optimal results. A reaction involving [AuCl(IPr)] proceeded with full conversion to product with all additives/reagents present. The removal of potassium carbonate from the reaction had no detrimental effect. Additionally, when it was the only additive used, no reaction took place. These results clearly eliminate the involvement of K_2CO_3 in direct deprotonation of the substrate [18]. Potassium carbonate reacts with pivalic acid to form KOPiv, leading to improved yields in the Larrosa methodology. However, this practice was not necessary in our work and the salt did not appear to have any other role in the mechanism. Further reactions did not utilise K_2CO_3.

The reaction between [AuCl(IPr)], **2** and Ag_2O yielded no product. A stoichiometric addition of pivalic acid was required for the reaction to proceed. The acid was believed to generate the reactive intermediate **3** [Au(OPiv)(IPr)] (OPiv = $(CH_3)_3CCO_2$) (Figure 1). To verify this hypothesis, the well-defined complex [19] was used in test reactions following the earlier conditions. Complex **3** reacted with **2** in conjunction with Ag_2O and gave complete conversion to **4** [Au($C_6H_2F_3$)(IPr)]. This strongly suggests that complex **3** is indeed an intermediate. However, the use of a silver salt was essential for the reaction to proceed.

The silver salt was suspected of abstracting the halide from [AuCl(IPr)] to generate a possibly active cationic gold(I) species [20]. To test this hypothesis, the well-defined cationic complex [(IPrAu$^+$)(NCMe)][BF_4^-] [21] was reacted with **2** in the absence of other reagents. No product was observed. Subsequent test reactions were performed using **1** (Table 1, entries 1–3), thus eliminating the possible in situ formation of cationic gold(I). The reaction proved successful in the presence of Ag_2O, suggesting that silver does not generate cationic gold. The reaction with pivalic acid gave a better conversion, indi-



Scheme 2: C–H functionalisation of **2** using gold-phosphine complexes and a silver additive.

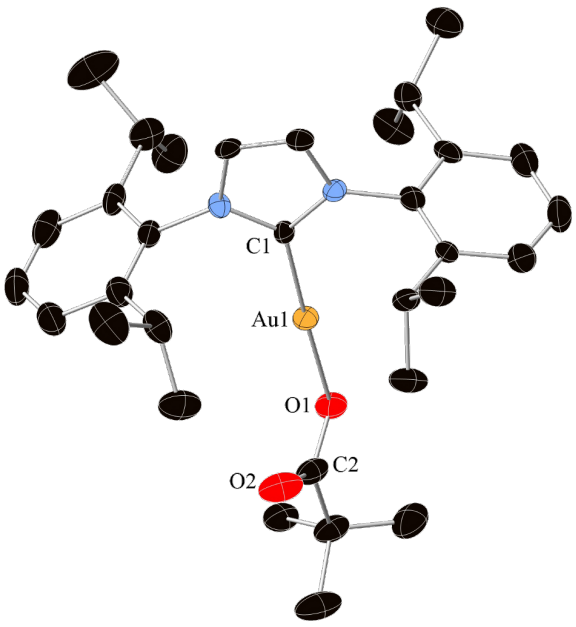


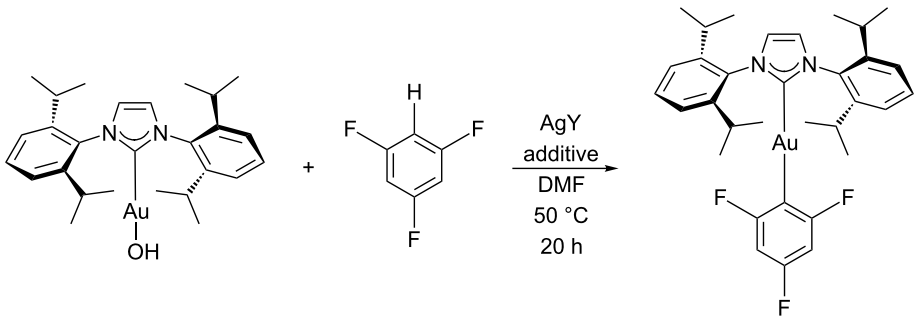
Figure 1: X-ray structure of [Au(OPiv)(IPr)] **3**. Thermal ellipsoids are shown at the 50% probability level. H atoms are omitted for clarity. Selected bond distances (Å) and angles (°) for **3**: Au1–C1 1.978(5), Au1–O1 2.048(4), O1–C2 1.299(8), C2–O2 1.231(9), C1–Au1–O1 178.0(2), Au1–O1–C2 120.7(4), O1–C2–O2 124.6(6).

cating that the gold proceeded via complex **3**. Further reactions used **1** as the gold species and no longer included PivOH.

The stoichiometric dependence of the silver salt was then examined. Both 0.50 and 0.25 equivalents of Ag_2O gave poor conversions to the product (entries 4 and 5) and further reducing the loading to 0.1 equivalents stopped the reaction entirely (entry 6).

A range of silver salts was compared in reactions involving **1** and **2**. Both AgF and AgOAc gave full conversion to product (entries 7 and 8), while the nature of the silver counter ion led reactivity to decrease in the order Ag_2O > AgI > AgO, $AgBF_4$, AgCl > Ag_2CO_3, $AgOCOCF_3$ > $AgNO_3$ > AgBr. Electronic effects can explain the general reactivity-decreasing trend on going from AgF to AgBr, but steric factors must also be considered to rationalise the anomalous activity of AgI. The Lewis acidity of the silver salts may contribute to initiate the reaction [22], but unsuccessful reactions using Al_2O_3, $AlCl_3$, Cu_2O or $ZnBr_2$ proved otherwise. The existence of a transient anion exchange between the gold (AuX) and the silver salt (AgY) may generate the active "AuY" complex. However, this was disproved by the successful reaction using AgCl. This would implicate [AuCl(IPr)] as the possible active species. This has

Table 1: C–H functionalisation of **2** using **1**.[a]



1 **2** **4**

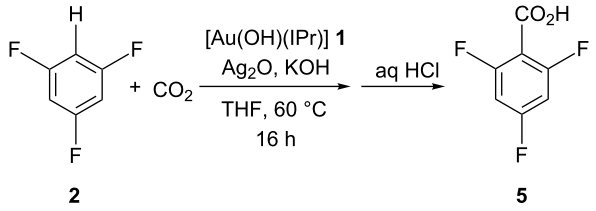
Entry	AgY	Additive	Conversion[b] (%)
1	Ag_2O	-	38
2	Ag_2O	PivOH	100
3	-	PivOH	0
4[c]	Ag_2O	-	15
5[d]	Ag_2O	-	11
6[e]	Ag_2O	-	0
7	AgF	-	100
8	AgOAc	-	100

[a]Unless otherwise noted, all reactions were carried out with **1** (1 equiv), **2** (4.5 equiv), salt (1.5 equiv) and additive (2.5 equiv) in a 0.2 M DMF solution. [b]Conversion to product was determined by ^{1}H NMR analysis relative to **1**. [c]AgY (0.5 equiv) was used. [d]AgY (0.25 equiv) was used. [e]AgY (0.1 equiv) was used.

already been discounted since it was shown to be unreactive in the model C–H bond functionalisation reaction.

To complete the examination of possibly important parameters enabling the reaction, the role of solvents was investigated. Solvent screening showed that the reaction could proceed in THF (59% conversion), DMF (38%), toluene (35%), 1,4-dioxane (21%) and poorly in cyclopentyl methyl ether (CPME) (3%). The conversions do not mirror the polarity of the solvents and the silver salts were sparingly soluble in every solvent tested [23].

As the functionalisation of C–H bonds was now found possible in the presence of silver additives, we reasoned that a test of the observation was to carry out a carboxylation reaction [12] with substrate **2** using catalyst **1** under optimised carboxylation conditions (Scheme 3).



Scheme 3: Carboxylation of **2** using **1** and Ag_2O.

The general procedure employed **2**, **1** (3 mol %), Ag_2O (3 mol %) and three equivalents of potassium hydroxide. Gratifyingly, whereas a reaction in the absence of silver leads to no carboxylation product, the addition of silver leads to formation of 2,4,6-trifluorobenzoic acid (**5**). The use of a stoichiometric amount of Ag_2O results in aggregation of the reagents that seemingly affects mass transport of CO_2 and halts the reaction. However, the catalytic use of Ag_2O gave a 22% isolated yield of **5**. This observation clearly shows that silver can have a positive role in the carboxylation of C–H bonds.

Conclusion

The C–H functionalisation of arenes using (NHC)gold(I) complexes has been shown to be significantly affected by the leaving group on the gold. The gold(I) chloride may only react by first forming the intermediates **1** or **3**. The gold(I) pivalate gives full conversion and is believed to form a six-membered transition state with the substrate. The gold(I) hydroxide gives incomplete conversion to product and the reaction pathway is currently unknown. The use of K_2CO_3 was shown to be unnecessary. The solvent used affects the conversion, although polarity appears not to be a factor. Silver does not act as a simple Lewis acid, as shown by the failure of other metal salts to facilitate the reaction. The reaction was shown to require stoichiometric amounts of the silver salt. The failed reaction of a cationic gold species hints that the silver salt has a role other than abstracting halides. The successful reactions of **1** and **3**, which cannot be dissociated by silver salts, reinforce this idea. The choice of silver salt is very important, and has been shown to widely influence the conversion achieved. The high electronegativity of the silver counter ion is of great importance. Finally, evidence of an interaction between silver salts and the substrate suggests that silver activates the aryl C–H bond and is then implicated in a transmetalation reaction with gold to provide the product. The value of silver additives in catalytic carboxylation of C–H bonds was then illustrated in the formation of 2,4,6-trifluorobenzoic acid, which was hitherto unattainable by gold(I)-catalysed carboxylation using catalyst **1** alone. This may provide a method to increase the range of C–H bonds amenable to functionalisation through gold-mediated carboxylation. Studies aimed at examining the extent of this effect are ongoing in our laboratories.

Supporting Information

Supporting Information File 1

Detailed experimental procedures for the synthesis of complexes **3**–**5**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-102-S1.pdf]

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Recent advances in the gold-catalyzed additions to C–C multiple bonds

He Huang, Yu Zhou and Hong Liu*

Review

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Address:
State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

Email:
He Huang - hhuang@mail.shcnc.ac.cn; Yu Zhou - zhouyu@mail.shcnc.ac.cn; Hong Liu* - hliu@mail.shcnc.ac.cn

* Corresponding author

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Abstract

C–O, C–N and C–C bonds are the most widespread types of bonds in nature, and are the cornerstone of most organic compounds, ranging from pharmaceuticals and agrochemicals to advanced materials and polymers. Cationic gold acts as a soft and carbophilic Lewis acid and is considered one of the most powerful activators of C–C multiple bonds. Consequently, gold-catalysis plays an important role in the development of new strategies to form these bonds in more convenient ways. In this review, we highlight recent advances in the gold-catalyzed chemistry of addition of X–H (X = O, N, C) bonds to C–C multiple bonds, tandem reactions, and asymmetric additions. This review covers gold-catalyzed organic reactions published from 2008 to the present.

Review

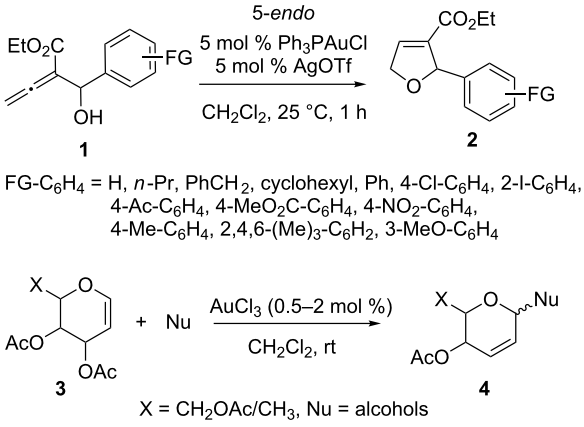
1 Introduction

Gold-catalyzed reactions have emerged as a powerful synthetic tool in modern organic synthesis. This past decade has been the boom time for homogeneous gold catalysis, which was rather limited in organic synthesis until the advantages of gold complexes as catalysts were discovered [1]. In comparison to other transition-metal catalysts, most gold-catalyzed reactions are atom-economic, remarkably mild with regard to reaction conditions, and most importantly, have a different reaction scope [2-4].

One of the most important fundamental reactions in gold-catalyzed synthesis is the addition of X–H (X = O, N, C) bonds to C–C multiple bonds, which features diverse functional group tolerance and the easy formation of carbon–carbon and carbon–heteroatom bonds [1,4,5]. Furthermore, the rapid growing area of tandem reactions has allowed chemists to assemble diverse complex molecular frameworks more conveniently. Although various research efforts have led to gold-catalyzed addition reactions, the area of asymmetric addition

has only recently been pioneered. Currently, a broad range of chiral gold catalysts (or gold combined with chiral ligands) has been developed and screened. However, only limited success has been achieved. The most notable example is the chiral BIPHEP-based catalyst, which has been successfully employed in several asymmetric cycloadditions.

Several early reviews have summarized well the progress of gold-catalyzed reactions up to 2008 [6-16]. Since then, the expansion of this field has continued unabated as evidenced by more than 500 publications to be found in the literature. Herein, we summarize the new research efforts that cover several aspects of gold-catalyzed additions to unsaturated bonds: (i) X–H (X = O, N, C) bonds to C–C multiple bonds; (ii) tandem reactions; and (iii) gold-catalyzed asymmetric additions. The literature published from 2008 up to the February of 2011 is covered. Only the most important recent studies have been selected to demonstrate the significance of gold catalysis.



Scheme 1: Gold-catalyzed addition of alcohols.

2 Gold-catalyzed C–O bond formations

The carbon–oxygen bond is one of the most widespread types of bonds in nature. Gold catalytic addition of oxygen nucleophiles to electronically non-activated C–C multiple bonds represents an attractive approach to the synthesis of functionalized ethers and ketones. In particular, the intramolecular addition of oxygen nucleophile to C–C multiple bonds has become a very effective tool in the synthesis of oxygen heterocycles from readily available starting materials [11].

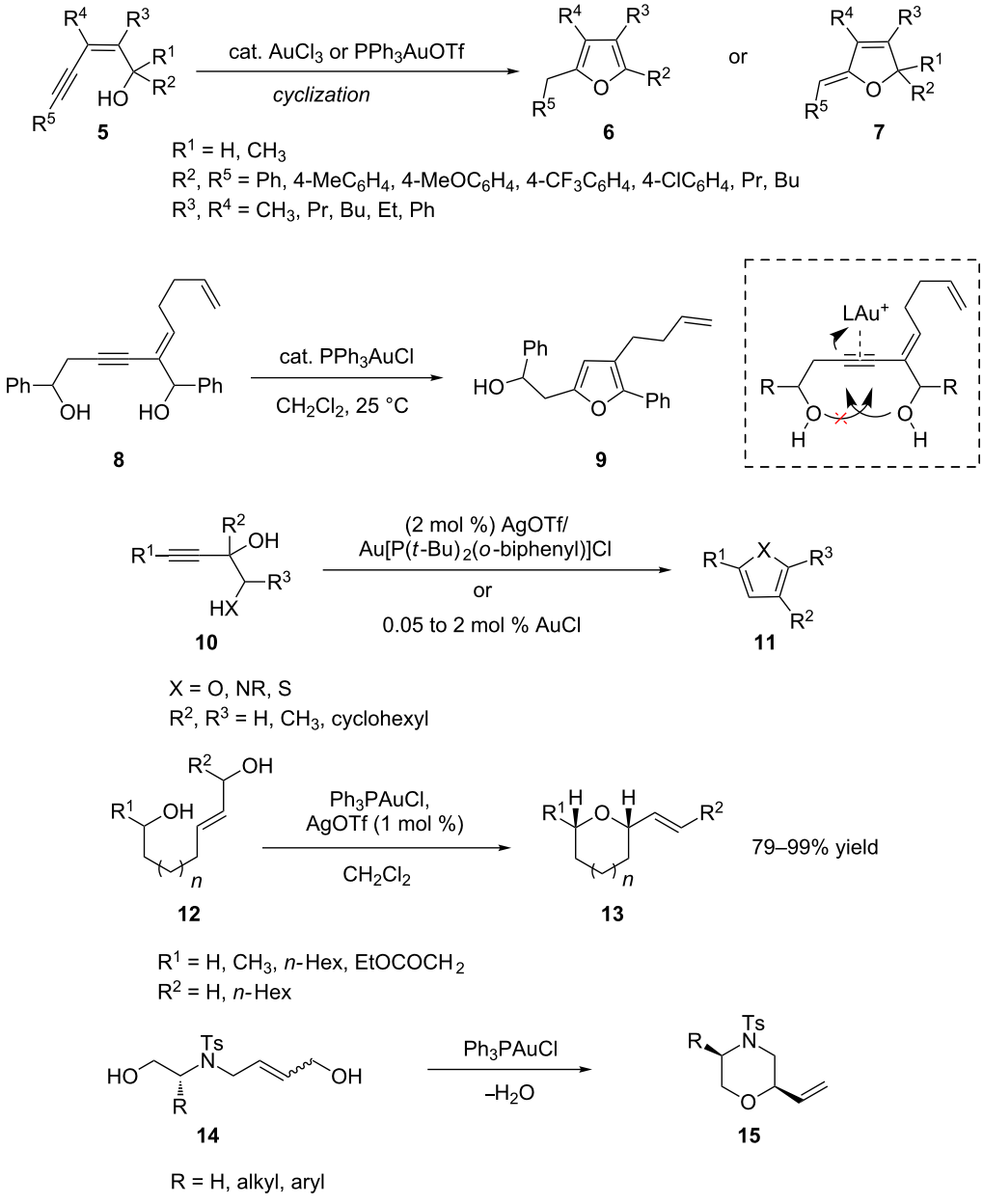
2.1 Alcohols, phenols and epoxides as nucleophiles

In general, dihydrofuran analogs can be constructed from alkynes by palladium-catalyzed intramolecular hydroalkoxylation reactions. However, the more common way to synthesize dihydrofurans is the gold catalyzed cyclization of vinyl allenols [17]. For instance, hydroxyallenic esters **1** can be selectively transformed into 2-alkyl- and 2-aryl-3-ethoxycarbonyl-2,5-dihydrofurans **2** by Ph_3PAuCl and AgOTf through intramolecular hydroalkoxylation via a 5-*endo* mode [18]. Gold(III) chloride in catalytic amounts activates 3,4,6-tri-*O*-acetyl-D-glucal, 3,4,6-tri-*O*-acetyl-D-galactal, and 3,4-di-*O*-acetyl-L-rhamnal **3** efficiently. The activated species can be employed in the Ferrier reaction with different nucleophiles at ambient conditions to yield the unsaturated derivatives **4** (Scheme 1) [19].

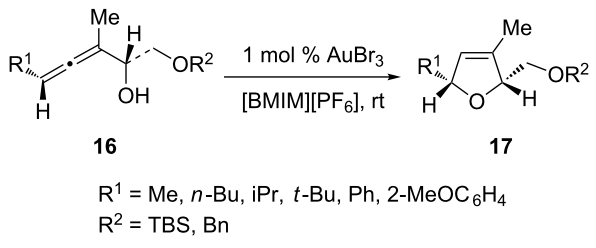
The intramolecular addition of a hydroxy group to a carbon–carbon triple bond is an effective strategy to construct furan analogues. Du et al. reported a highly efficient Au-catalyzed cyclization of (*Z*)-enynols that proceeded under mild reaction conditions. This methodology provided rapid access to substituted furans **6** and stereo-defined (*Z*)-5-ylidene-2,5-dihydrofurans **7** in a regioselective manner from suitably substituted (*Z*)-2-en-4-yn-1-ols **5** [20]. A similar strategy has been applied to an efficient formation of substituted furans **9** through gold-catalyzed selective cyclization of enyne-1,6-diols **8** [21]. Nucleophilic attack of the hydroxy oxygen atom on 1-position to a gold-coordinated C–C triple bond formed the vinyl–gold complex. Surprisingly, no other cyclic compound formed by nucleophilic attack of the hydroxy oxygen atom on C-6-position to a gold-coordinated C–C triple bond was formed. A new efficient route to furans **11** by gold-catalyzed intramolecular nucleophilic attack of readily available heteroatom-substituted propargyl alcohols **10** has been developed by Aponick and co-workers [22]. For the formation of tetrahydropyran analogs **13** and **15**, the gold(I)-catalyzed cyclization of monoallylic diols **12** and **14** is an efficient method (Scheme 2) [23,24].

In addition to common organic solvents, an attractive alternative is the use of ionic liquids as the reaction solvent, which often affords inexpensive, recyclable (and therefore environmentally benign), and sustainable catalyst systems. For example, Aksin et al. demonstrated that ionic liquids were highly suitable reaction media for the gold-catalyzed cycloisomerization of α-hydroxyallenes **16** to 2,5-dihydrofurans **17** (Scheme 3) [25]. The best system was found to be $AuBr_3$ in [BMIM][PF_6]. The cycloisomerization of various alkyl- or aryl-substituted α-hydroxyallenes gave corresponding 2,5-dihydrofuran with complete axis-to-center chirality transfer.

Rüttinger et al. reported a gold-catalyzed synthetic route for the preparation of enynes (Scheme 4) [26]. The gold-catalyzed cyclization provided the corresponding *exo*-enol ethers **19** in moderate to high yield with complete regioselectivity. By contrast, Wilckens et al. reported the gold-catalyzed *endo*-cyclizations of 1,4-diynes **20** to seven-membered ring heterocycles **21** [27]. The cyclization occurs exclusively in an *endo*-



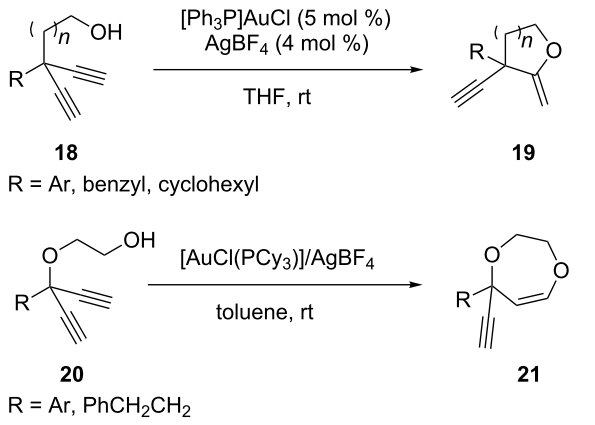
Scheme 2: Gold-catalyzed cycloaddition of alcohols.



Scheme 3: Ionic liquids as the solvent in gold-catalyzed cycloaddition.

fashion under mild conditions and provides access to dihydrodioxepines and tetrahydrooxazepines.

The dioxabicyclo[4.2.1] ketal **23** and its further transformation product tetrahydropyran **24** were produced by an efficient gold(I) chloride catalyzed cycloisomerization of 2-alkynyl-1,5-diol **22** [28]. A plausible mechanism for the gold-catalyzed transformation of dioxabicyclo[4.2.1]ketal **25** to tetrahydropyran **31** is outlined in Scheme 5. The gold catalyst activates one of the oxygen atoms to form the intermediates **26** or **27**,

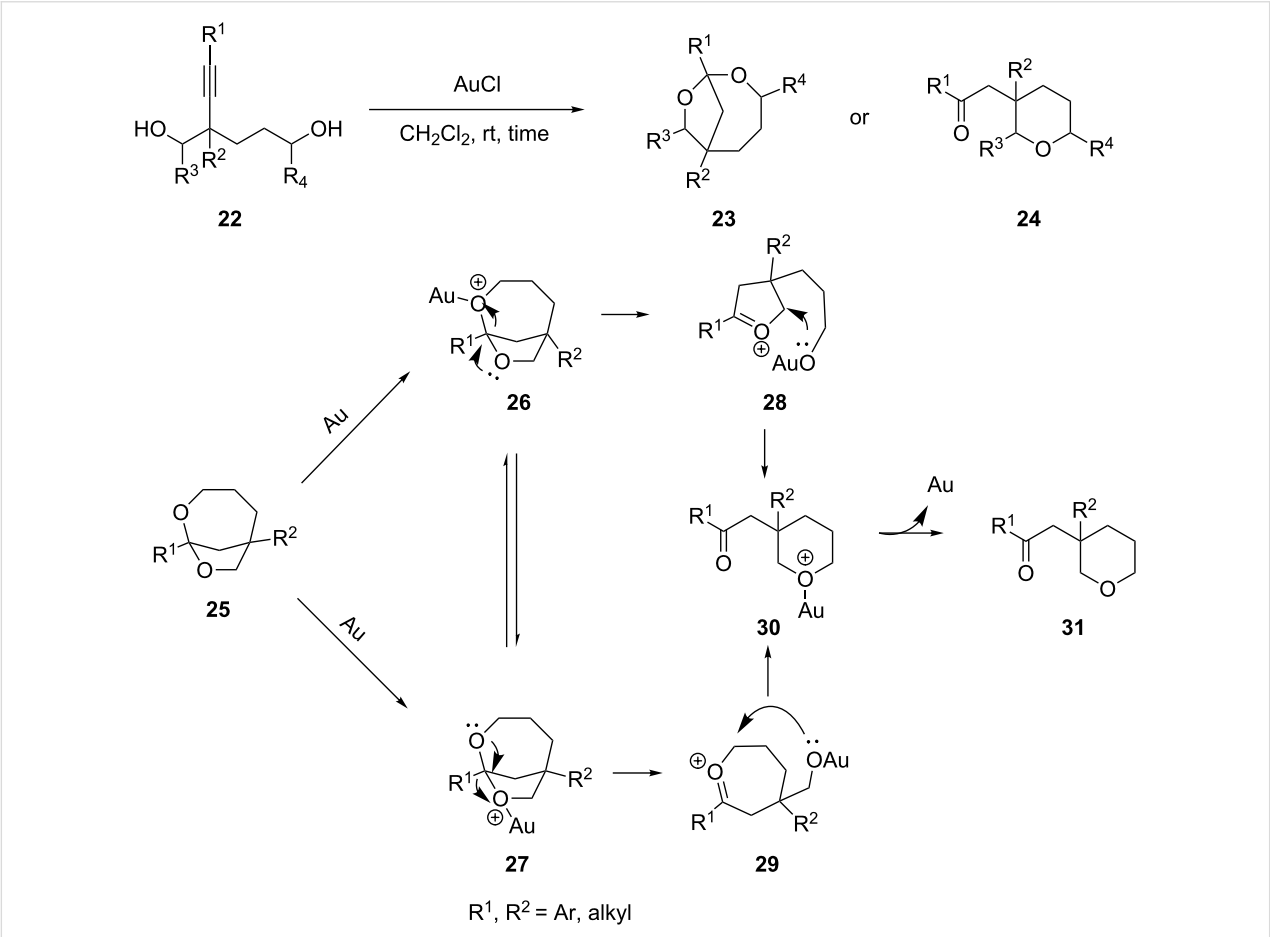


Scheme 4: Gold-catalyzed cycloaddition of diynes.

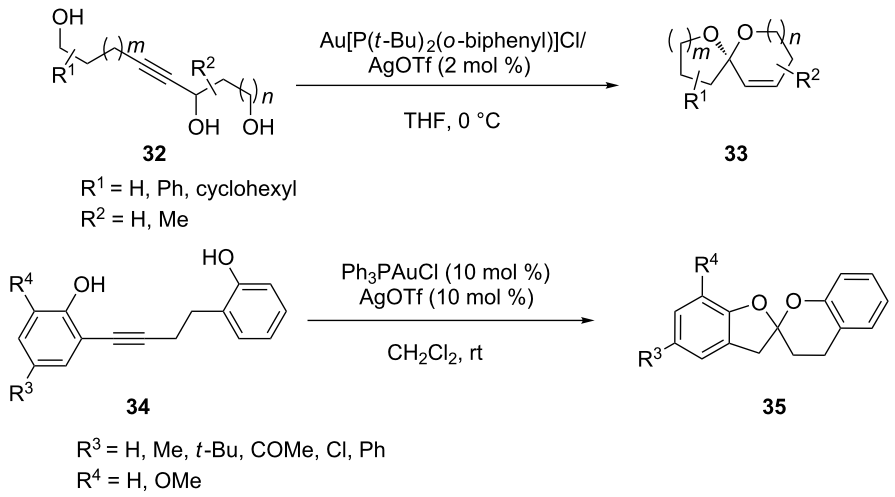
which then rearrange to yield the oxonium intermediates **28** or **29**, respectively.

Gold(I)-catalyzed intramolecular cyclization of monopropargylic triols **32** has been reported to be a novel and mild approach [29] for producing olefin-containing spiroketals **33** (and enantiomer) in excellent yields (Scheme 6). A range of variously substituted triols was prepared which were cyclized to give substituted 5- and 6-membered ring spiroketals. Similarly, the synthesis of the bisbenz-annelated spiroketal core **35** of natural bioactive rubromycins via a gold-catalyzed double intramolecular hydroalkoxylation was reported by Zhang and co-workers [30]. A tandem cyclization mechanism was proposed by the authors.

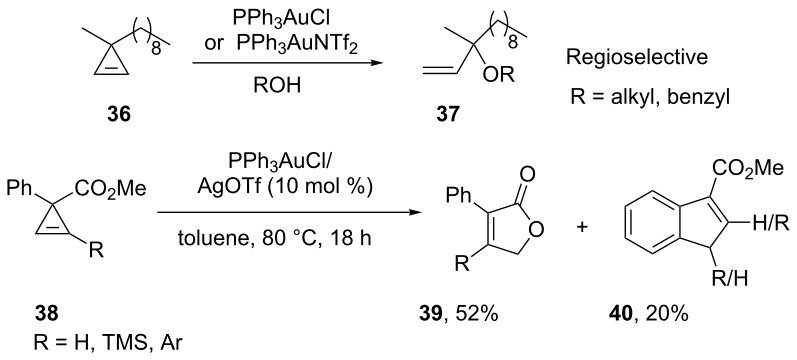
The first example of gold-catalyzed ring-opening addition of cyclopropenes has been developed by Lee's group [31,32]. The reaction of alkyl-disubstituted cyclopropene **36** with a series of alcohols generated the corresponding *tert*-allylic ethers **37** with high regioselectivity. Gold(I) catalysts were found to be unique and superior in terms of reactivity and regioselectivity. A notable observation in some of these studies is that gold(I) catalyzed rearrangement to furanones **39** and indenes **40** is observed upon introduction of ester and phenyl substituents on the cyclopropene (Scheme 7). $AuPR_3NTf_2$ complexes (PR_3 = **41**–**45**) are selective catalysts for the intermolecular



Scheme 5: Gold(I) chloride catalyzed cycloisomerization of 2-alkynyl-1,5-diols.



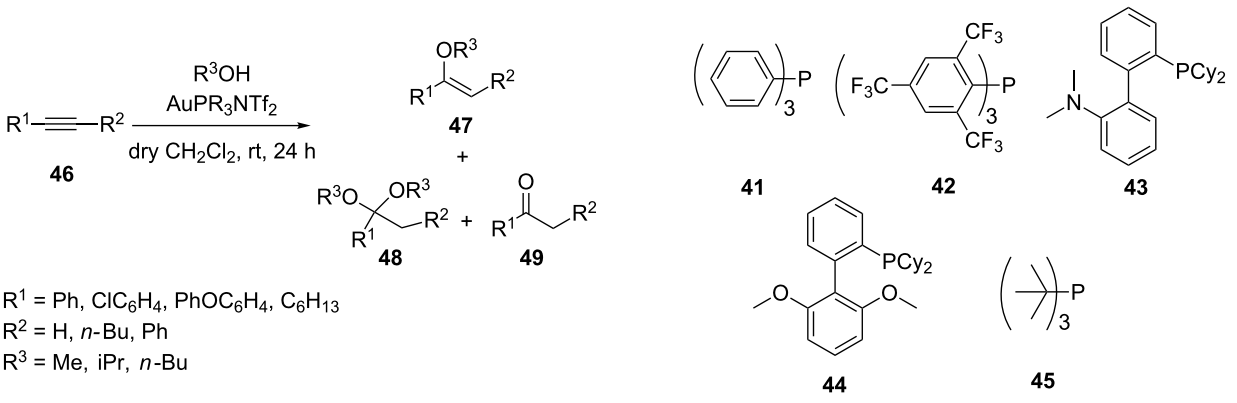
Scheme 6: Gold-catalyzed cycloaddition of glycols and dihydroxy compounds.



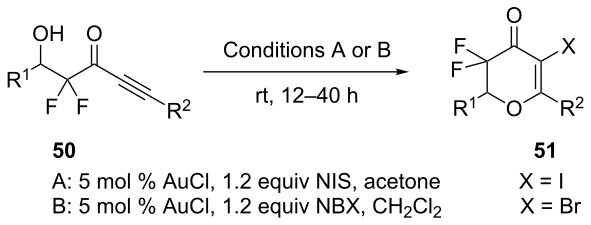
Scheme 7: Gold-catalyzed ring-opening of cyclopropenes.

hydroalkoxylation of electron-poor alkynes of type R−C≡C−EWG and dimethyl acetylenedicarboxylate [33]. In reactions of phenylacetylene the ratio of vinyl ether **47** to ketal **48** can be controlled by the choice of catalyst (Scheme 8).

The gold-catalyzed intramolecular 6-endo-dig cyclization of β-hydroxy-α,α-difluoroynones **50** under mild conditions has been developed (Scheme 9) [34]. The result indicated that gold catalysis is compatible with electrophilic fluorinating reagents.

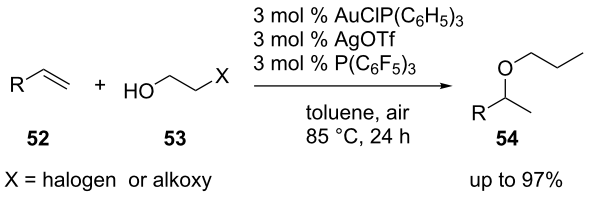


Scheme 8: Gold-catalyzed intermolecular hydroalkoxylation of alkynes. PR_3 = **41–45**.



Scheme 9: Gold-catalyzed intramolecular 6-endo-dig cyclization of β-hydroxy-α,α-difluoroynones.

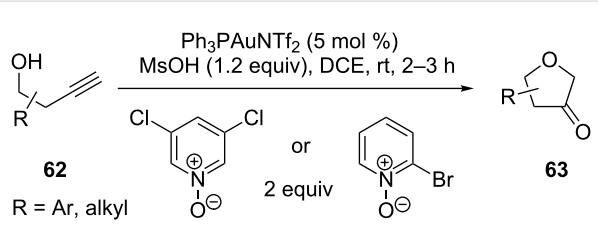
Furthermore, it is possible to couple the 6-endo-dig cyclization with iodination and bromination of the presumed vinyl–gold intermediate. However, attempted alkoxychlorination with *N*-chlorosuccinimide failed. Intermolecular hydroalkoxylation of non-activated olefins catalyzed by the combination of gold(I) and electron deficient phosphine ligands has been developed [35]. Gold-catalyzed hydroalkoxylations of non-activated olefins **52** and simple aliphatic alcohols **53** gave unsatisfactory results. However, a significant improvement of reaction efficiency was observed by employing alcohol substrates bearing coordination functionalities. In addition, the catalyst system with electron deficient phosphines was also found to catalyze the desired reaction effectively (Scheme 10).



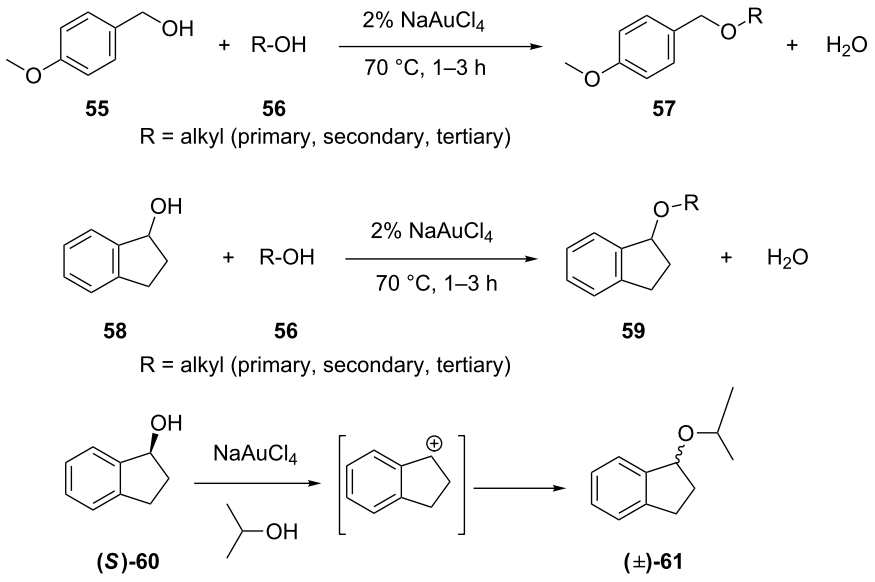
Scheme 10: Gold-catalyzed intermolecular hydroalkoxylation of non-activated olefins.

An efficient approach [36] for the preparation of unsymmetrical ethers from alcohols has been developed by utilizing $NaAuCl_4$. The benzylic and secondary alcohols (**55** and **58**) worked well under mild conditions with low catalyst loading (Scheme 11). The chiral benzyl alcohol **60** gave racemic ether **61**, which suggested the intermediacy of a carbocation.

Ye et al. reported an expedient gold-catalyzed synthesis of dihydrofuran-3-ones **63**, in which terminal alkynes **62** were used as equivalents of α-diazo ketones to generate α-oxo gold carbenes (Scheme 12) [37]. The α-oxo gold carbenes were produced via gold-catalyzed intermolecular oxidation of **62**. This provides



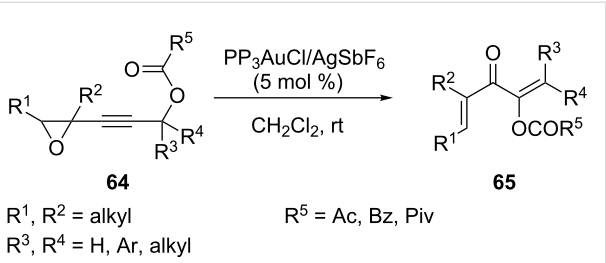
Scheme 12: Expedient synthesis of dihydrofuran-3-ones.



Scheme 11: Preparation of unsymmetrical ethers from alcohols.

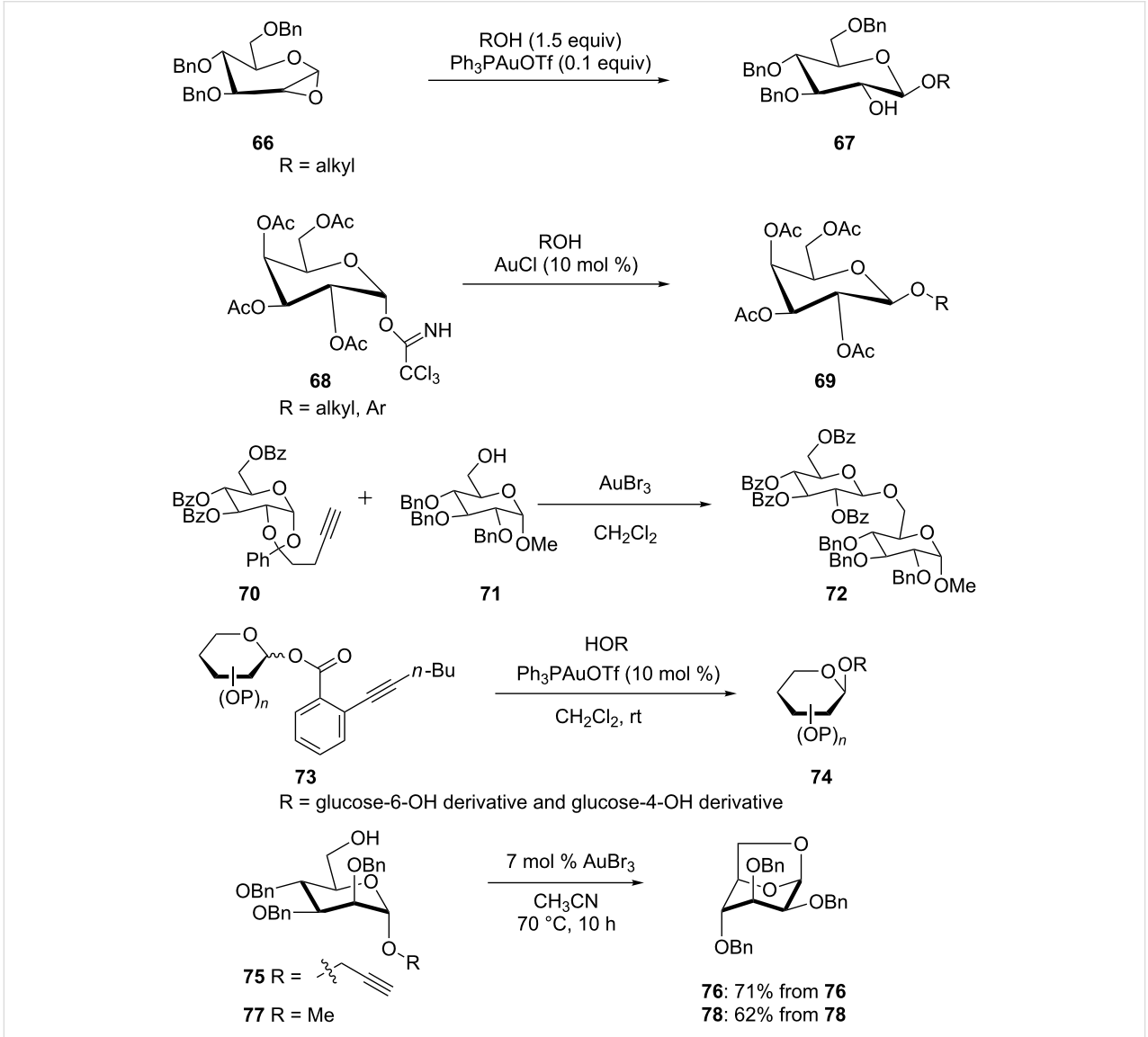
improved synthetic flexibility in comparison with the intramolecular strategy and offers a safe and economical alternative to those based on diazo substrates.

A catalytic approach to functionalized divinyl ketones through a gold-catalyzed rearrangement of (3-acyloxyprop-1-ynyl)oxiranes **64** has also been developed [38]. The reaction proceeds via rearrangement of (3-acyloxyprop-1-ynyl)oxiranes to acyloxydivinyl ketones, migration of the adjacent acyloxy group, as well as cycloreversion of oxetene and provides easy access to a variety of acyloxyl divinyl ketones **65** (Scheme 13).



Scheme 13: Catalytic approach to functionalized divinyl ketones.

A number of interesting gold-catalyzed glycosylations have appeared in recent years. $Ph_3PAuOTf$ is reported to be a superior catalyst (yield increases by >20%) compared to conventionally used $ZnCl_2$ for the well-established glycosylation reaction with 1,2-anhydrosugars **66** as donors (Scheme 14) [39]. The gold(I)-catalyzed reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (**68**) with alcohols gave



Scheme 14: Gold-catalyzed glycosylation.

β-galactosides **69** stereoselectively and in much higher yields compared to those obtained with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide [40]. Subsequently, a method to activate the propargyl 1,2-orthoesters **70** selectively in the presence of propargyl glycosides and propargyl ethers was developed [41]. Recently, Li et al. reported the gold(I)-catalyzed glycosylation with glycosyl *ortho*-alkynylbenzoates **73** as donors [42]. This glycosylation protocol was used in an efficient synthesis of a cyclic triterpene tetrasaccharide **74**, which demonstrated its versatility and efficacy. Another study [43] showed that 1,6-anhydro sugars **76** and **78** could be synthesized by utilizing salient features of gold-catalyzed glycosidations.

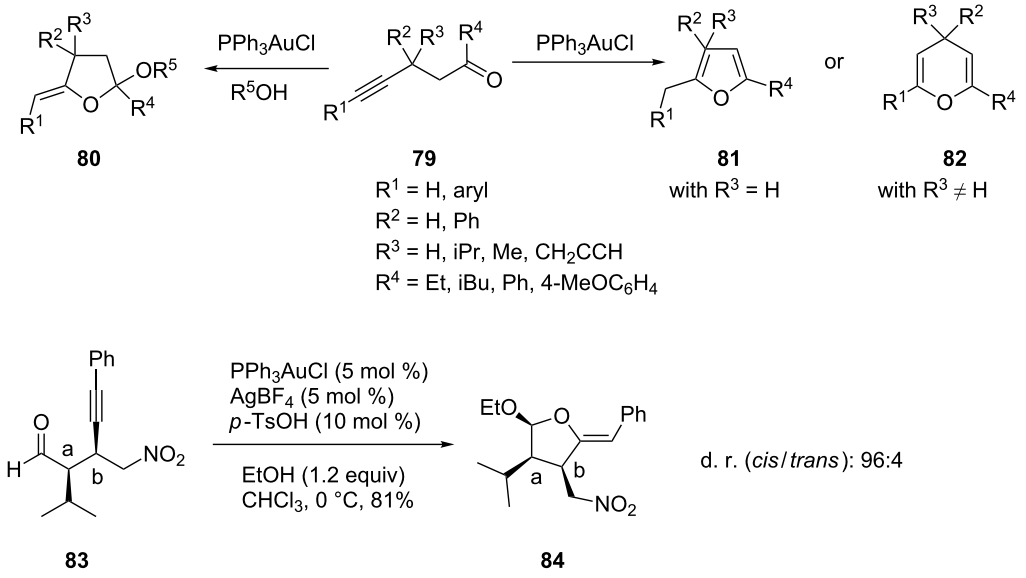
2.2 Aldehydes and ketones as nucleophiles

Different oxygen heterocycles can be obtained from the gold-catalyzed cyclization of alk-4-yn-1-ones **79** depending on the substitution pattern in the substrate and the reaction solvent. Thus, alkynones with one substituent at C-3 undergo a *5*-exo-dig cycloisomerization to yield substituted furans **81**, whilst substrates bearing two substituents at C-3 undergo a *6*-endo-dig cyclization to give 4*H*-pyrans **82**. By contrast, alkylidene/benzylidene-substituted tetrahydrofuranyl ethers **80** are formed in a tandem nucleophilic addition/cycloisomerization in alcoholic solvents [44]. Similarly, Belot et al. reported a gold-catalyzed cyclization which led to nitro-substituted tetrahydrofuranyl ethers **84** (Scheme 15) [45].

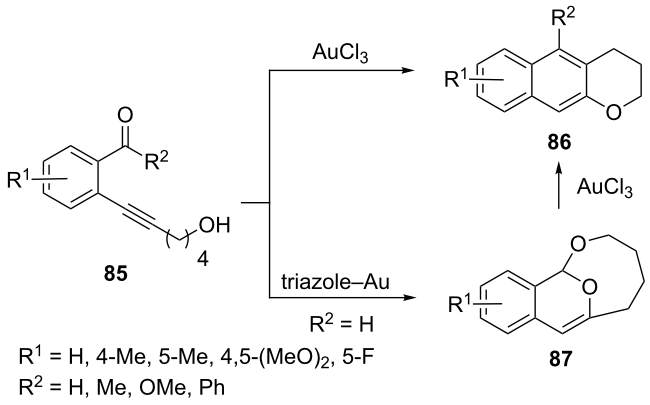
Liu et al. have developed a facile synthesis of benzochromanes **86** and benzobicycloacetals **87** from the gold-catalyzed cascade annulations of 2-(ynol)aryl aldehydes **85** [46]. Benzochromanes were obtained when $AuCl_3$ was employed as the catalyst, whereas benzobicyclo[5.3.1]acetals **87** were produced when triazole–gold was employed as the catalyst. With alcohol nucleophiles, gold(I)-catalyzed cyclization of *o*-alkynyl benzaldehyde **88** and benzaldimine–chromium complexes gave stereoselectively 1-anti-functionalized heterocycle chromium complexes **89** (Scheme 16) [47]. This made the methodology useful for the synthesis of enantiomerically pure *trans*- and *cis*-1,3-dimethylisochromans starting from a single planar chiral chromium complex.

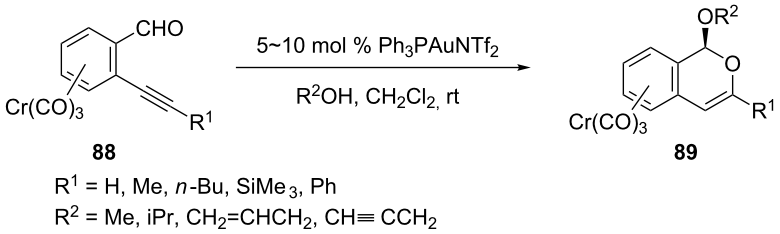
2.3 Carboxylates as nucleophiles

Seraya has reported the gold-catalyzed rearrangement of cyclopropenylmethyl acetates as a route to (*Z*)-acetoxydienes [48]. Thus, treatment of 4-nitrobenzaldehyde derived cyclopropene **90** with a catalytic amount of PPh_3AuNTf_2 in DCM led to quantitative formation of acetoxy diene **91** with a 4:1 *Z*:*E* selectivity within 5 min at −50 °C. Wang et al. developed an efficient method for the preparation of polysubstituted C–vinyl butyrolactones through a gold-catalyzed highly diastereoselective cyclization of malonate substituted allylic acetates [49]. As an example, treatment of *syn*-4-acetoxycyclohexenyl malonate **92** with a catalytic amount of $AuPPh_3Cl/AgSbF_6$ in DCE at 70 °C for 3 h led to the isolation of 3,4-*anti*-4,5-*syn*-3-methoxycarbonyltetrahydrobenzobutyrolactone **93** in 80% yield. The possible intermediate is shown in Scheme 17. Using the $AuPPh_3Cl/AgOTf$ system as the equivalent of $AuPPh_3OTf$, Liu et al. found that the in situ generated cationic Au(I) reagent reacted with ethyl α-methyl-γ-cyclohexyl allenoate in dichloromethane at room temperature to form the gold complex

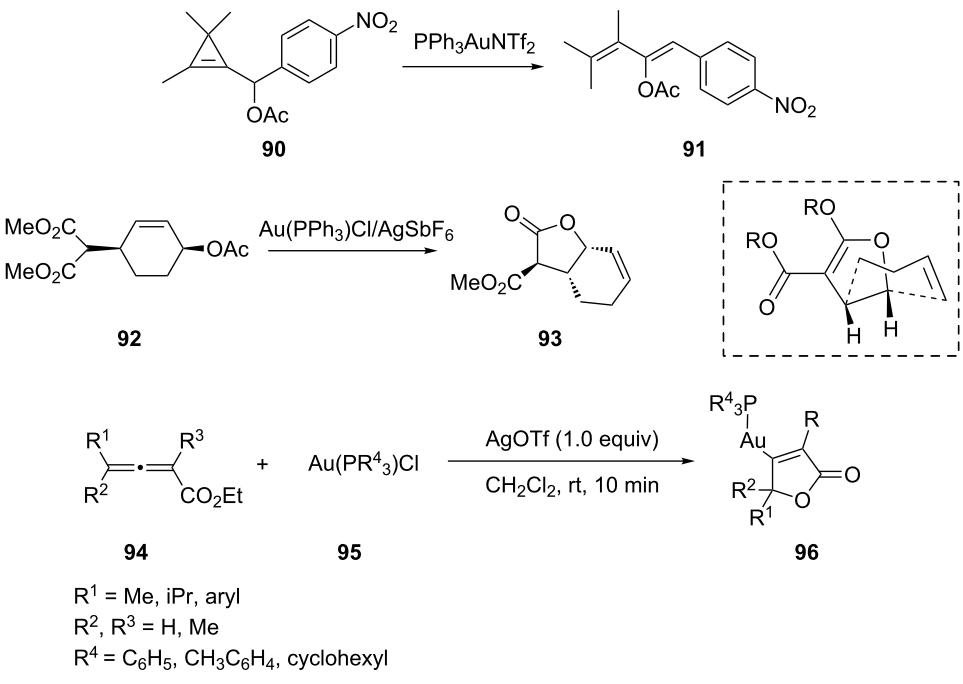


Scheme 15: Gold-catalyzed cycloaddition of aldehydes and ketones.





Scheme 16: Gold-catalyzed annulations of 2-(ynol)aryl aldehydes and *o*-alkynyl benzaldehydes.



Scheme 17: Gold-catalyzed addition of carboxylates.

96 in 85% yield (Scheme 17) [50]. This result could provide the experimental evidence required to support the postulated mechanism of Au-catalyzed reactions.

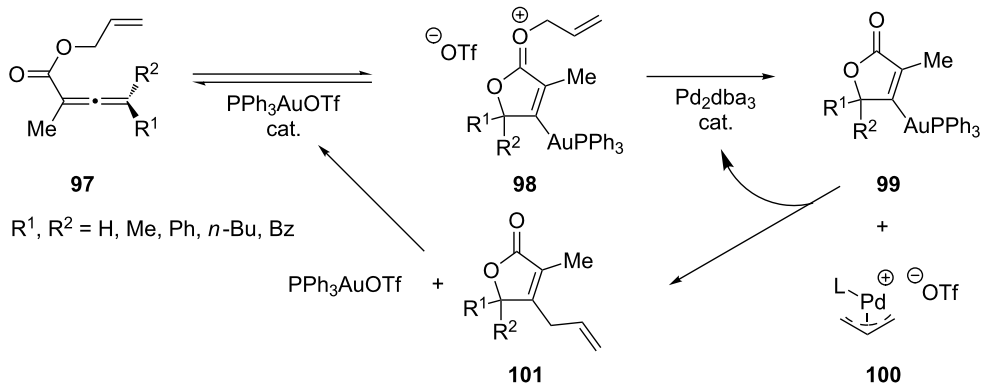
Dual-catalyzed rearrangement reactions have been reported by Shi and co-workers for the preparation of substituted butenolides **101** and isocoumarins [51]. In this study, the authors

employed a carbophilic Lewis acidic Au(I) catalyst to catalyze the cross-coupling reactivity of a second Lewis basic Pd catalyst in order to functionalize vinyl–gold intermediates arising from intramolecular substrate rearrangements (Scheme 18).

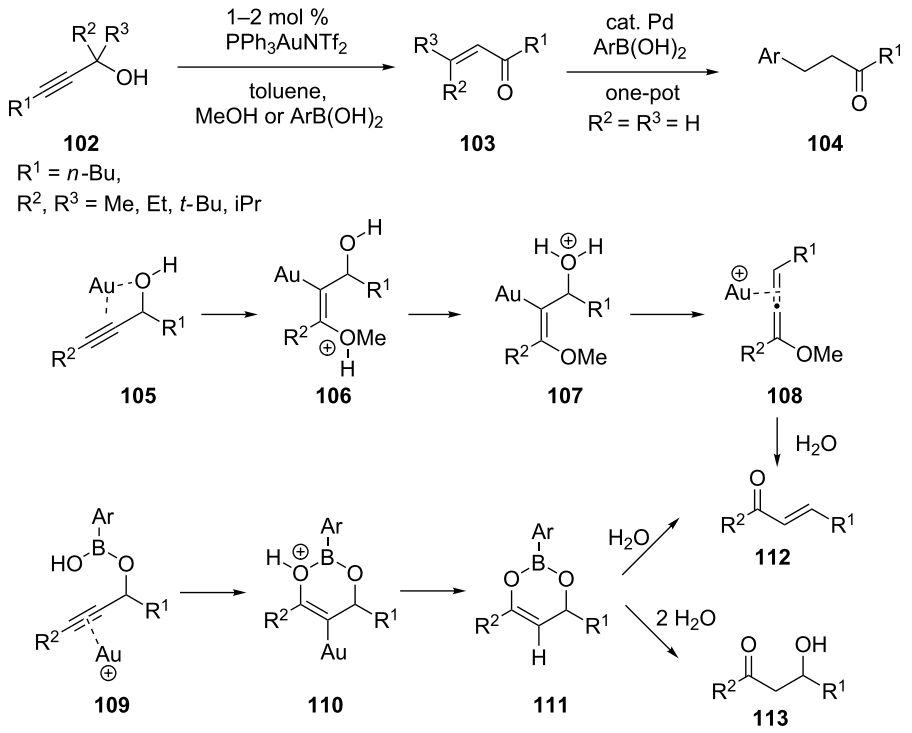
2.4 Propargylic alcohols and propargylic carboxylate rearrangements

Pennell et al. reported Meyer–Schuster rearrangements of propargylic alcohols **102** at room temperature in toluene with 1–2 mol % PPh_3AuNTf_2, in the presence of 0.2 equiv of 4-methoxyphenylboronic acid or 1 equiv of methanol [52]. Mechanistically, it was proposed that the enones **103** were produced through two pathways (Scheme 19).

The gold(I)-catalyzed rearrangement of propargylic *tert*-butyl carbonates gave diversely substituted 4-alkylidene-1,3-dioxolan-2-ones **115** [53]. For example, treatment of propargylic *tert*-butyl carbonate **114** with 1 mol % PPh_3AuNTf_2 in CH_2Cl_2 at room temperature led to isolation of the cyclic carbonate in 83% yield. Syntheses of oxetan-3-ones typically demand multiple synthetic steps and/or highly functionalized substrates. Alternatively, Ye et al. [54] developed a practical gold-catalyzed



Scheme 18: Dual-catalyzed rearrangement reaction of allenoates.



Scheme 19: Meyer–Schuster rearrangement of propargylic alcohols.

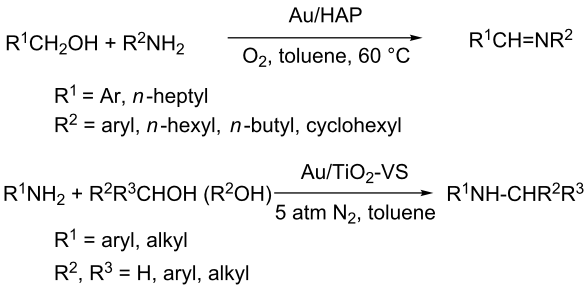
one-step synthesis of oxetan-3-ones **117** and **119** from readily available propargylic alcohols **116** and **118**. Since chiral propargylic alcohols are readily available, this methodology provides easy access to chiral oxetan-3-ones. For example, the reaction of enantiomerically enriched secondary propargyl alcohols led to the chiral oxetan-3-one with no apparent racemization (Scheme 20).

3 Gold-catalyzed C–N bond formations

Many organic compounds containing nitrogen exhibit important biological and pharmaceutical properties. As with gold-catalyzed C–O bond formation, the directly catalytic addition of a nitrogen nucleophile to a C–C multiple bond represents an attractive approach to the formation of C–N bonds [55]. This is a direct and efficient procedure for the synthesis of nitrogen containing compounds of industrial importance.

3.1 Alkyl- and aromatic amines as nucleophiles

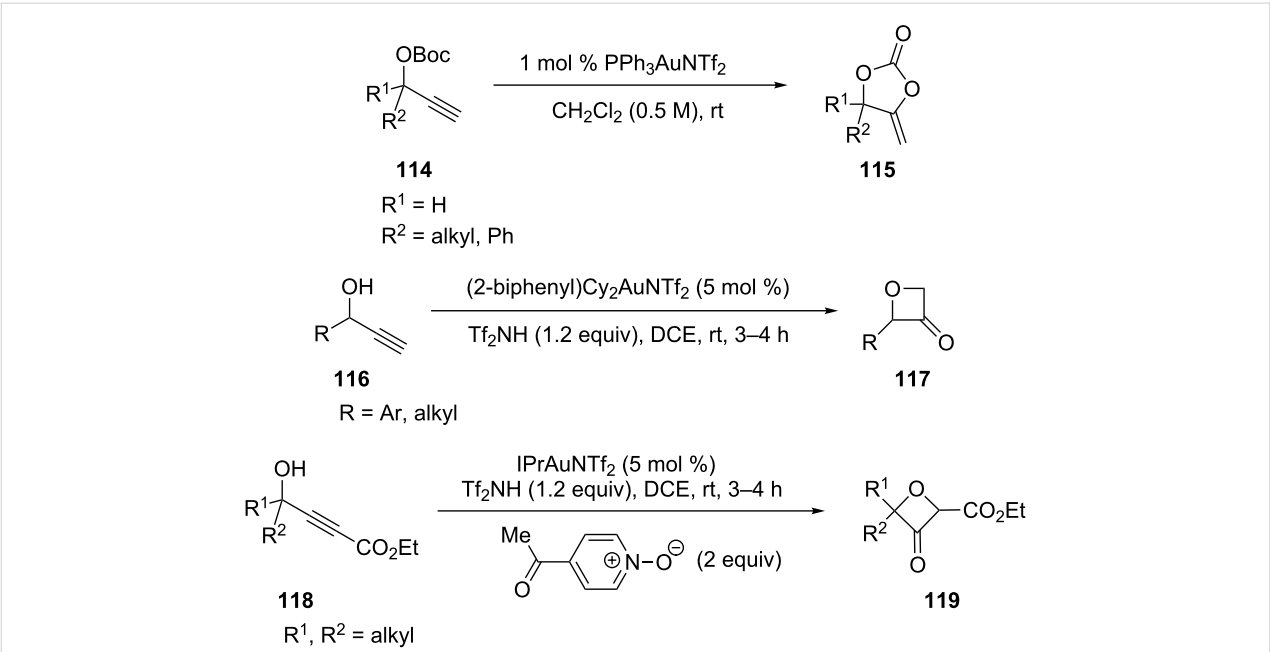
Imines and oximes are versatile synthetic intermediates for the preparation of dyes, pharmaceuticals, and agricultural chemicals. Sun et al. have reported a multi-task Au/hydroxyapatite reagent for the heterogeneous catalyzed oxidation of alcohols and amines to imines or oximes [56]. *N*-alkylation of primary amines is an important reaction in organic synthesis. He et al. developed an efficient gold-catalyzed one-pot selective *N*-alkylation of amines with alcohols [57]. In their study, gold nanoparticles supported on titania act as an efficient heterogeneous catalyst for the reaction to give the *N*-alkylated amines in excellent yields (Scheme 21).



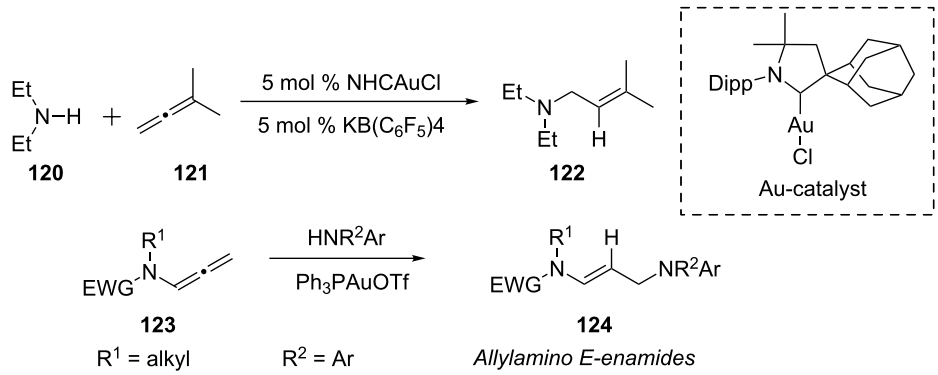
Scheme 21: Gold-catalyzed synthesis of imines and amine alkylation.

Zeng and co-workers reported that cationic gold(I) complexes promote the addition of all types of non-tertiary amines **120** to a variety of allenes **121** to afford allylic amines **122** in good to excellent yields [58]. Importantly, the Markovnikov adduct was obtained in all cases. A similar Markovnikov hydroamination [59] could also be achieved via an intermolecular hydroamination of allenamides **123** with arylamines under mild $AuPPh_3OTf$ catalysis conditions to furnish allylamino (*E*)-enamides stereoselectively (Scheme 22).

Hesp and co-workers have identified a gold pre-catalyst **125** featuring a P,N-ligand that has significantly extended the substrate scope and synthetic utility of alkyne hydroamination [60]. The hydroamination of unsymmetrical internal aryl acetylenes **126** with dialkylamines **127** has been achieved with synthetically useful regioselectivities. In addition to intermolecular addition, Mukherjee and Widenhoefer recently reported a gold(I)-



Scheme 20: Propargylic alcohol rearrangements.



Scheme 22: Hydroamination of allenes and allenamides.

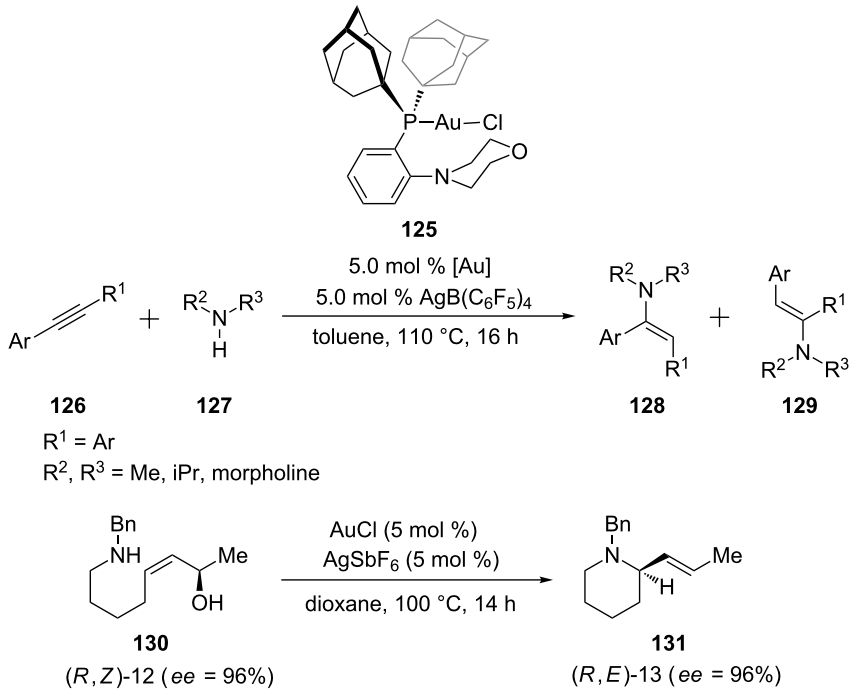
catalyzed intramolecular amination of allylic alcohols **130** with alkylamines (Scheme 23) [61].

3.2 Imines as nucleophiles

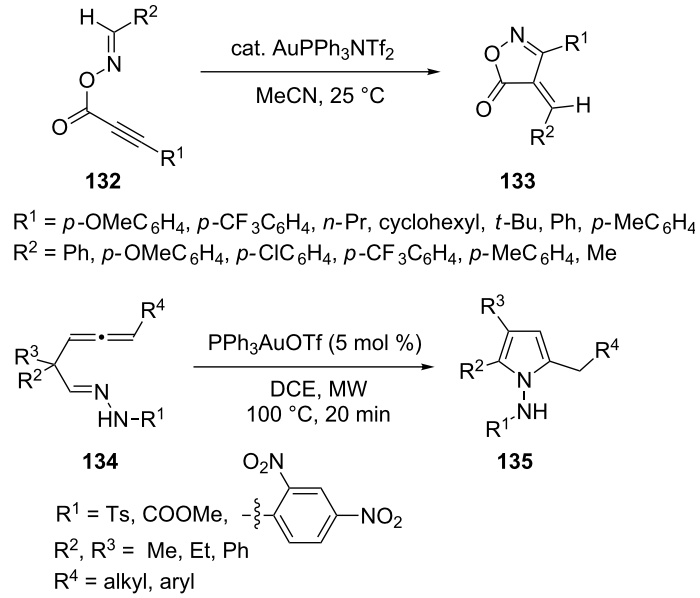
Gold-catalyzed cyclizations of *O*-propioloyl oximes via C–N bond formation followed by arylidene group transfer were developed as a method for the preparation of 4-arylidene isoxazol-5(4*H*)-ones [62]. For example, (*E*)-benzaldehyde *O*-3-phenylpropioloyl oxime **132** was reacted in acetonitrile at 25 °C in the presence of $AuPPh_3NTf_2$ (5 mol %) to give 4-benzylidene-3-phenylisoxazol-5(*4H*)-one **133** in 90% yield. An efficient synthesis of multi-substituted *N*-aminopyrroles **135** via gold(I)-catalyzed cyclization of β-allenylhydrazones **134** was developed by Benedetti and co-workers (Scheme 24) [63]. This intramolecular cyclization method can be applied to both alkyl- or aryl-substituted allenes and involves mild conditions and short reaction times.

3.3 Amides, sulfamides and ureas as nucleophiles

Using $AuPPh_3Cl/Ag_2CO_3$-catalyzed 5-endo-dig cyclization in water under microwave irradiation, our group developed a fast and green route to prepare indole-1-carboxamides **137** from *N*′-substituted *N*-(2-alkynylphenyl)ureas **136** (Scheme 25) [64]. A variety of functional groups including *N*′-aryl, alkyl, hetero-



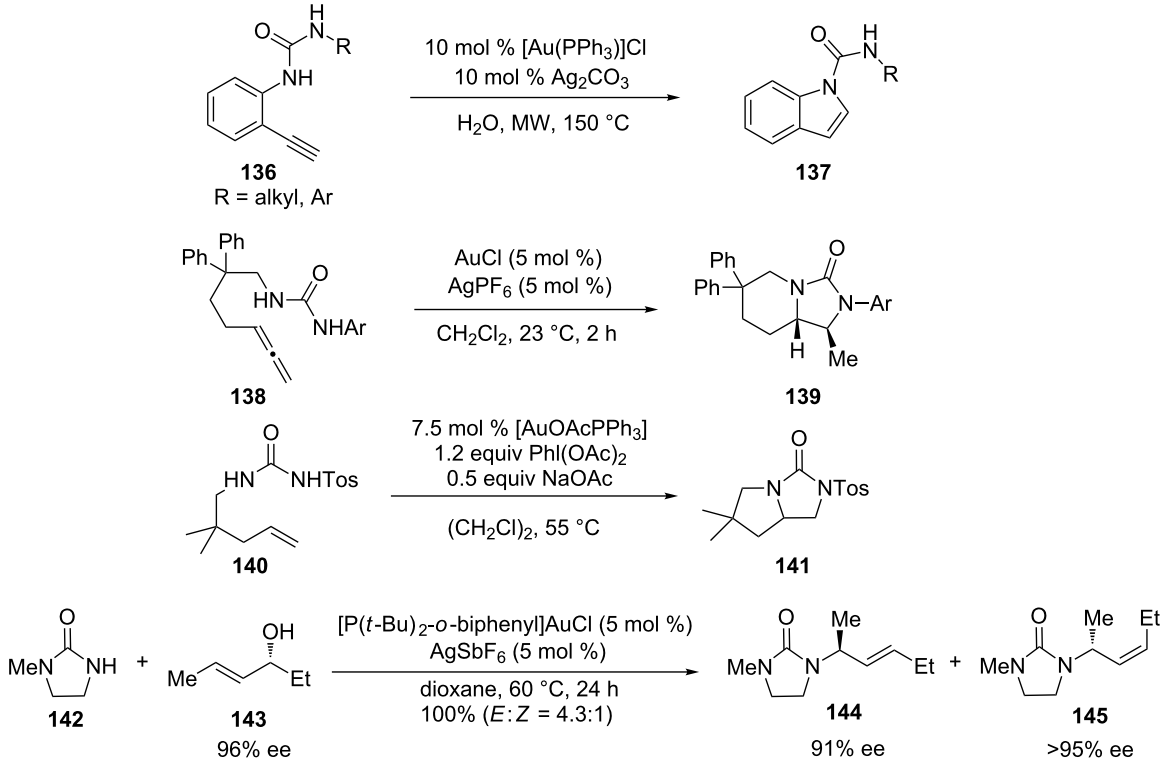
Scheme 23: Gold-catalyzed inter- and intramolecular amination of alkynes and alkenes.



Scheme 24: Gold-catalyzed cycloisomerization of *O*-propioloyl oximes and β-allenylhydrazones.

cyclic, various *N*-substituted-2-ethynylphenyl and *N*-(2-ethynylpyridin-3-yl)ureas, are tolerated and gives moderate to high yields of the desired products.

In another study [65], bicyclic imidazolidin-2-ones **139** were obtained via gold(I)-catalyzed intramolecular dihydroamination of allenes with *N,N′*-disubstituted ureas **138**. Iglesias et al.



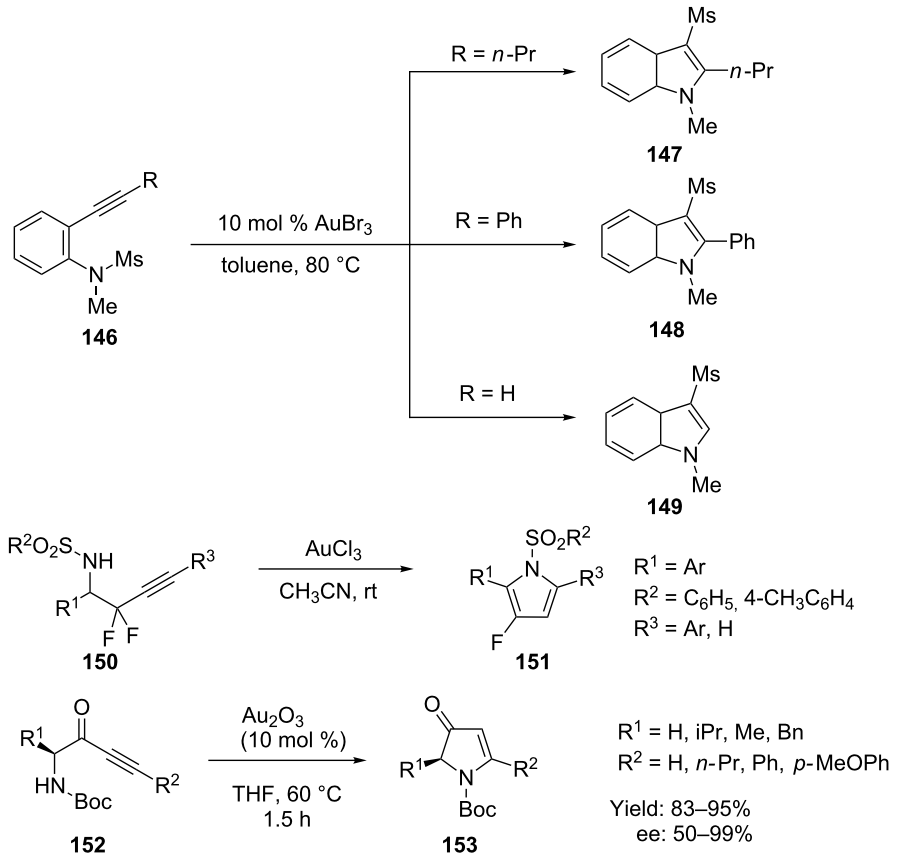
Scheme 25: Intra- and intermolecular amination with ureas.

reported a complimentary diamination of alkenes **140** with homogeneous gold catalysts [66]. The key step is an intramolecular alkyl–nitrogen bond formation from a gold(III) intermediate. Besides the intramolecular addition of ureas, Widenhoefer's group reported a gold(I)-catalyzed intermolecular amination of allylic alcohols **143** with cyclic ureas **142** (Scheme 25) [67].

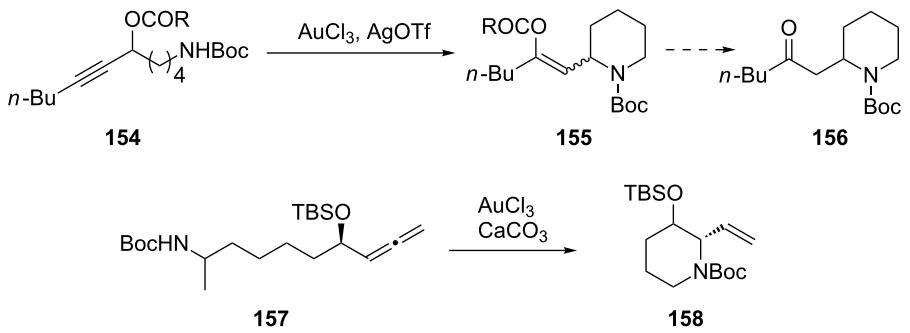
Gold-catalyzed reactions of *ortho*-alkynyl-*N*-sulfonylanilines **146** produced the corresponding 3-sulfonylindoles in good to high yields (Scheme 26). Nakamura and co-workers synthesized 3-mesyl-1-methyl-2-propylindole **147**, 3-mesyl-1-methyl-2-phenylindole **148**, and 3-mesyl-1-methylindole **149** from *N*-mesyl-*N*-methyl-2-(1-pentynyl)aniline, *N*-mesyl-*N*-methyl-2-(phenylethynyl)aniline, and 2-ethynyl-*N*-mesyl-*N*-ethylaniline in moderate to high yield with $AuBr_3$ as the catalyst [68]. Surmont and co-workers later explored a similar strategy for the synthesis of 2-aryl-3-fluoropyrroles **151** [69]. Gouault et al. reported a gold-catalyzed approach to synthesize substituted pyrrolin-4-ones **153** from 1-aminobut-3-yn-2-one analogs **152** under mild conditions [70]. The use of gold(III) oxide as catalyst allows moderate to total stereo control during the cyclization.

Huang et al. has developed an efficient gold-catalyzed method to access piperidinyl enol esters **155** and piperidinyl ketones **156** under mild reaction conditions from ε-*N*-protected propargylic esters **154** [71]. This intramolecular piperidine cyclization methodology shows different reactivity and substrate applicability compared with the former intermolecular nucleophilic addition. The mechanism speculated by the authors involves a gold-catalyzed intramolecular rearrangement followed by nucleophilic attack of the Boc-protected nitrogen atom. A similar method to synthesize the 2-vinylpiperidin-3-ol **158** by a highly stereoselective gold-catalyzed allene cyclization has been reported (Scheme 27) [72].

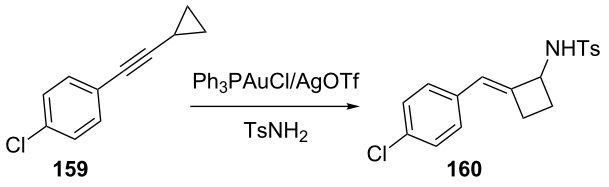
The ring expansion of cyclopropane derivatives provides a powerful method to construct synthetically useful four-membered carbocycles. Ye et al. reported a new type of gold(I)-catalyzed ring expansion of an non-activated alkynylcyclopropane/sulfonamide to obtain (*E*)-2-alkylidenecyclobutanamines [73]. For example, treatment of alkynylcyclopropane **159** with $TsNH_2$ and 5 mol % PPh_3AuCl/5 mol % AgOTf in dichloroethane at 80 °C gave alkylidenecyclobutanamine **160** in 65% yield as a single olefin isomer (Scheme 28).



Scheme 26: Gold-catalyzed cyclization of *ortho*-alkynyl-*N*-sulfonylanilines and but-3-yn-1-amines.



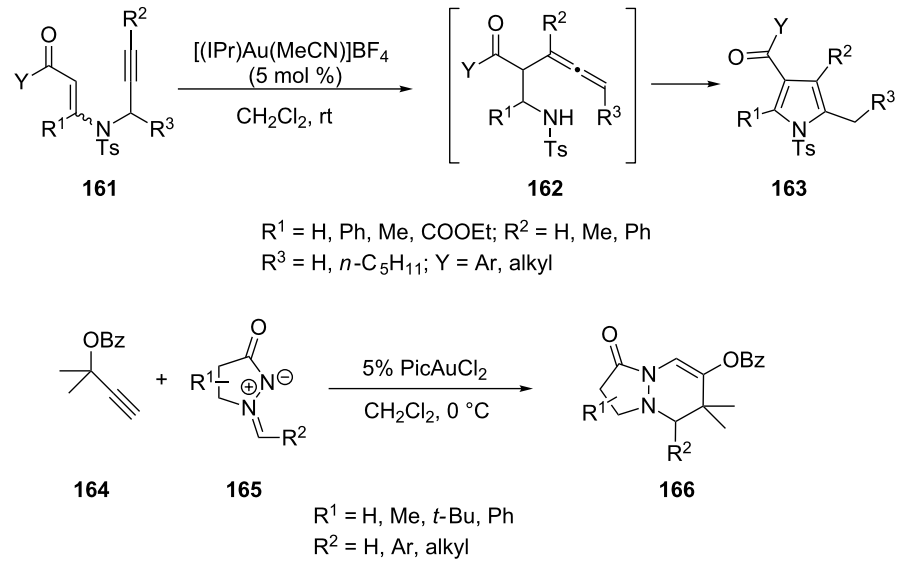
Scheme 27: Gold-catalyzed piperidine ring synthesis.



Scheme 28: Ring expansion of alkylnyl cyclopropanes.

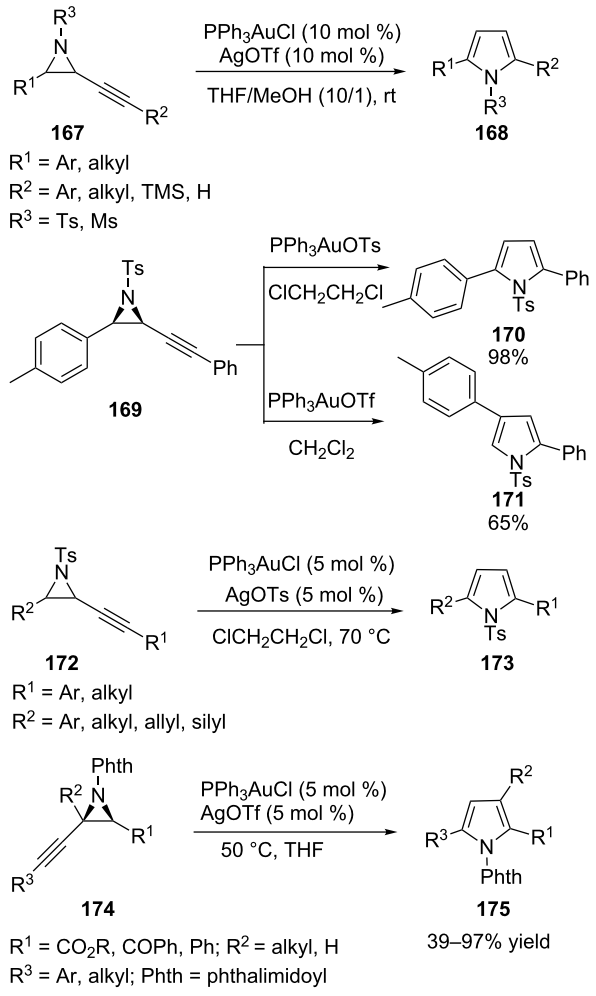
The formation of tri- and tetrasubstituted pyrroles **163** [74] via cationic *N*-heterocyclic carbene–gold(I) complex catalyzed amino Claisen rearrangement of *N*-propargyl-β-enaminone derivatives **161** and the cyclization of α-allenyl-β-enaminone intermediates has been developed by Saito and co-workers (Scheme 29) [75]. Toste's group has reported a novel gold(III)-catalyzed [3 + 3]-annulation of azomethine imines **165** with propargyl esters **164**. Substitution of the β-position of the pyrazolidinone generally provides the bicyclic product **166** with high *cis* selectivity, which is determined during ring closing rather than in the formation of allyl–gold intermediate [76].

Gold-catalyzed cycloisomerization reaction of alkynyl aziridines **167** can give 2,5-disubstituted pyrroles **168** in high yields [77]. However, in some cases, aryl-substituted *N*-tosyl alkynyl aziridines **169** undergo a gold-catalyzed ring expansion to afford 2,5-substituted or 2,4-substituted pyrrole products [78]. Interestingly, the reaction pathway is determined by the counter ion of the gold catalyst. The formation of 2,5-substituted pyrroles **170** proceeds with PPh_3AuOTs as the catalyst whilst a novel reaction pathway is accessed on changing the catalyst system to PPh_3AuOTf and leads to 2,4-substituted pyrroles **171**. Recently, the same group reported an efficient and selective synthesis of 2,5-substituted pyrroles **173** by gold-catalyzed ring expansion of alkynyl aziridines **172** [79]. In this study a combination of Ph_3PAuCl and AgOTs generates a catalyst system that provides clean cycloisomerisation reactions.



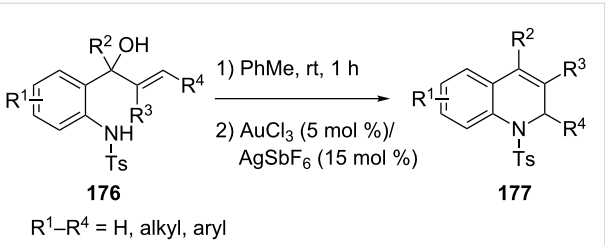
Scheme 29: Gold-catalyzed annulations of *N*-propargyl-β-enaminones and azomethine imines.

Similarly, *N*-Phth pyrrroles **175** are obtained via gold-catalyzed cycloisomerization of *N*-Phth alkynyl aziridines **174** (Scheme 30) [80].



Scheme 30: Gold(I)-catalyzed cycloisomerization of aziridines.

Chan's group developed an efficient synthetic route to 1,2-dihydroquinolines **177** via $AuCl_3/AgSbF_6$-catalyzed intramolecular allylic amination of 2-(tosylamino)phenylprop-1-en-3-ols **176** (Scheme 31) [81]. The mechanism is suggested to involve activation of the alcohol substrate by the $AuCl_3/AgSbF_6$ catalyst and ionization of the starting material, which causes intramolecular nucleophilic addition of the sulfonamide unit to the allylic cation moiety and construction of a 1,2-dihydroquinoline.



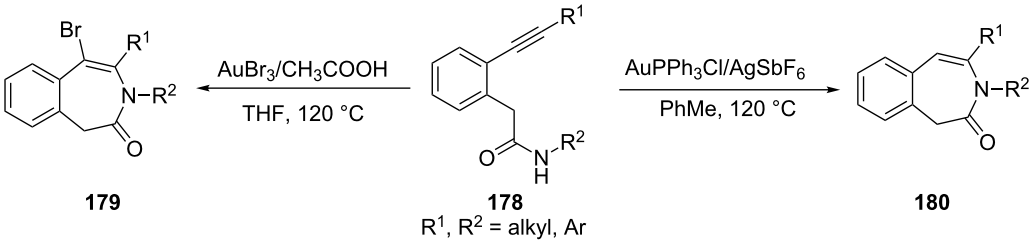
Scheme 31: $AuCl_3/AgSbF_6$-catalyzed intramolecular amination of 2-(tosylamino)phenylprop-1-en-3-ols.

Our group also discovered that a regioselective hydroamidation of 2-(1-alkynyl)phenylacetamides **178** could be achieved with $AuPPh_3Cl/AgSbF_6$ as the catalyst and gave 3-benzazepin-2-ones **180** via 7-endo-dig pathway [82]. Moreover, a $AuBr_3$-mediated transformation of 2-(1-alkynyl)phenylacetamides **178** to 5-bromo-3-benzazepin-2-ones **179** was discovered, which indicated that the gold catalyst not only played an activation role but also acted as a reactant in the reaction (Scheme 32).

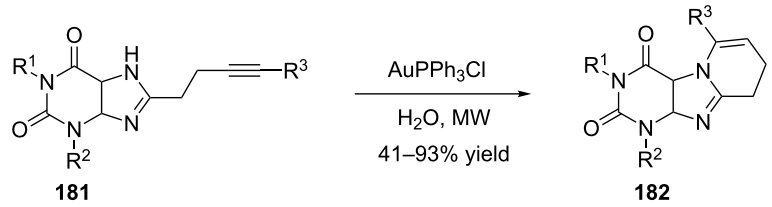
A simple, convenient, and green synthetic approach to diverse fused xanthines **182** has also been developed by gold-complex catalyzed intramolecular hydroamination of terminal alkynes **181** under microwave irradiation in aqueous media (Scheme 33). This transformation is atom-economical and has high functional group tolerance [83].

3.4 Nitriles and nitrines as nucleophiles

Ibrahim et al. reported a new and mild method for the synthesis of amide **184** from readily available benzhydrol **183** and nitriles catalyzed by a gold(I)-complex with a trimesitylene ligand [84]. Mechanistic control experiments with chiral alcohol **185** prove the intermediacy of carbenium ions. Further studies with not readily ionizable alcohols also indicate that for the benzhydrols

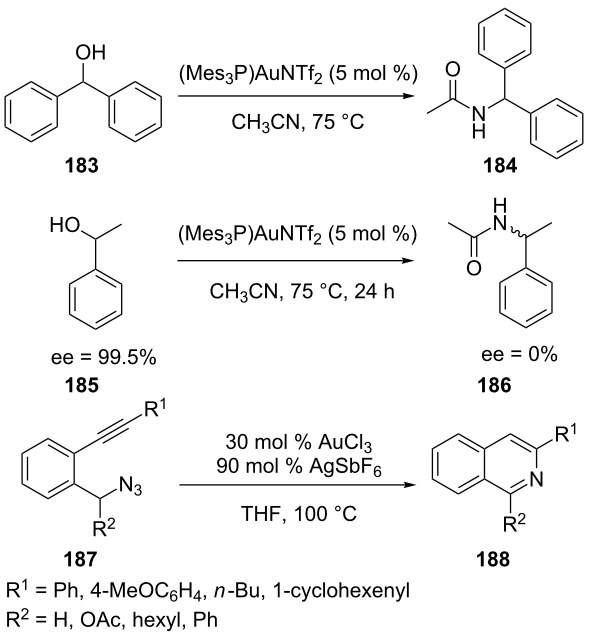


Scheme 32: Gold-catalyzed cyclization via a 7-endo-dig pathway.



Scheme 33: Gold-catalyzed synthesis of fused xanthines.

the carbenium ions and gold(I)-hydroxy complexes are intermediates (Scheme 34). Yamamoto's group reported that intramolecular cyclization of 2-alkynylbenzyl azides **187** in the presence of $AuCl_3$ and $AgSbF_6$ in THF under pressure at 100 °C gives the corresponding isoquinolines **188** in good yields [85].



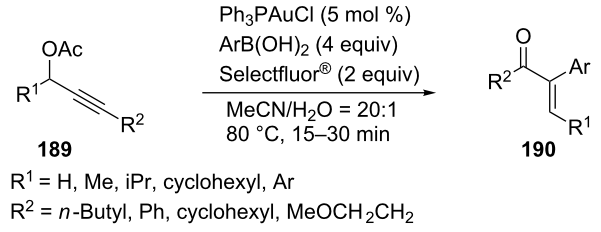
Scheme 34: Gold-catalyzed synthesis of amides and isoquinolines.

4 Gold-catalyzed C–C bond formations

The formation of carbon–carbon bonds by using various transition metals such as Pd, Ni, Ru, Rh has been extensively investigated and is well documented in the literature. Recent years have witnessed a tremendous growth in the number of gold-catalyzed highly selective chemical transformations. Although gold was considered to be an inert metal for a long time, its ability to behave as a soft Lewis acid has only been recently recognized. Such a property allows it to activate unsaturated functionalities such as alkynes, alkenes, and allenes, to create C–C bonds under extremely mild conditions [15].

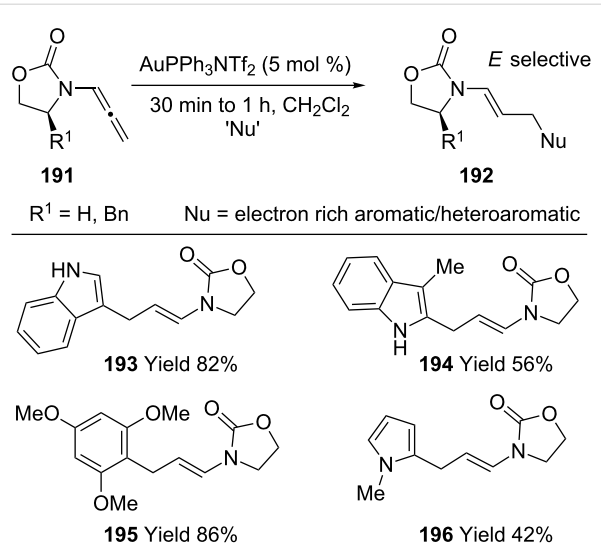
4.1 Intermolecular coupling

An unprecedented homogeneous gold-catalyzed oxidative cross-coupling which leads to α-arylenones **190** from propargylic acetates **189** and arylboronic acids has been developed by Zhang's group (Scheme 35) [86]. This cross-coupling reaction reveals the synthetic potential of Au(I)/Au(III) catalytic cycles.



Scheme 35: Gold-catalyzed oxidative cross-coupling reactions of propargylic acetates.

Kimber reported a facile and mild synthesis of enamides (**193**–**196**) by a gold-catalyzed nucleophilic addition to allenamides **191** (Scheme 36) [87]. For example, treatment of

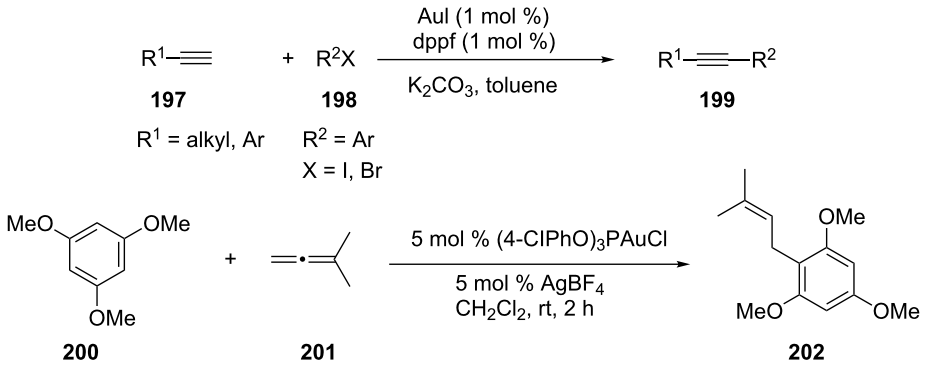


Scheme 36: Gold-catalyzed nucleophilic addition to allenamides.

allenamide and 1-methylindole with 5.0 mol % of PPh_3AuNTf_2 in CH_2Cl_2 at room temperature gave the corresponding enamide in 83% yield.

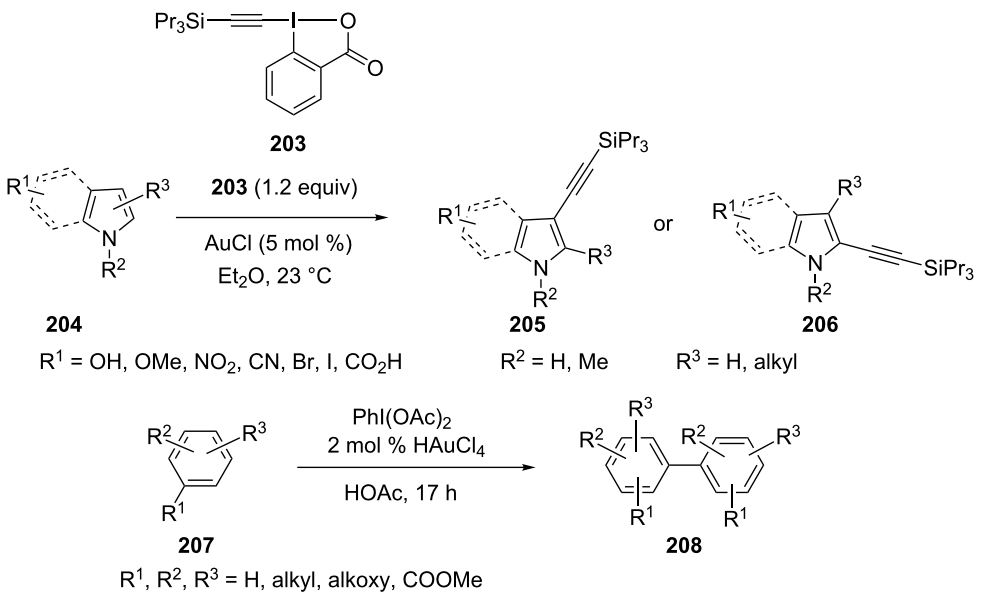
Gold-catalyzed direct carbon–carbon bond coupling reactions have been less explored [88,89]. In 2008, Li et al. reported a gold(I) iodide catalyzed Sonogashira reaction [88]. Terminal alkynes **197** reacted smoothly with aryl iodides and bromides **198** in the presence of 1 mol % AuI and 1 mol % dppf to generate the corresponding cross-coupling products **199** in good to excellent yields (Scheme 37). Another direct carbon–carbon bond coupling reaction was reported by Tarselli and co-workers [90]. In their study, the addition of nucleophilic methoxyarenes **200** to allenes **201** proceeded at room temperature in dichloromethane with a catalytic amount of phosphite–gold(I) pre-catalyst and a silver additive. Notably, the addition is regioselective for the allene terminus, and generates (*E*)-allylation products **202**.

The direct C–H functionalization of indoles or pyrroles is an efficient method for the introduction of vinyl and aryl groups. A gold-catalyzed direct alkynylation of indole and pyrrole heterocycles **204** with a benziodoxolone-based hypervalent iodine reagent **203** has been developed [91]. The functional group tolerance was greatly increased when compared with direct alkynylation of indoles reported previously. Kar et al. reported a general gold-catalyzed direct oxidative homo-coupling of non-activated arenes **207** (Scheme 38). The reaction protocol toler-



197 198 199 200 201 202

Scheme 37: Gold-catalyzed direct carbon–carbon bond coupling reactions.



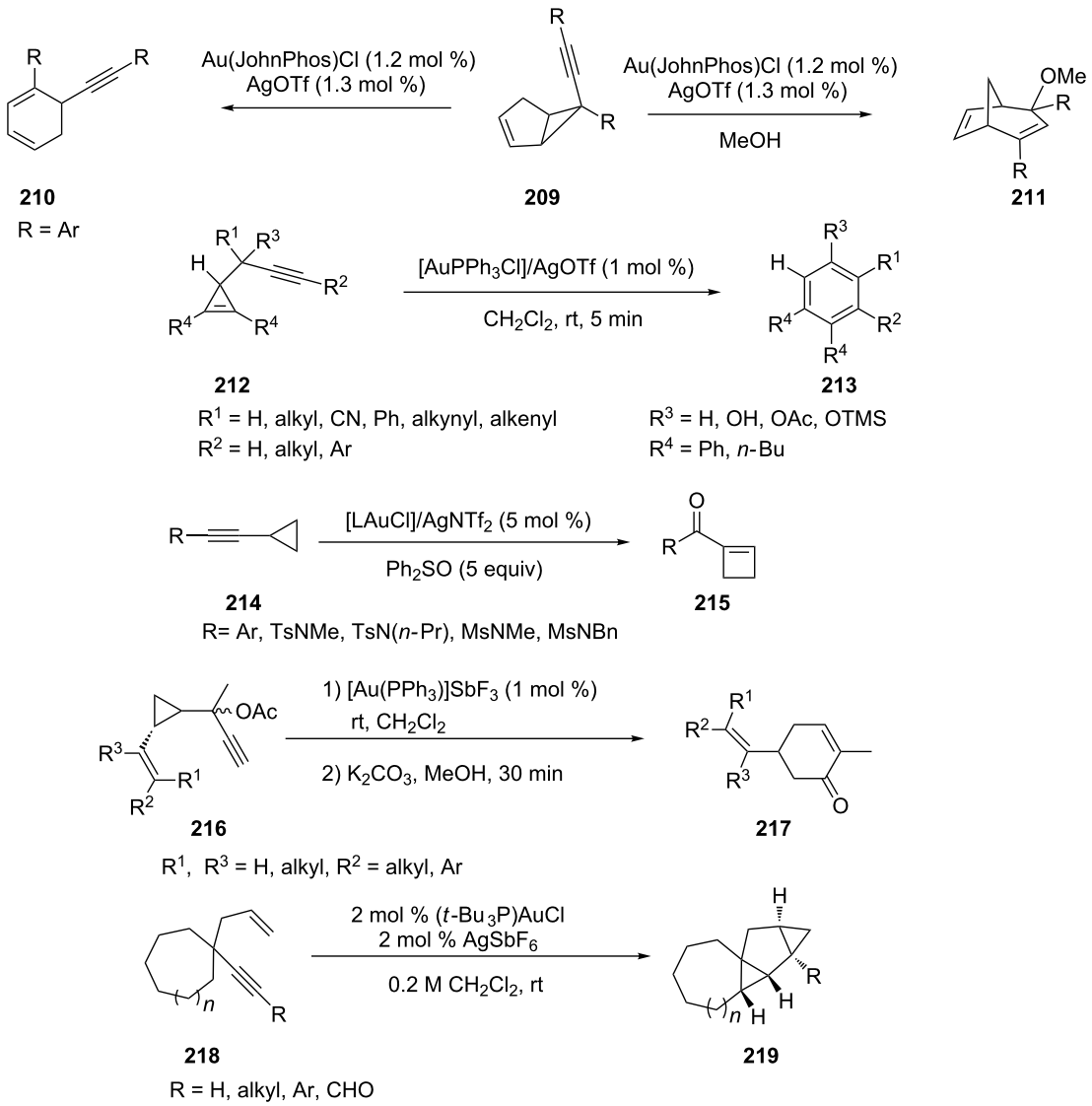
Scheme 38: Gold-catalyzed C−H functionalization of indole/pyrrole heterocycles and non-activated arenes.

ates a wide range of functional groups [92]. All halogens survive the reaction, which provides the potential for further reactions.

4.2 Rearrangements and ring enlargement

A gold-catalyzed rearrangement of 6-alkynylbicyclo[3.1.0]hexen-2-enes **209** has been developed [93]. In this reaction, divergent structural rearrangements are observed in the absence/presence of nucleophiles. The process results in a novel five-to-six-membered ring expansion that involves cleavage of the bridging C–C bond and a formal [1,2]-alkynyl shift. Li et al. reported the first gold-catalyzed reaction of propargylcyclopropene systems **212** which affords benzene derivatives **213** in high yields [94] (Scheme 39).

Only few efficient methods have emerged for the synthesis of cyclobutane derivatives, which are important structural units in several natural products. Li et al. reported a novel gold-catalyzed oxidative ring-expansion of non-activated cyclopropylalkynes using Ph_2SO as an oxidant [95]. Various alkynylcyclopropane derivatives **214** have been converted to cyclobutenyl ketones **215** in moderate to high yields under optimal conditions. Zou et al. has developed a versatile approach to 5-, 6-, and 7-membered carbocycles via the gold-catalyzed cycloisomerization of cyclopropyl alkynyl acetates [96]. The homo-Rautenstrauch rearrangement of 1-cyclopropylpropargylic esters **216** gave cyclohexenones **217** under mild conditions. Toste's group reported a gold(I)-catalyzed sequential cycloisomerization/sp^3 C–H bond functionalization



Scheme 39: Gold-catalyzed cycloisomerization of cyclic compounds.

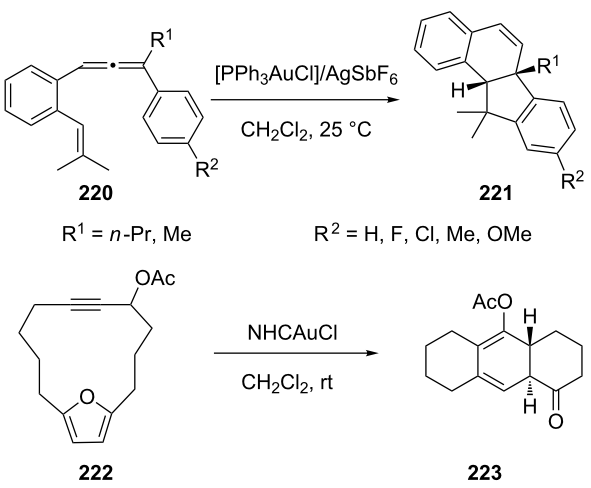
(Scheme 39) of 1,5-enynes **218** and 1,4-enallenes to yield tetracyclododecane **219** and tetracyclotridecane derivatives, respectively [97]. These transformations represent rare examples of sp^3 C–H bond insertion via a cationic gold(I)–carbenoid intermediate.

4.3 Cycloadditions

Intramolecular [M + N]-type cycloaddition reactions are powerful tools for accessing complex molecular frameworks [98]. Several gold-catalyzed [3 + 2] [99], [4 + 2] [100-105], and [4 + 3] [106-108] cycloaddition reactions have been developed in last 3 years. Treatment of 1-aryl-1-allen-6-enes **220** with $[PPh_3AuCl]/AgSbF_6$ (5 mol %) in CH_2Cl_2 at 25 °C led to intramolecular [3 + 2] cycloadditions to afford *cis*-fused dihydrobenzo[*a*]fluorenes **221** efficiently and selectively [99]. As pointed out by the researchers, the reactions proceeded with the initial formation of *trans*/*cis* mixtures of 2-alkyl-1-isopropyl-2-phenyl-1,2-dihydronaphthalene cations, which were converted into the desired *cis*-fused cycloadducts through the combined action of a gold catalyst and a Brønsted acid. Gung and co-workers developed a 3,3-rearrangement/transannular [4 + 3] cycloaddition reaction (Scheme 40) in the presence of either a Au(I) or Au(III) catalyst [109]. In these reactions, the regiochemistry of the product **223** is controlled by the position of the acetoxy group in the starting material **222**, while the stereochemistry of the reaction depends on the ring size.

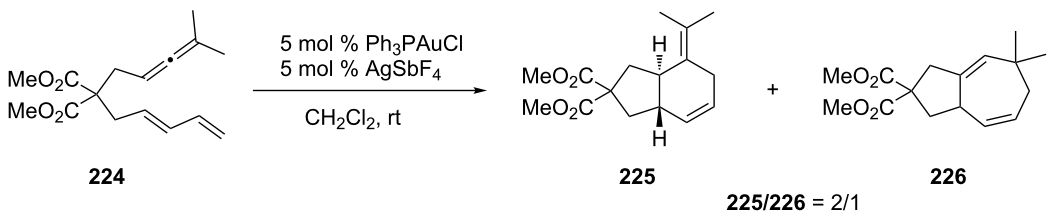
In some gold(I)-catalyzed cycloaddition reactions, regiochemistry of the product is controlled by the ligand [100,101]. For example, the triphenylphosphinegold(I)-catalyzed reaction of allene–diene **224** provided a 2:1 mixture of the [4 + 3] and [4 + 2] cycloadducts (**225** and **226**) [101]. The selectivity was improved to 96:4 in favor of the [4 + 3] cycloadduct when di-*tert*-butylbiphenylphosphinegold(I) was employed as the catalyst. On the other hand, the use of arylphosphitegold(I) complexes exclusively produced the formal [4 + 2] cycloaddition product in very good yield (Scheme 41).

Enynes [110-116], diynes [117-120], allenynes [121-128], and dienes [129-131] are common substrates for intramolecular cycloaddition reactions.

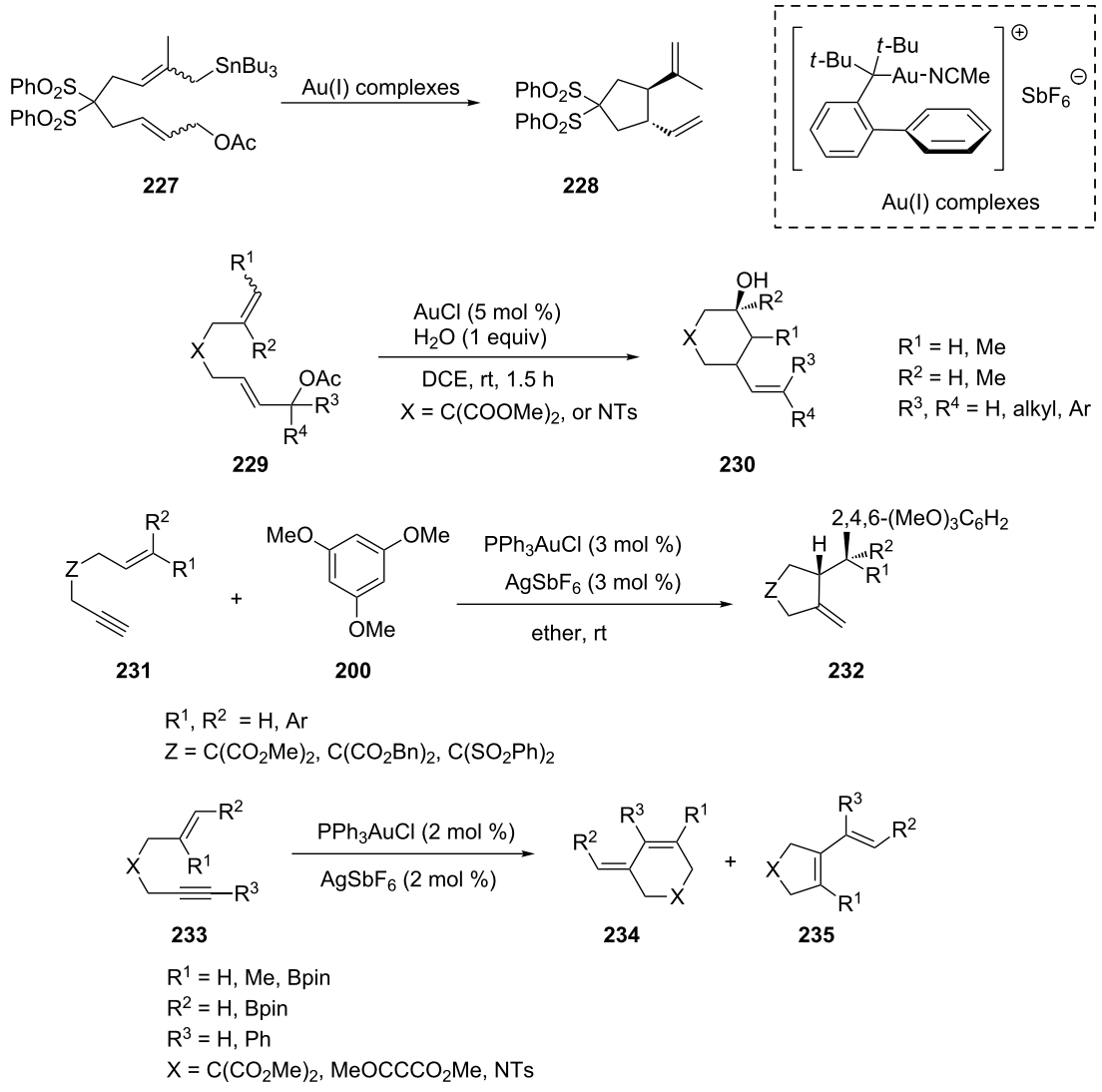


Scheme 40: Gold-catalyzed cycloaddition of 1-aryl-1-allen-6-enes and propargyl acetates.

Porcel et al. found that cationic Au(I) complexes are the most efficient catalysts for the intramolecular coupling of allyl acetates with allylstannanes (compound **227**) [129]. Zhu and co-workers reported a gold-catalyzed carbocyclization of dienyl acetates **229** to construct multi-functionalized 3-vinylcyclohexanol derivatives **230** [130]. The reaction proceeded through the nucleophilic addition of the alkene to the allylic cation via a 6-endo-trig process. The structure of the substrate affected the configurational orientation of the allylic cation in a boat-like transition state, which led to either *trans*-cyclohexanols or *cis*-piperidine derivatives. Some functionalized carbo- and heterocycles **232** were synthesized via gold-catalyzed cycloisomerization reactions of enynes **231** [110]. The $PPh_3AuCl/AgSbF_6$ catalytic system promotes a Friedel–Crafts type addition of electron-rich aromatic and heteroaromatic derivatives to the non-activated alkene followed by a C–C bond cyclization reaction. The carbon, oxygen and nitrogen tethered 1,6-enynes react smoothly with methoxy substituted benzenes, indoles, pyrroles and furans as nucleophilic partners (Scheme 42). The cycloisomerization reactions of boronated enynes **233** was achieved with gold(I) complexes generated from a mixture of gold and silver salts [111]. Both, alkynyl and alkenyl pinacol boronates were tolerated. The ratio of the different *endo*- and *exo*-prod-



Scheme 41: Gold(I)-catalyzed cycloaddition with ligand-controlled regiochemistry.



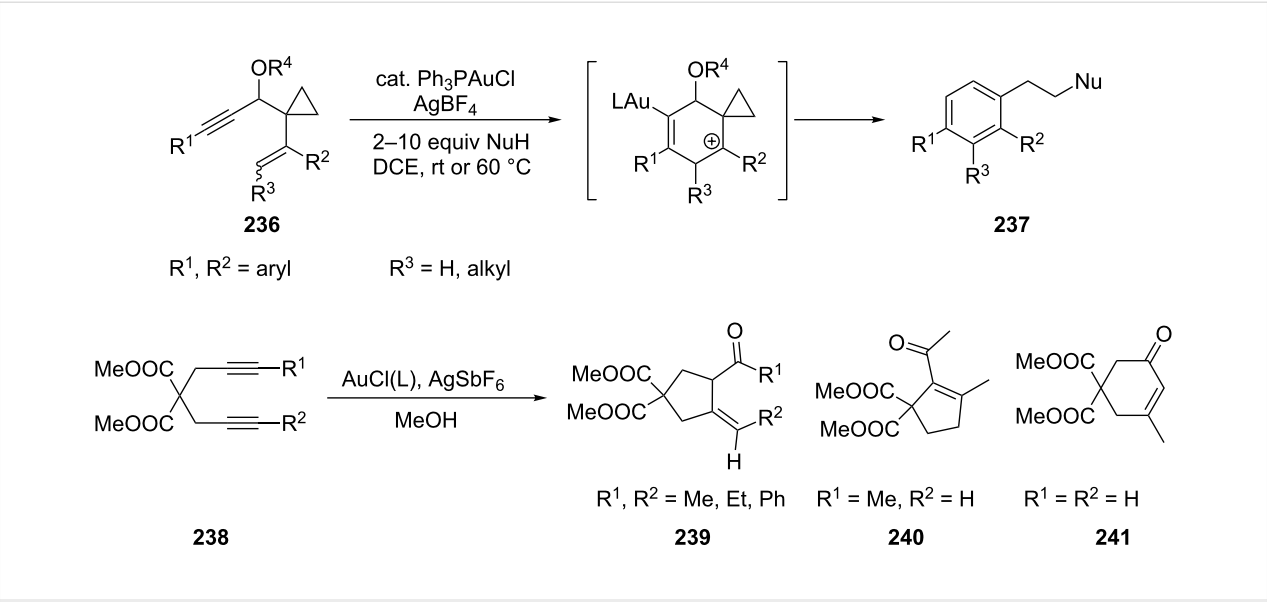
Scheme 42: Gold(I)-catalyzed cycloaddition of dienes and enynes.

ucts was heavily dependent on the position of the boronate functionality (Scheme 42).

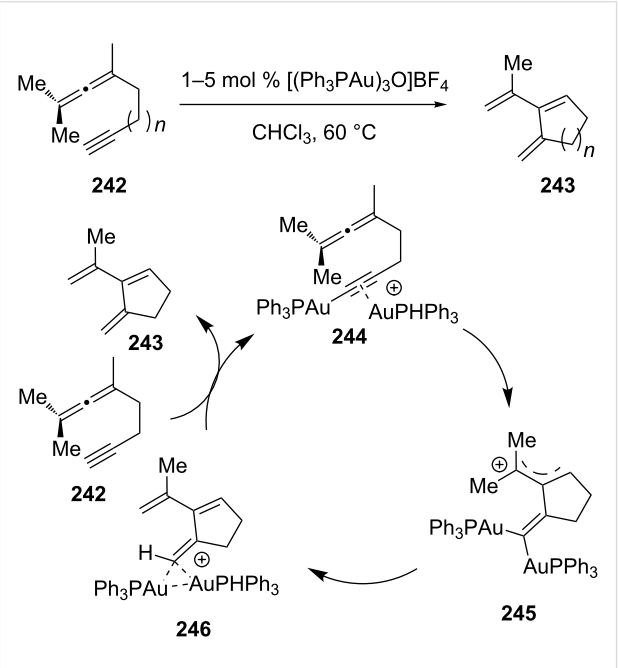
Li et al. reported a gold-catalyzed benzannulation of 3-alkoxy-1,5-enynes **236** to produce functionalized benzenes **237** [112]. The reaction occurs selectively through a 6-endo-dig pathway to give tri- and tetrasubstituted benzenes efficiently. Cyclization reactions of 1,6-diynes (2,2-dipropargylmalonates **238**) could be achieved with gold(I) catalysts. Disubstituted 1,6-diynes furnished the (*Z*)-cyclopentylidene derivative **239** stereoselectively [117]. Monosubstituted terminal diyne afforded the cyclopentene derivative **240**, while the diterminal 1,6-diyne produced a cyclohexenone derivative **241** (Scheme 43).

Cheong and co-workers demonstrated that 1,5-allenynes **242** could be transformed to cross-conjugated trienes **243** via rearrangement with $[(Ph_3PAu)_3O]BF_4$ as the catalyst [121]. Computational results indicated that the ene-reaction proceeded through a unique nucleophilic addition of an allene double bond to a cationic phosphine-gold(I)-complexed phosphine-gold(I) acetylide, followed by a 1,5-hydrogen shift (Scheme 44).

A range of indole based cycloaddition products were obtained by concerting the initial regioselective site-selective indole attack (C3 position) to the C–C multiple bonds [132-134]. In the case of gold(I)-catalyzed reactions initiated by 1,2-indole migrations [132], the starting material, indole **247**, was converted to an intermediate with $[AuNTf_2(Ph_3P)]$. Intramolecular attack of the indole on the activated alkyne gives the vinyl–gold complex, which is transformed into the gold carbene complex through a 1,2-migration of the indole. Further intramolecular nucleophilic attack of the phenyl group on the



Scheme 43: Gold-catalyzed intramolecular cycloaddition of 3-alkoxy-1,5-enynes and 2,2-dipropargylmalonates.

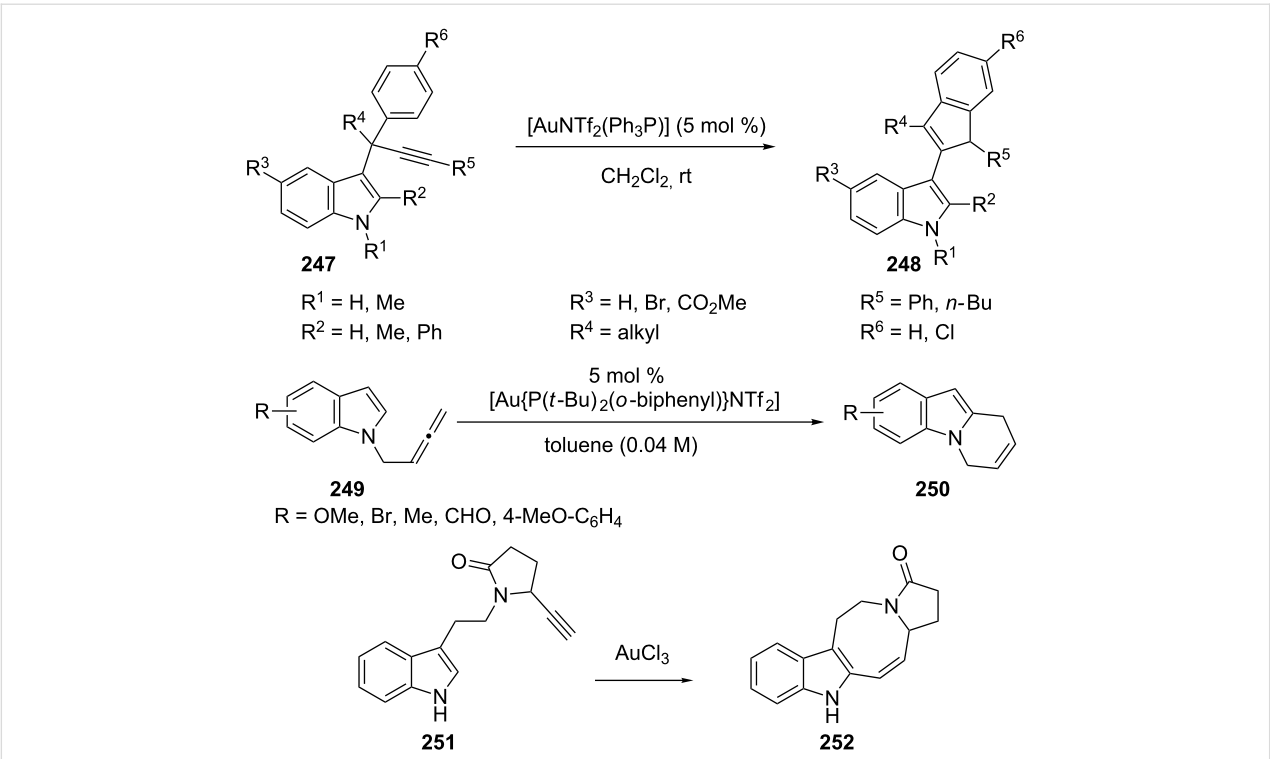


Scheme 44: Gold-catalyzed intramolecular cycloaddition of 1,5-allenynes.

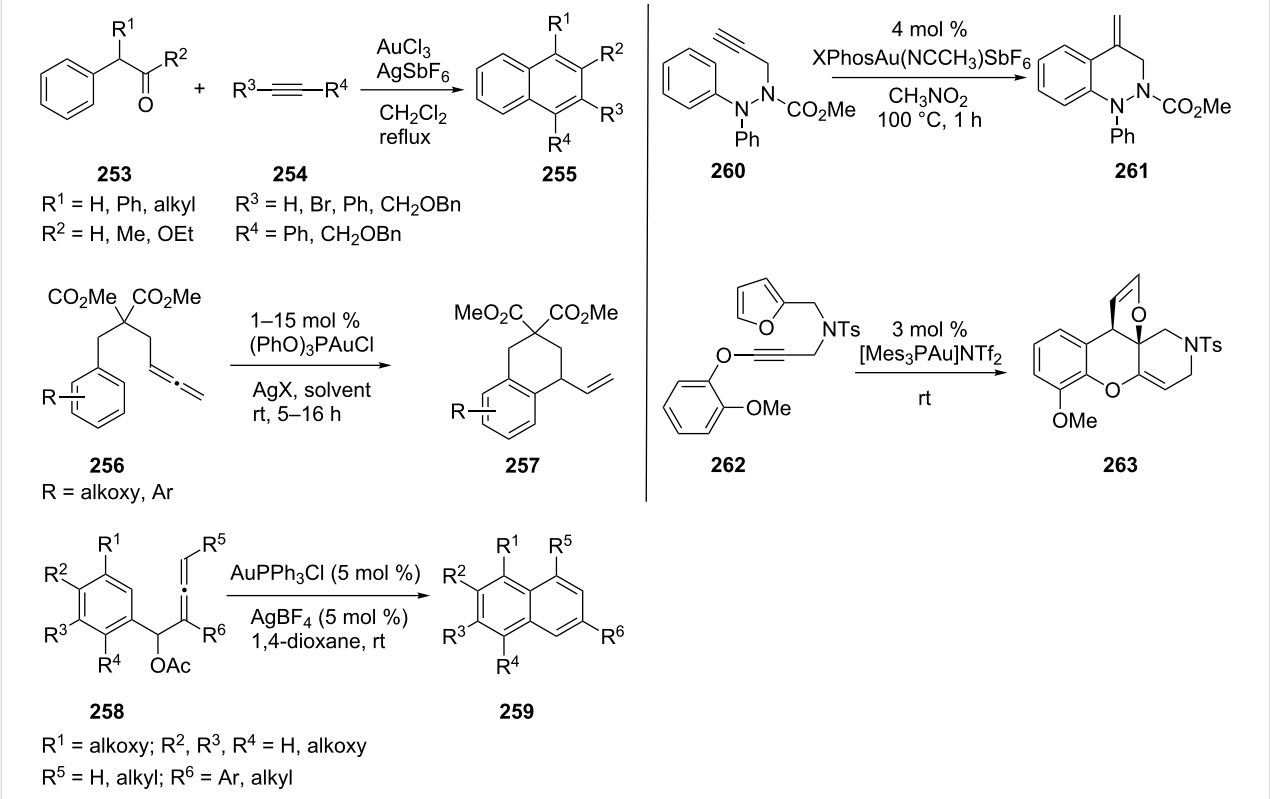
carbene carbon center, followed by a re-aromatization step and subsequent protodemetalation, affords **248** as the final product. Treatment of *N*-tethered 2,3-butadienyl-1*H*-indole **249** with di-*tert*-butyl(*o*-biphenyl)phosphine and $AuNTf_2$ led to 6-*endo* cyclization [133]. The methodology was applied in a direct synthesis of the relevant 6,9-dihydropyrido[1,2-*a*]-1*H*-indole core **250**. A similar strategy was adopted by Ferrer and co-workers [134], who prepared the 1*H*-azocino[5,4-*b*]indole skeleton **252** of the lundurines by the 8-endo-dig cyclization of the alkynylindole **251** using gold(III) chloride as the catalyst (Scheme 45).

Electron-rich arenes are, in some cases, good nucleophiles [135,136]. An interesting gold-catalyzed electrophilic addition to an arylalkyne for the synthesis of substituted naphthalenes **255** has been developed [137]. Tarselli et al. reported a gold(I)-catalyzed intramolecular hydroarylation of allenes [138]. Gold(I) complexes react with 4-allenylarenes **256** in an *exo* fashion to furnish vinyl-substituted benzocycles **257**. Interestingly, if 1-arylbuta-2,3-dienyl acetate **258** was used as the substrate, naphthalenes **259** are formed through a $AuPPh_3Cl$ catalyzed cyclization reaction [139]. Using gold complex $[XPhosAu(NCCH_3)SbF_6]$ as the catalyst, Jurberg and Gagosz prepared the cinnoline derivatives **261** by the hydroarylation of *N*-propargyl-*N*-arylhydrazines **260** [140]. With the gold complex $[Mes_3PAu]NTf_2$, an alkynyl ether moiety triggered a new reaction mode of furan–yne cyclization and delivered a new class of tetracyclic system **263** rather than a phenol (Scheme 46) [141].

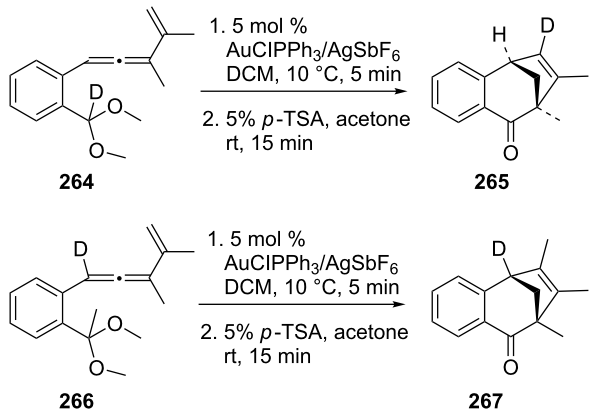
Insertion of a C–H bond into a metal–carbenoid is a highly useful method for forming a new carbon–carbon bond. An atypical gold–carbenoid induced cleavage of a sp^3-hybridized C–H bond can be achieved by undergoing 1,3-addition to a vinyl–carbenoid intermediate [142]. The bicyclo[3.2.1]oct-6-en-2-ones **265** and **267** could be synthesized stereoselectively by this method. Deuterium labeling experiments indicated the cyclization involved an unprecedented 1,3-addition of a sp^3-hybridized C–H bond to the vinyl–carbenoid moiety (Scheme 47).



Scheme 45: Gold(I)-catalyzed cycloaddition of indoles.



Scheme 46: Gold-catalyzed annulation reactions.



Scheme 47: Gold–carbenoid induced cleavage of a sp^3-hybridized C−H bond.

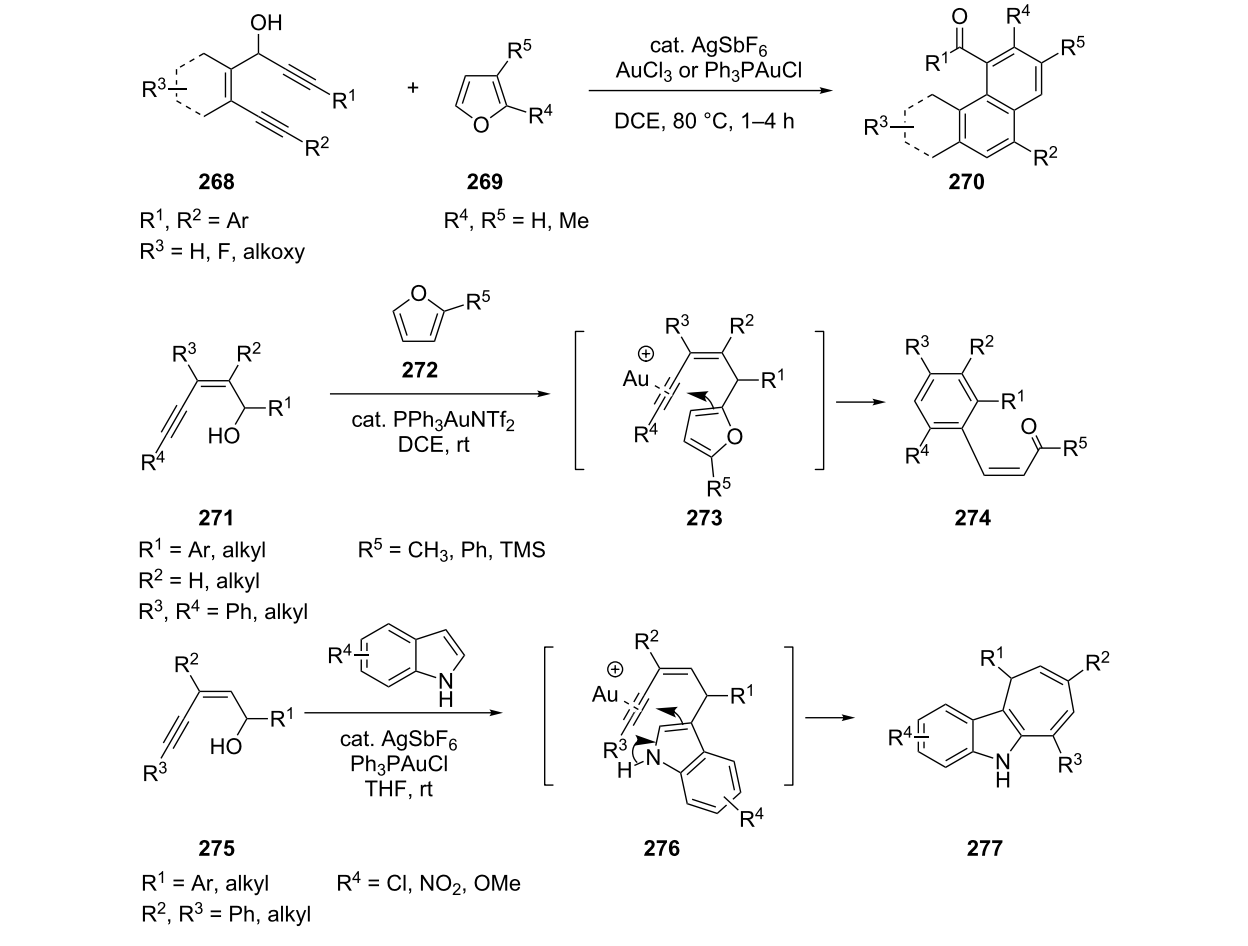
5 Gold-catalyzed tandem reactions

Tandem catalysis refers to the synthetic strategies of modular combination of catalytic reactions into one synthetic operation with minimum workup or change in conditions [143]. The gold-catalyzed tandem reactions have allowed chemists to assemble diverse complex molecular frameworks more conveniently.

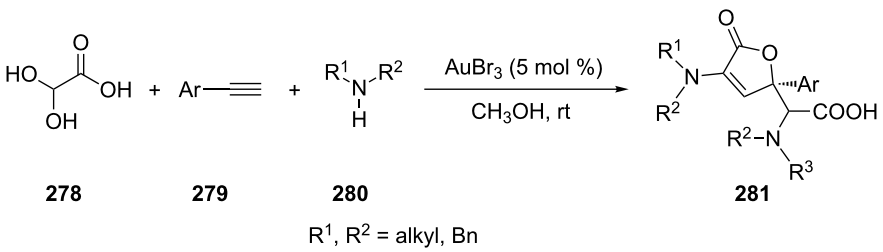
5.1 Sequential inter-and intramolecular reactions

Phenanthrenyl ketones are very important subunits in material science and also occur in numerous natural products. A gold-catalyzed cascade Friedel–Crafts/furan–yne cyclization/heteroenyne metathesis was developed for the highly efficient construction of phenanthrene derivatives **270** [144]. Both $AuCl_3$ and PPh_3AuCl are effective catalysts for all the processes in the reaction and a variety of diyne substrates **271** could be used (Scheme 48). Similar strategies [145,146] were applied to synthesize arylated (*Z*)-enones, -enals or dihydrocyclohepta[*b*]indole skeletons **277** by gold-catalyzed cascade Friedel–Crafts/furan (or indole)–alkyne cycloisomerizations (Scheme 48).

The polysubstituted butenolides **281** could be obtained through a gold-catalyzed multi-component tandem reaction that



Scheme 48: Furan- and indole-based cascade reactions.



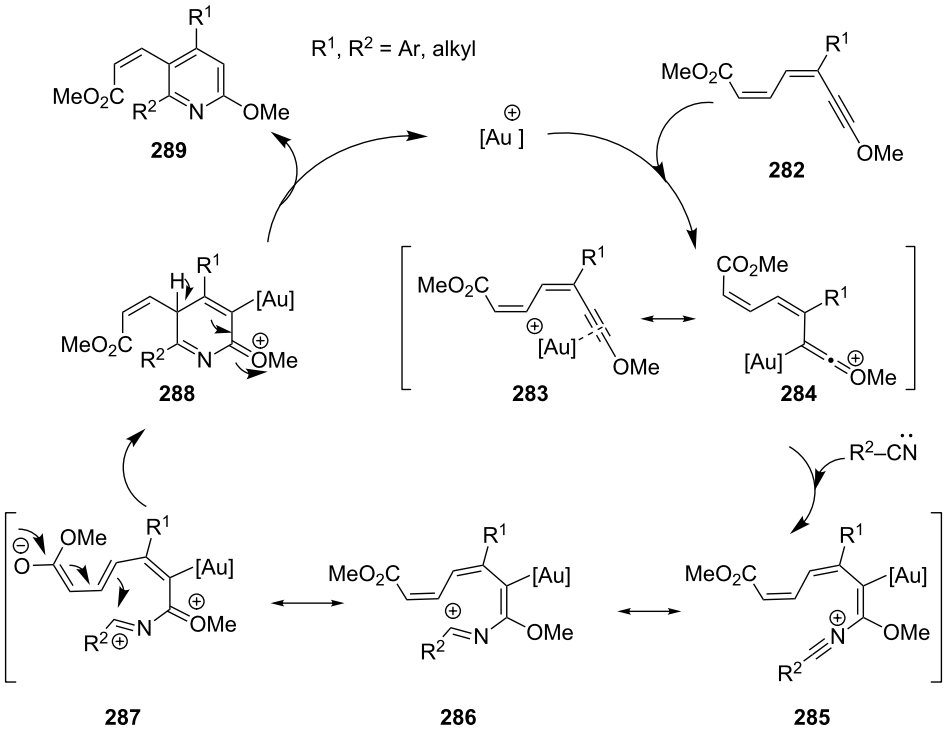
Scheme 49: Tandem process using aromatic alkynes.

involved novel direct alkyne **279**–amine **280**–glyoxylic acid (**278**) coupling, intramolecular cyclization of α-*N*-substituted β-alkynoic acid, and subsequent reaction (Scheme 49) [147].

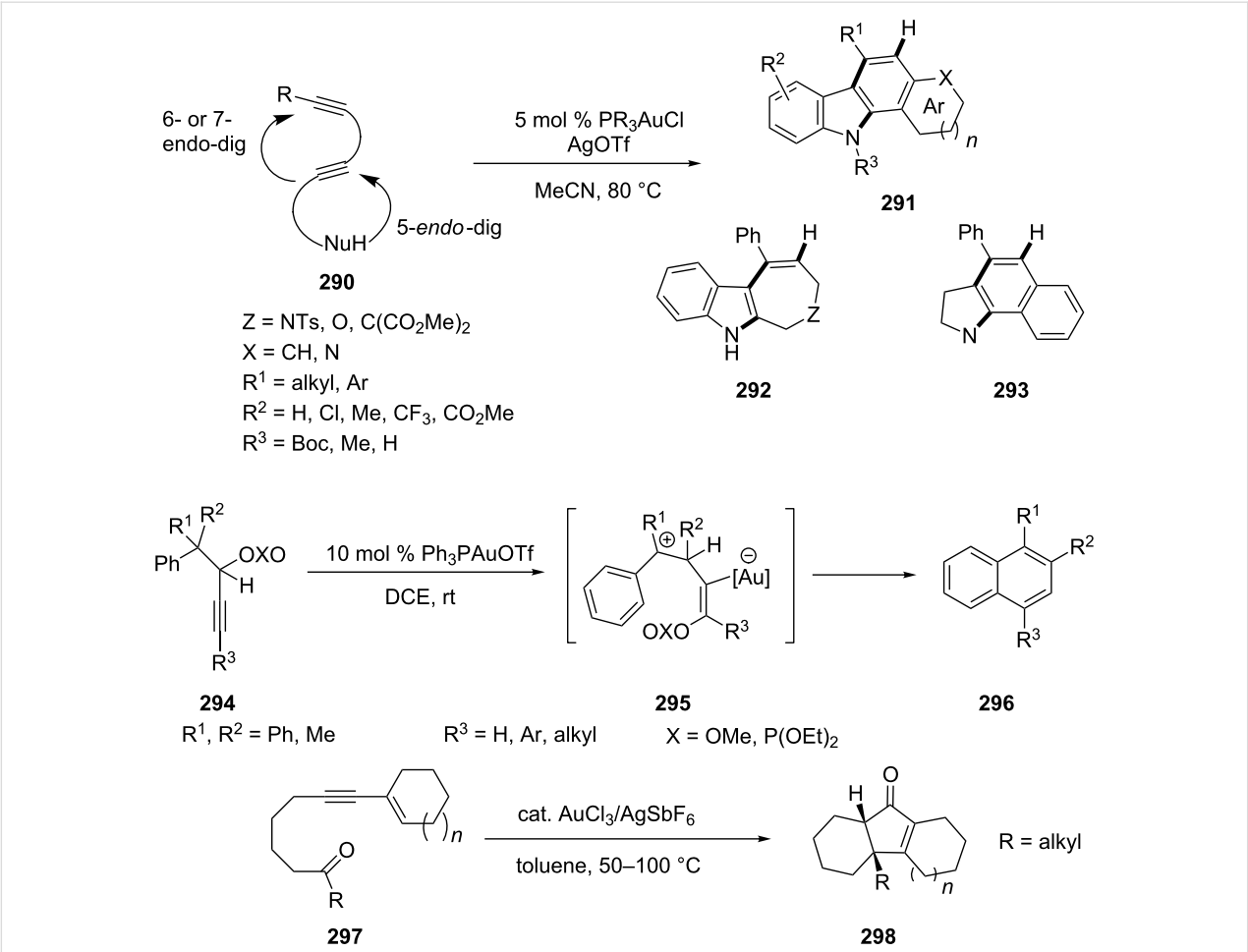
An intermolecular hetero-dehydro-Diels–Alder reaction between captodative 1,3-dien-5-ynes **282** and non-activated nitriles was introduced by Barluenga and co-workers [148]. The sequence is promoted by both, gold(I) and gold(III) catalysts and leads to the regioselective formation of tetrasubstituted pyridines **289**. The initial coordination of the triple bond to the gold catalyst forms intermediate **284**, followed by the regioselective nucleophilic attack of the nitrile, leading to the formation of **285**. Cyclization may occur through resonance structure **286** or **287** followed by final metal de-coordination (Scheme 50).

5.2 Sequential intramolecular reactions

Sequential intramolecular reactions result in the formation of multi-ring products from a single substrate [149]. In 2010, a concise synthetic method for the generation of fused indoles (**291**–**293**), by a gold-catalyzed cascade cyclization of diynes **290** was developed by Hirano and co-workers [150]. The reaction gave aryl annulated[*a*]carbazoles, dihydrobenzo[*g*]indoles, and azepino- or oxepinoindole derivatives through an intramolecular cascade 5-endo-dig hydroamination followed by a 6- or 7-endo-dig cycloisomerization. Dudnik et al. reported a gold(I)-catalyzed cycloisomerization of propargylic esters **294** which led to unsymmetrically substituted naphthalenes **296** [151]. This cascade reaction involves a tandem sequence of 1,3- and 1,2-migration of two different migrating groups. Jin and Yamamoto prepared the fused tri- and tetracyclic enones **298** through an



Scheme 50: Gold-catalyzed cycloaddition of 1,3-dien-5-ynes.

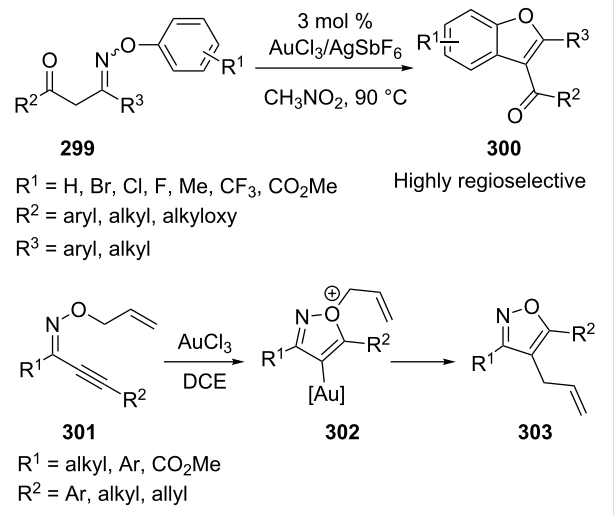


Scheme 51: Gold-catalyzed cascade cyclization of diynes, propargylic esters, and 1,3-enynyl ketones.

efficient gold(III)-catalyzed tandem reaction, heteroenyne metathesis, and Nazarov cyclization of 1,3-enynyl ketones **297** [152]. The gold(III) catalyst exhibits dual roles for activating both the alkyne and carbonyl moieties (Scheme 51).

More recently, Liu et al. developed a gold(III)-catalyzed tandem rearrangement/cyclization reaction of β-phenoxyimino ketone **299 (**produced from *O*-arylhydroxylamines with 1,3-dicarbonyl compounds in situ) to give 3-carbonylated benzofuran derivatives **300** [153]. Trisubstituted isoxazoles **303** were obtained from alkynyl oxime ether **301** through a gold-catalyzed domino reaction involving cyclization and subsequent Claisen-type rearrangement [154]. The presence of additional substituents on the allyl moiety required an increase in catalyst loading and a prolonged reaction time for complete consumption of the substrate (Scheme 52).

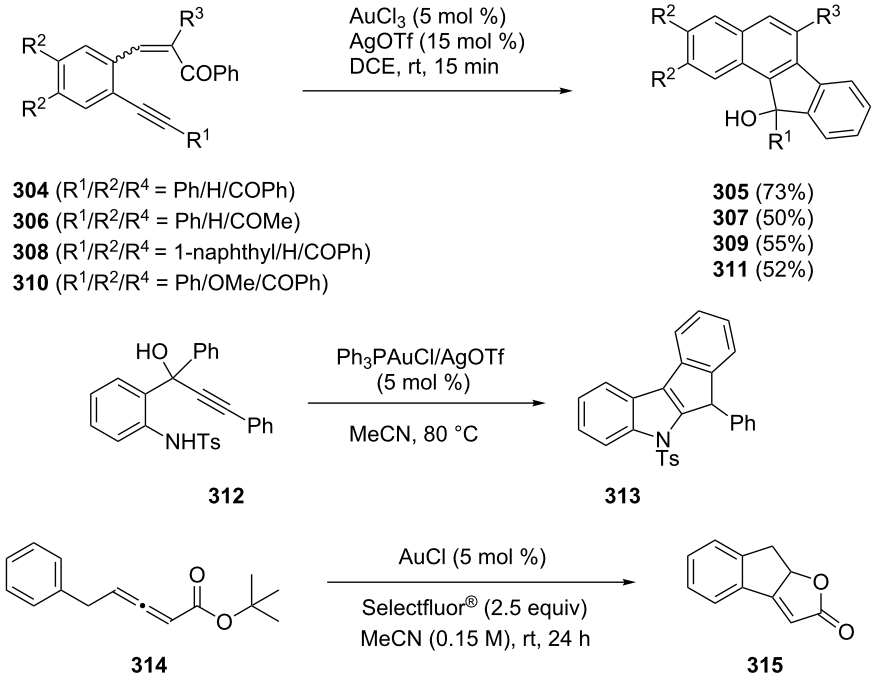
Liu and Zhang have developed a gold-catalyzed region-divergent tandem cationic cyclization/ring expansion terminated by a pinacol rearrangement to produce naphthalen-2(1*H*)-ones or



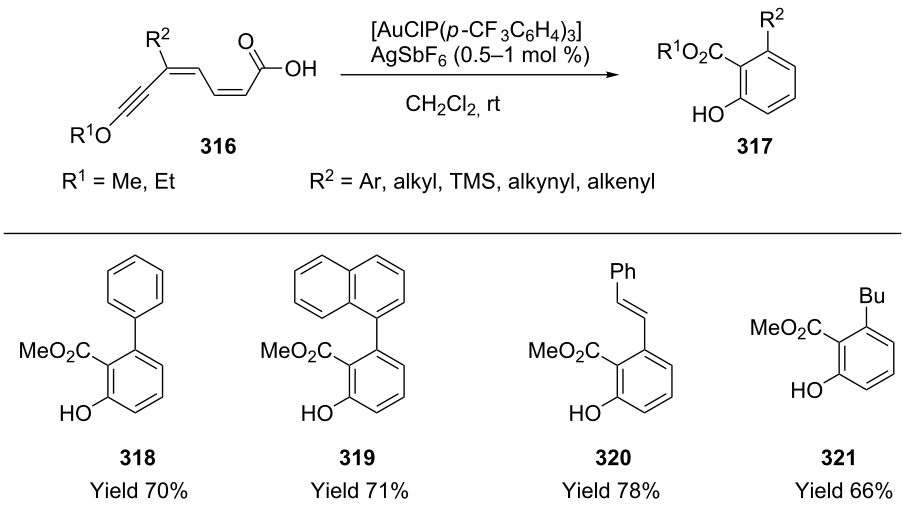
Scheme 52: Tandem reaction of β-phenoxyimino ketones and alkynyl oxime ethers.

naphthalenes **305**, **307**, **309**, and **311** selectively (Scheme 53) [155]. The synthesis of indole **313** [156] and tricyclic dihydroindenofuranone-type product **315** from 2-(tosylamino)phenylprop-1-yn-3-ol **312** [157] and allenoates **314** [158], respectively, has been reported (Scheme 53). The latter is the first example of a gold-catalyzed intramolecular C–C cross-coupling reaction involving aryl C–H functionalization with Selectfluor® as the oxidant.

2,4-Dien-6-ynecarboxylic acids **316** undergo gold-catalyzed tandem 1,6-cyclization/decarboxylation to afford 2,3-disubstituted phenols (**318**–**321**) and unsymmetrical bi- and terphenyls (Scheme 54) [159]. The reaction is greatly affected by the electronic properties of dienyne acid. The regioselective 1,6-cyclization/decarboxylation sequence only takes place when a strong electron-donating group is not directly linked to the triple bond.

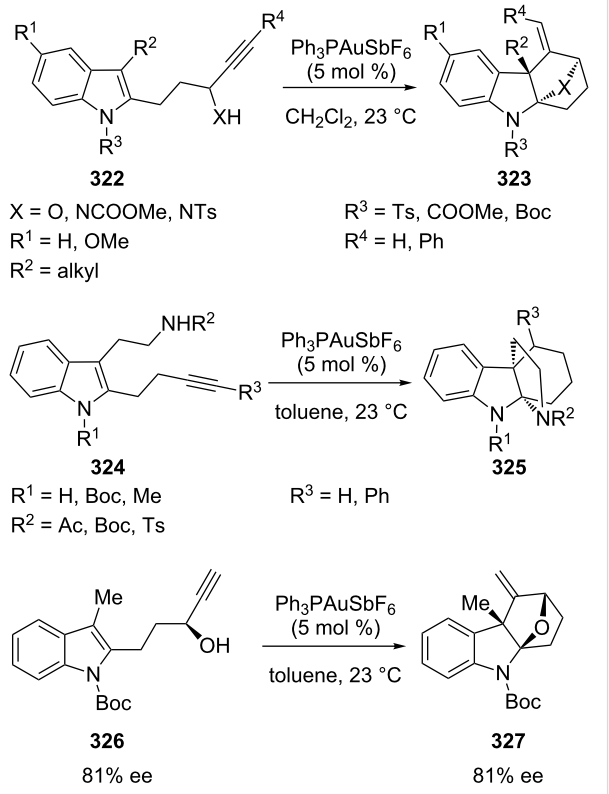


Scheme 53: Gold-catalyzed tandem cyclization of enynes, 2-(tosylamino)phenylprop-1-yn-3-ols, and allenoates.



Scheme 54: Cyclization of 2,4-dien-6-yne carboxylic acids.

Liu et al. has developed two highly stereoselective cationic gold(I)-catalyzed tandem cyclization reactions of alkynylindoles **322** [160]. The reaction proceeds with remarkable retention of chirality and allows the efficient enantioselective synthesis of polycyclic indolines **327** from the corresponding enantiomerically enriched alkynylindole **326** (Scheme 55).



Scheme 55: Gold(I)-catalyzed tandem cyclization approach to tetracyclic indolines.

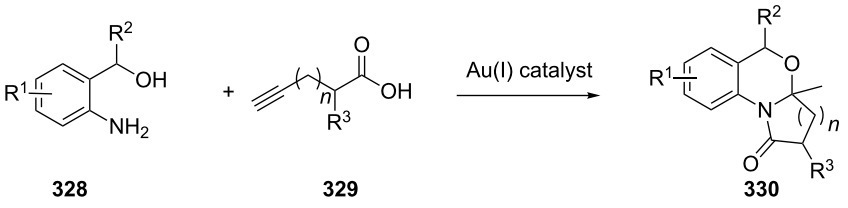
5.3 Sequential intra-and intermolecular reactions

In an attempt to devise an efficient synthesis of potential bioactive fused heterocyles, our group developed a highly efficient, [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6-catalyzed cascade cycloisomerization to produce pyrrolo/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones **330** [161], pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones **332** [162], benzo[*e*]indolo[1,2-*a*]-pyrrolo[2,1-*c*][1,4]diazepine-3,9-diones **335** [163], and fused quinoxalinones **337** [164]. These cascades are proposed to occur from an initial enol lactone intermediate via an intramolecular cycloaddition [165]. A subsequent intermolecular hydroamination of the intermediate, followed by a cyclization, leads to the observed products. Our group also investigated the construction of highly functionalized pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones **340** via a $AuBr_3$/$AgSbF_6$-catalyzed cascade transformation sequence (Scheme 56). The strategy affords a straightforward and efficient construction of tricyclic lactam molecular architectures in which several carbon–carbon and carbon–nitrogen bonds are formed in a one-pot reaction from simple starting materials [166].

The catalytic conversion of C(sp^3)–Au bonds into C(sp^3)–C(sp^2) bonds is an ongoing challenge. In 2010, Zhang's group reported the first example in an intermolecular oxidative cross-coupling manner [167]. In their pioneering work, carboamination, carboalkoxylation and carbolactonization of terminal alkenes **341** was achieved via oxidative gold catalysis and provided expedient access to various substituted *N*- or *O*-heterocycles (**344**–**351**) (Scheme 57). Deuterium labeling experiments were carried out to unveil the reaction mechanism. The results established the anti nature of the alkene functionalization and the indispensable role of Au(I)/Au(III) catalysis. Toste's group and Russell's group subsequently reported the aminoarylation and oxyarylation of alkenes (**352** and **355**) following a similar protocol [168,169]. In the gold-catalyzed intramolecular aminoarylation of alkenes, ligand and halide effects played a dramatic role for the addition to alkenes. The experimental studies suggest that the C–C bond-forming reaction occurs through a bimolecular reductive elimination. Furthermore, a gold-catalyzed three-component coupling was also developed for the oxidative oxyarylation of alkenes **358** via a similar strategy [170].

From the discovery and development of metal–carbenoids in cycloadditions with alkenes, as well as the internal redox reactions on alkynes, a further extensive investigation was focused on the new redox/cycloaddition cascades on alkynes to obtain azacyclic compounds **363** [171]. The central cores of the products were constructed through a formal [2 + 2 + 1] cycloaddition that involved α-carbonyl–carbenoids, nitroso species and external alkenes (Scheme 58).

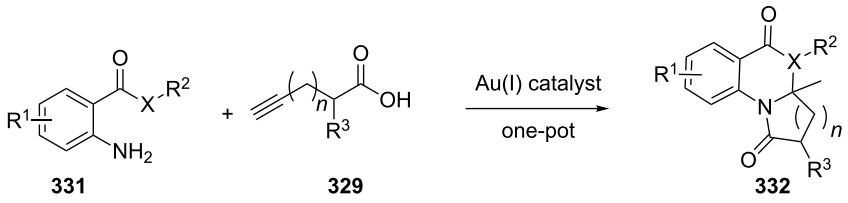
A gold(I)-catalyzed cascade cyclization/oxidative cross-coupling process has been devised to prepare β-alkynyl-γ-butenolides **366** directly from allenoates **364** and various terminal alkynes [172]. The González group developed an intermolecular reaction of internal alkynes and imines, in which the propargyl tosylates **367** react with *N*-tosylaldimines **368** to afford cyclopent-2-enimines **369** [173]. The final product was achieved through a 1,2-migration of the tosylate followed by the interaction with the imine and a Nazarov-like cyclization. Barluenga et al. reported a gold-catalyzed cascade reaction involving an unusual intramolecular redox process in which 5-heteroaryl-substituted ketone derivatives **372** were obtained from secondary 5-hexyn-1-ols **370** (Scheme 59) [174]. The first step is supposed to be an intramolecular addition of the hydroxy group to the internal carbon of the triple bond, which is similar to the mechanism mentioned above [161,163].



328 **329** **330**

n = 1, 2

R^1 = H, halogen, Ar; R^2 = H, Me; R^3 = H, alkyl

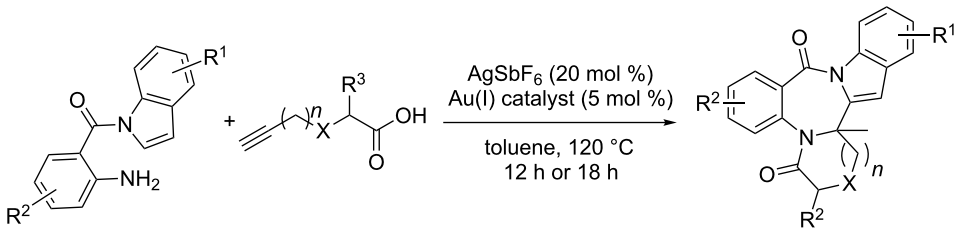


331 **329** **332**

n = 1, 2

X = O, N

R^1 = H, Me, Cl, OMe; R^2 = H, alkyl; R^3 = H, alkyl

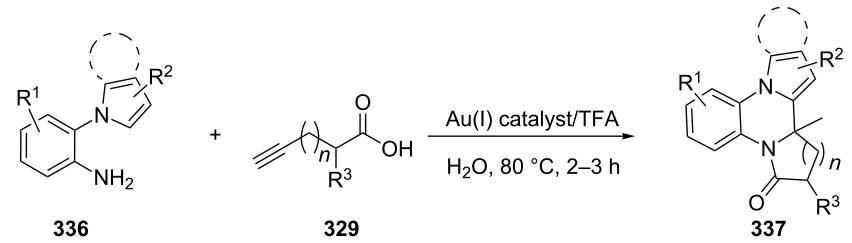


333 **334** **335**

n = 0, 1

X = CH_2, O

R^1 = H, Me, F, Cl, CN; R^2 = H, Me, F, Cl; R^3 = H, alkyl

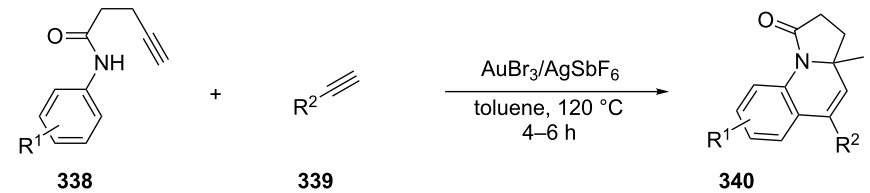


336 **329** **337**

n = 1, 2

R^1 = H, Me, F, OMe, CN, CF_3; R^2 = H, Me, F, OMe; R^3 = H, alkyl

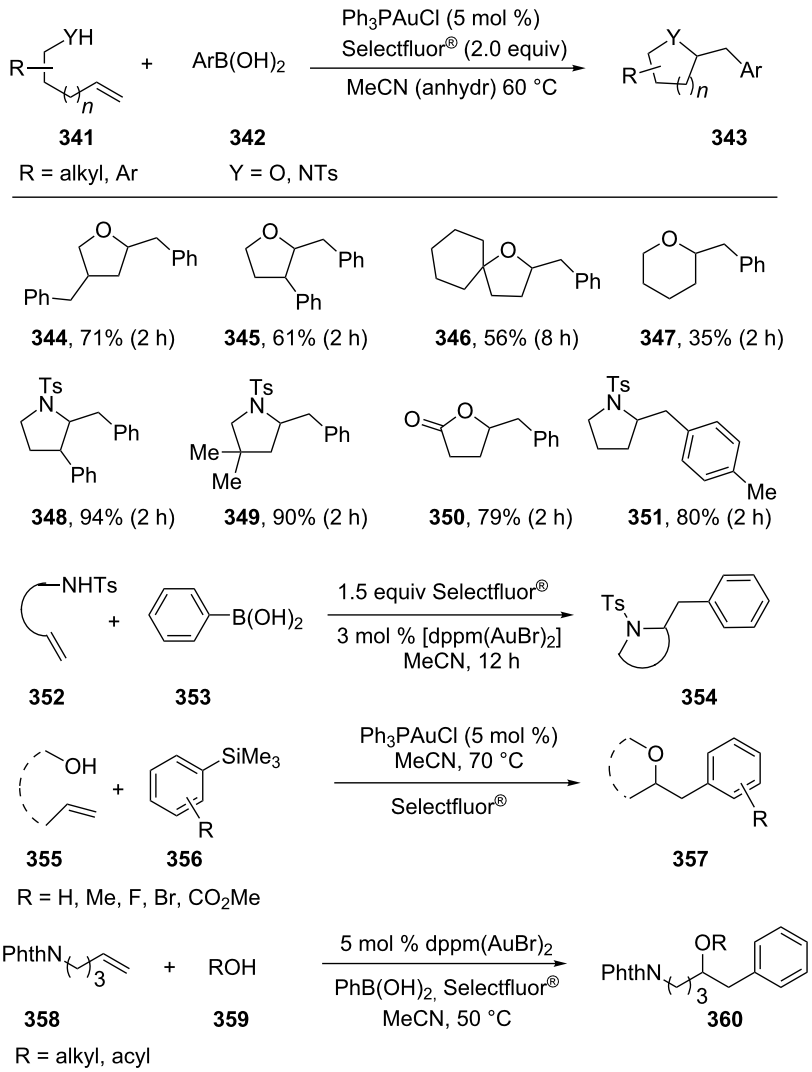
Au(I) catalyst = [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6



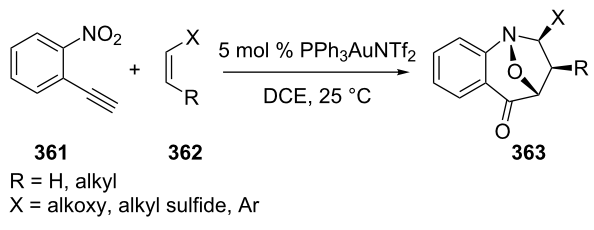
338 **339** **340**

R^1 = H, Br, F, OPh, COOEt; R^2 = H, Cl, F, Ph

Scheme 56: Gold-catalyzed tandem reactions of alkynes.



Scheme 57: Aminoarylation and oxyarylation of alkenes.

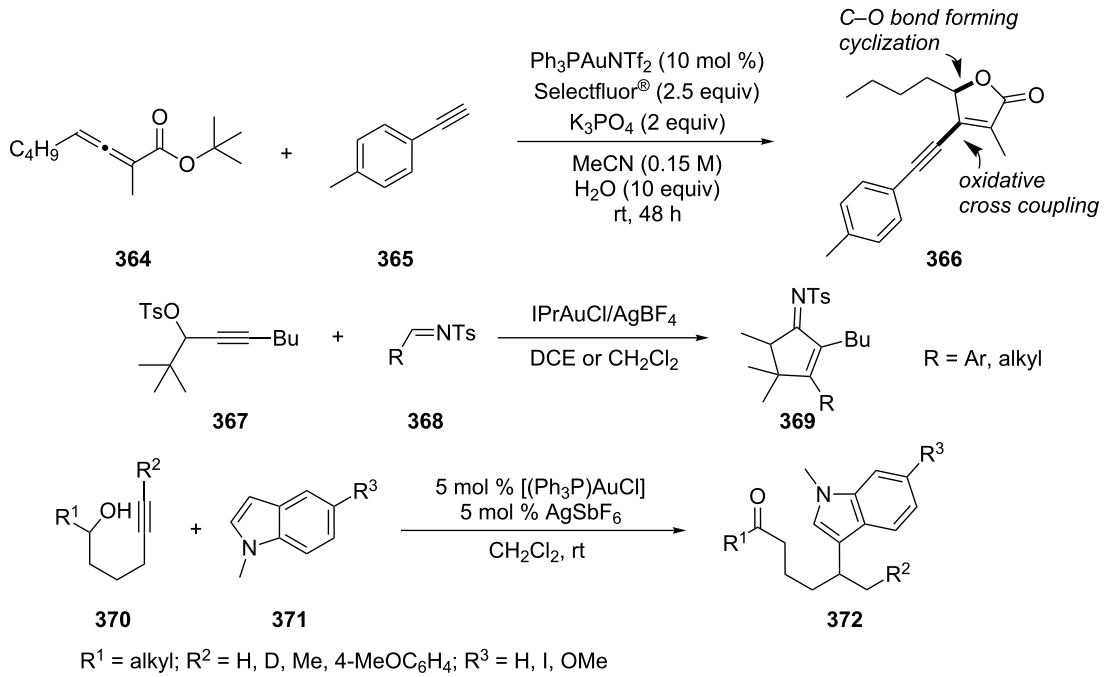


Scheme 58: Cycloaddition of 2-ethynylnitrobenzene with various alkenes.

6 Gold-catalyzed asymmetric addition reactions

The chiral ligand used for the transition metal-catalyzed reactions are the main determinant of enantioselectivity. Although asymmetric catalysis using chiral organometal complexes and chiral organomolecules have shown many advantages and a range of catalytic asymmetric reactions have been well documented [175], gold-catalyzed asymmetric addition reactions do not feature often. More recently this situation has been changing with significant progress being made in this area. To date, a broad range of chiral catalysts have been developed. Despite the large amount of chiral ligands used, only a few provided good to high enantioselectivities. The best ee values have been obtained with thiourea-cinchonine [176], chiral carbene [177], BINAP [178-180], and BIPHEP [181-190] analogs.

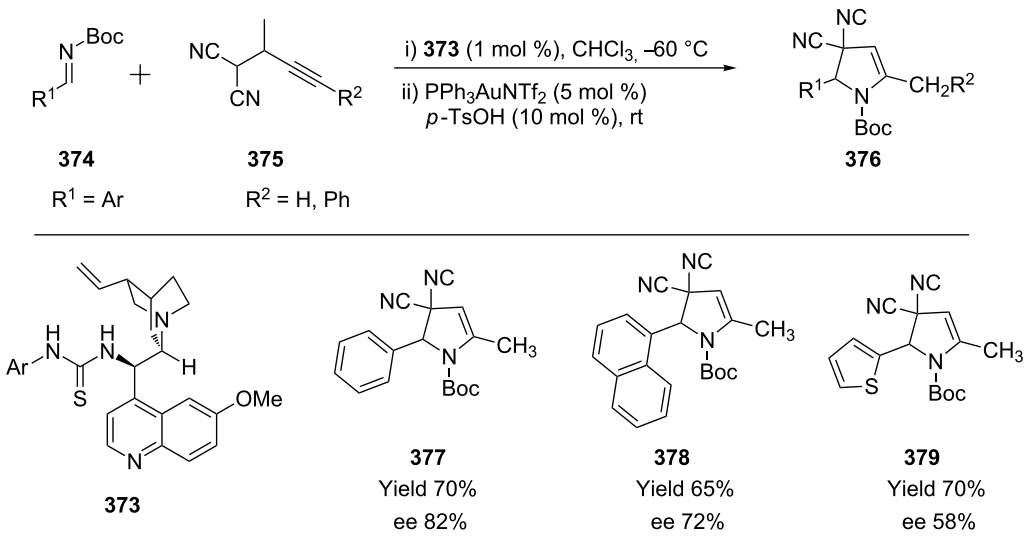
Monge et al. reported a direct asymmetric one-pot synthesis of optically active 2,3-dihydropyrroles from propargyl malononitriles **375** and *N*-Boc-protected imines **374** (Scheme 60) [176]. In the alkyne hydroamination (which is based on a bifunctional organocatalytic Mannich-type reaction, subsequent gold-



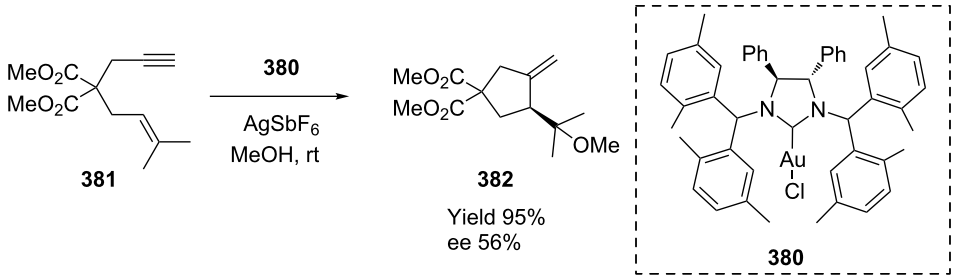
Scheme 59: Gold-catalyzed tandem reactions of allenoates and alkynes.

catalyzed alkyne hydroamination and isomerization) thiourea-based hydrogen bonding organocatalyst **373** and PPh_3AuNTf_2 proved to be compatible upon protonation with *p*-TsOH. Electron-poor aromatic imines can be employed to give the corresponding 2,3-dihydropyrroles **376** in good yields (74–80%) and enantioselectivities (68–72% ee). However, lower enantioselectivity may result from the more electron-rich substituent groups. For example, the heteroaromatic thiophene-based imine gave the desired products **379** in good yield (70%), albeit in moderate enantioselectivity (58% ee).

In the study of enantioselective cyclization, for example, of 1,6-enynes **381** for the synthesis of cyclopentane derivatives **382**, Matsumoto and co-workers found chiral carbene–AuCl catalyst precursor **380** gave moderate enantioselectivity of up to 59% (Scheme 61) [177].

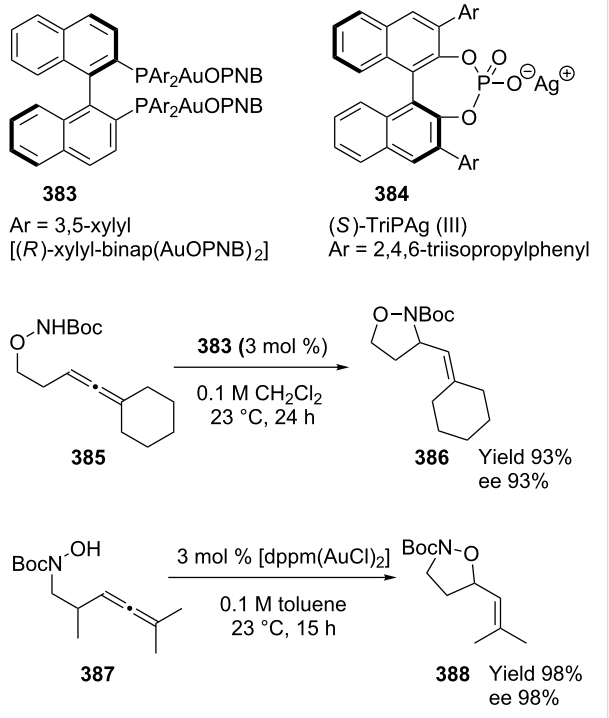


Scheme 60: Gold-catalyzed asymmetric synthesis of 2,3-dihydropyrroles.



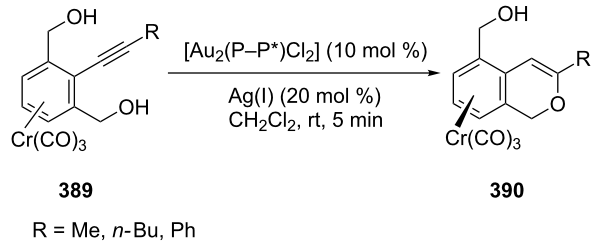
Scheme 61: Chiral [NHC–Au(I)]-catalyzed cyclization of enyne.

In the last 3 years, enantioselective gold-catalyzed reactions with BINAP and BIPHEP analogs have been far more documented compared to other ligands. In 2009, Toste's group reported the application of [(*R*)-xylyl-binap-(AuOPNB)$_2$] **383** in gold-catalyzed hydroaminations and hydroalkoxylations of allenes with hydroxylamines and hydrazines, which gave ee values of up to 99% [178]. Whereas chiral biarylphosphine-gold(I) complexes are suitable catalysts for the enantioselective addition of nitrogen nucleophiles to allenes, the addition of oxygen nucleophiles requires the use of chiral anions **384** (Scheme 62).



Scheme 62: Gold-catalyzed hydroaminations and hydroalkoxylations.

Gold(I)-catalyzed asymmetric cyclization of 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes **389** gave planar chiral isochromene–chromium complexes **390** with high enantioselectivity [179]. Enantioselectivities of the cyclized isochromene–chromium complexes are largely dependent on the combination of gold pre-catalysts and silver salts. The use of $AgSbF_6$ resulted in excellent enantioselectivities, regardless of the nature of the gold pre-catalyst (Scheme 63).

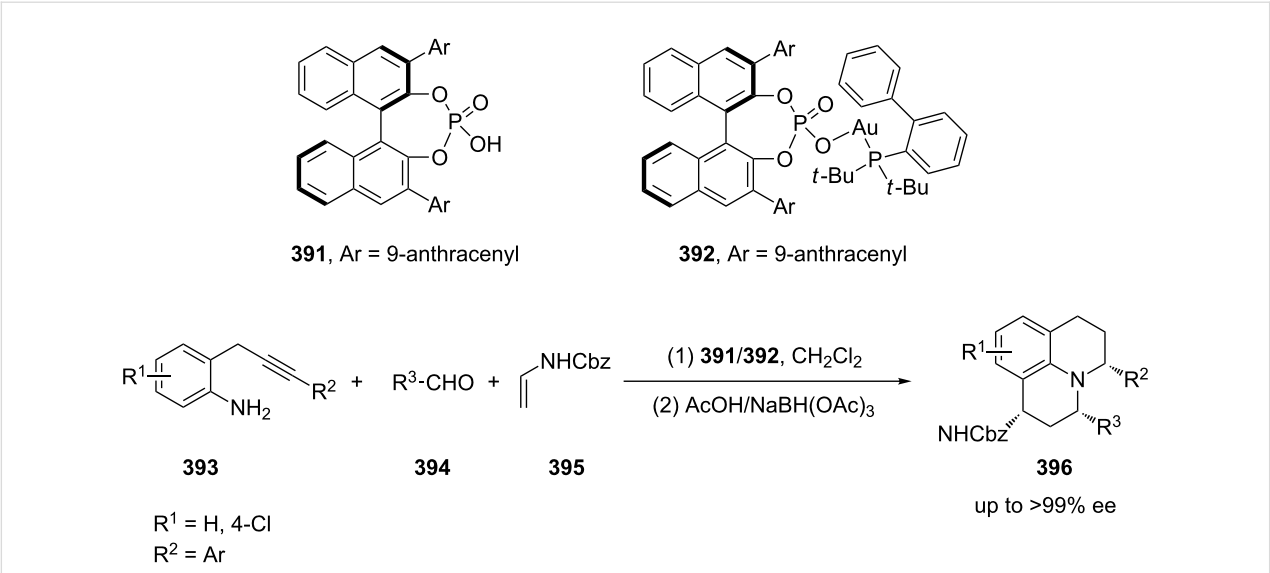


Scheme 63: Gold(I)-catalyzed asymmetric hydroalkoxylation of 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes.

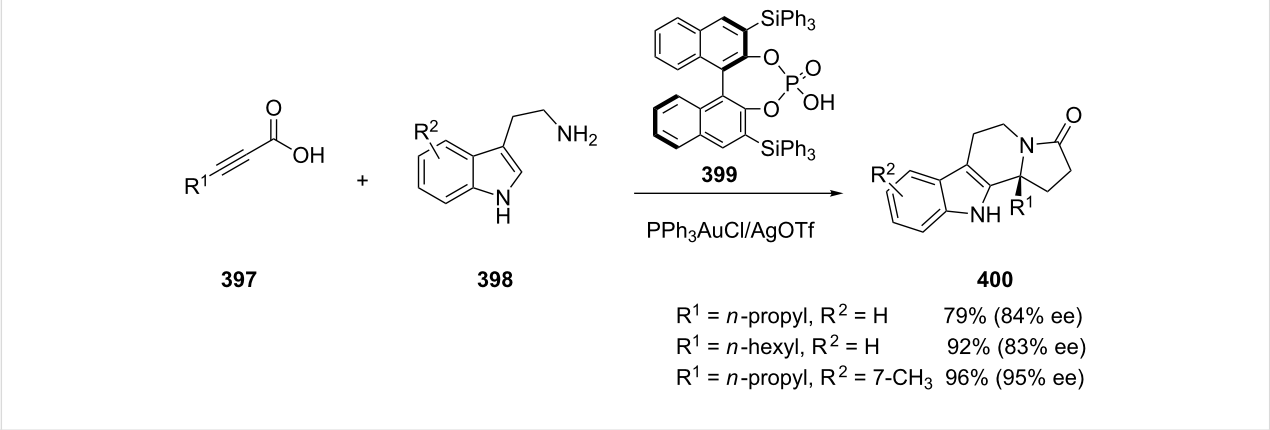
Julolidine derivatives **396** were obtained via a highly enantioselective three-component (**393**–**395**) cascade reaction which involved an enantioselective [4 + 2] cycloaddition reaction catalyzed by a chiral phosphoric acid and a subsequent catalytic intramolecular hydroamination by a gold(I) complex (Scheme 64) [180]. Further studies revealed that the Brønsted acid is both a chiral catalyst for the asymmetric cycloaddition and assists to facilitate the gold complex catalyzed hydroamination.

Muratore et al. have reported an interesting example of C–N bond formation for the construction of chiral nitrogen-containing fused heterocycles **400** [191]. In this case, different alkynoic acids **397** were treated with Ph_3PAuCl/AgOTf and tryptamines **398** in the presence of (*R*)-3,3'-bis(triphenylsilyl)BPA **399**. The multi-catalyst cascade products were isolated in good yields and with high ee values (Scheme 65).

BIPHEP is the most extensively used chiral atropisomeric biaryl diphosphine ligand in the gold catalytic enantioselective addi-

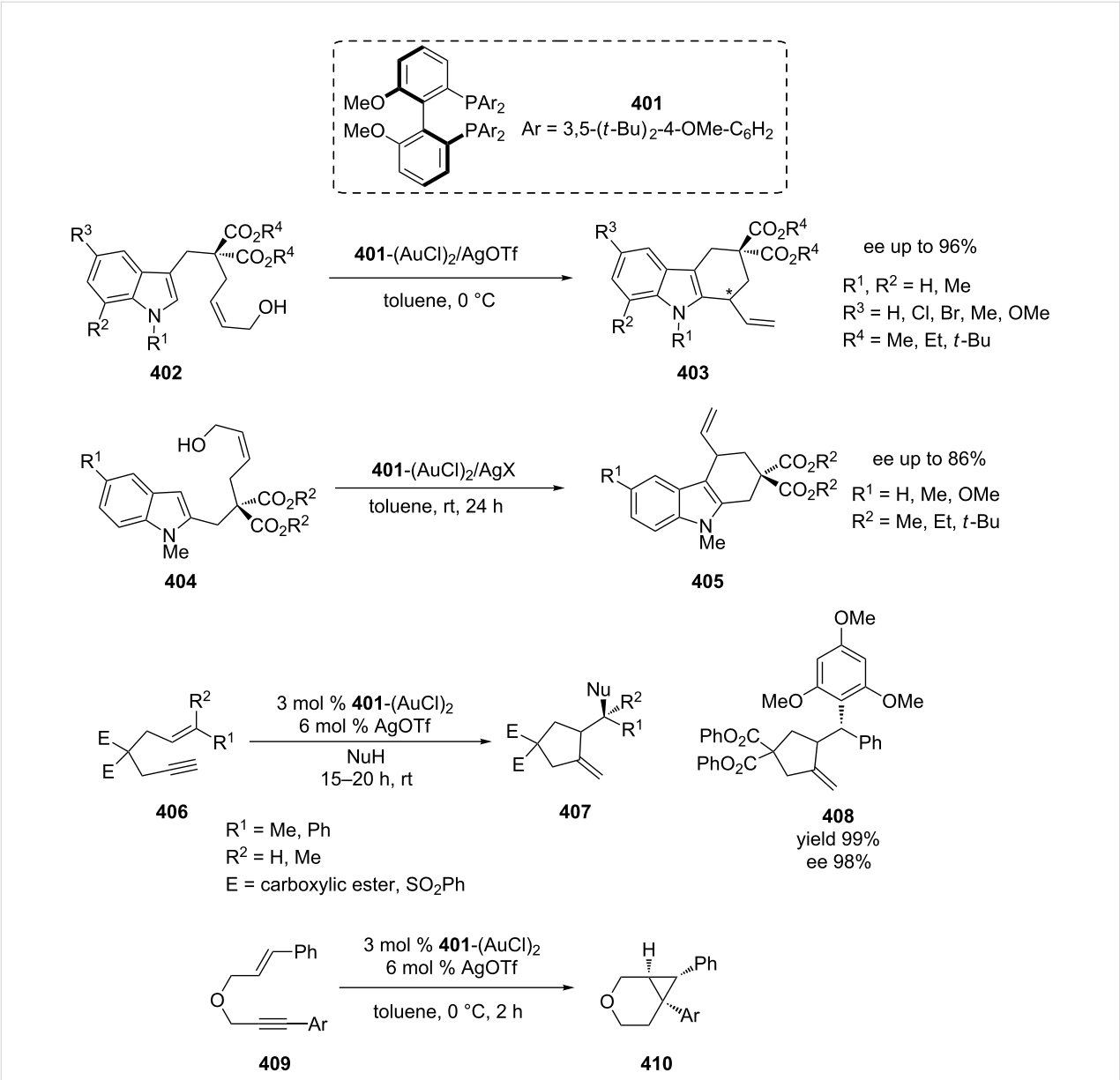


Scheme 64: Gold-catalyzed synthesis of julolidine derivatives.



Scheme 65: Gold-catalyzed the synthesis of chiral fused heterocycles.

tion. Although the gold catalysis has been well developed, the use of non-activated olefinic C–C double bonds is still largely unexplored due to the intrinsic inertness of C=C (with respect to allenes and alkynes) in taking part in nucleophilic addition reactions assisted by π-electrophilic activation [183]. The first example of a direct catalytic enantioselective Friedel–Crafts allylic alkylation reaction with alcohols was reported by Bandini's group [182]. In terms of stereo-induction, 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP **401** (Scheme 66) gave the best results. Their method exploits the unprecedented capability of chiral gold(I) catalysts to activate selectively prochiral π-activated alcohols **402** toward aromatic functionalization in a highly enantioselective manner. On the basis of the above results, the same group extended the substrate scope of the 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP–Au-catalyzed Friedel–Crafts-type alkylation to indolyl alcohols **404** bearing an unsaturated side chain at the C2 position of the indole [183]. 1,6-Enyne derivatives and their analogs are the most frequently used substrates for gold-catalyzed cycloisomerization. Chao et al. discovered that the combination of atropisomeric electron-rich and hindered chiral ligand 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP **401** with Au(I) and silver salts promoted the enantioselective hydroarylation/cyclization reaction of 1,6-enynes **406** under mild conditions [181]. Treatment of enynes with catalytic amount of 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP(AuCl)$_2$ and AgOTf in Et_2O at room temperature for 15–20 hours led to the desired arylated products with ee values up to 98%. A similar strategy was also applied by the same group in the asymmetric Au(I)-catalyzed synthesis of bicyclo[4.1.0]heptene derivatives **410** via a cycloisomerization process of 1,6-enynes **409** [184].

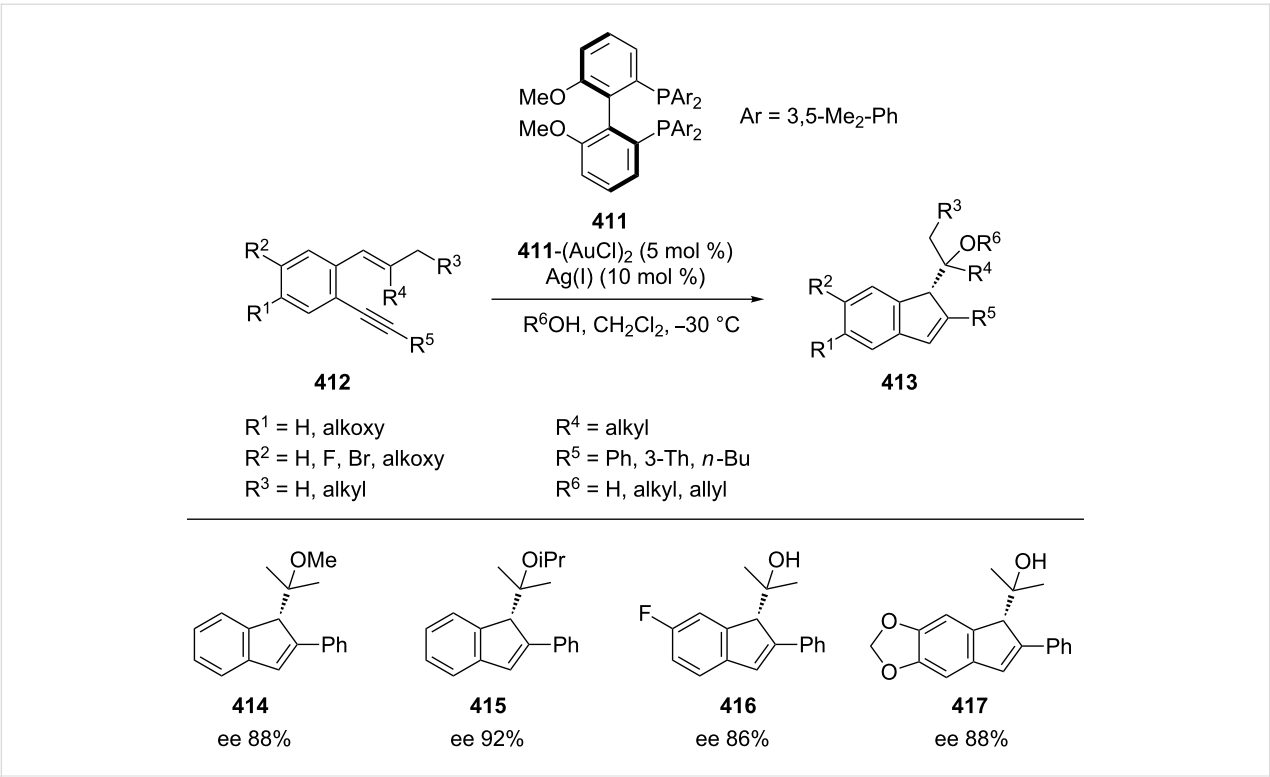


Scheme 66: Gold-catalyzed asymmetric reactions with 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP.

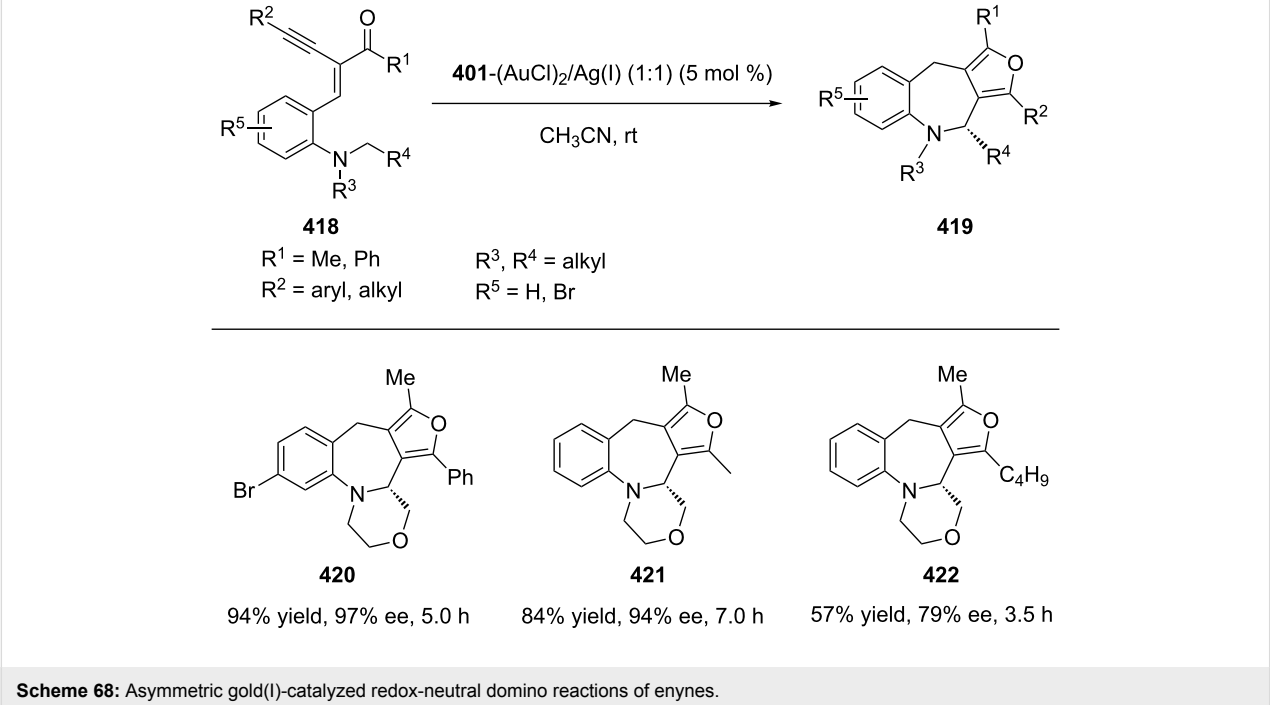
Employing the atropisomeric electron-rich ligand 3,5-xylyl-MeOBIPHEP **411** (Scheme 67), Sanz's group has developed an asymmetric gold-catalyzed cycloisomerization or alkoxycyclization of *o*-alkynylstyrenes **412** to prepare enantiomerically enriched functionalized 1*H*-indene derivatives **413** (including **414**–**417**) with high ee values (up to 92%) [190].

Due to the strength of sp^3 C–H bonds and because it can be difficult for the metal to reach sterically hindered C–H bonds, direct functionalization of sp^3 C–H bonds remained a challenge for a long time. Recently, however, Zhang's group have presented the first example of an enantioselective redox-neutral domino reaction catalyzed by gold(I) that results in the direct functionalization of unreactive sp^3 C–H bonds. Furan-fused azepine derivatives **419** (including **420**–**422**) have been obtained from enyne **418** with high enantioselectivities (Scheme 68) [185].

Toste's group developed the first example of a highly enantioselective polyene (**423**, **425**, **427**, **429**) cyclization reaction in which transition metal-promoted alkyne activation serves as the cyclization initiating event [186]. The reactions of the enyne with the monocationic gold(I) complexes and $AgSbF_6$ were carried out in the presence of sterically encumbered phosphines.



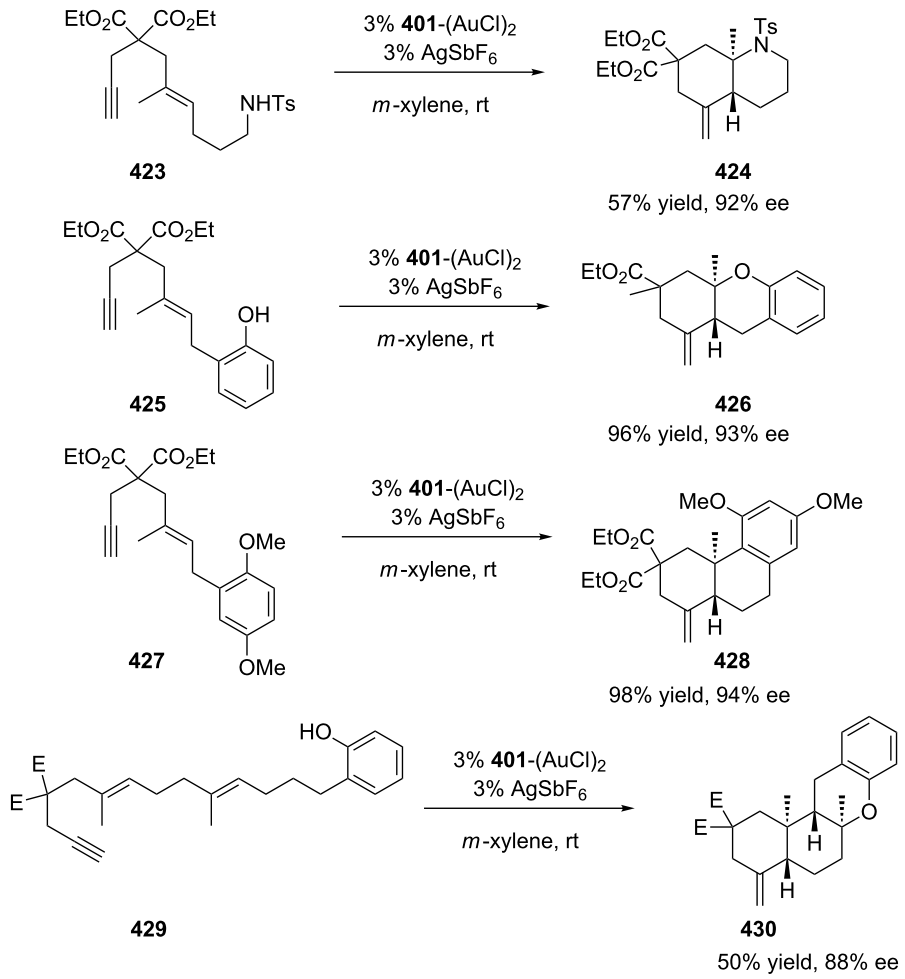
Scheme 67: Gold-catalyzed cyclization of *o*-(alkynyl) styrenes.



Scheme 68: Asymmetric gold(I)-catalyzed redox-neutral domino reactions of enynes.

The use of 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP **401** resulted in the formation of fused bicyclic compounds (**424**, **426**, **428**, **430**) with good ee values (Scheme 69).

The 3,5-(*t*-Bu)$_2$-4-MeO-MeOBIPHEP–Au complex was also employed in the carboalkoxylation reaction of propargyl esters **431** to afford benzopyrans **432** containing quaternary stereocen-

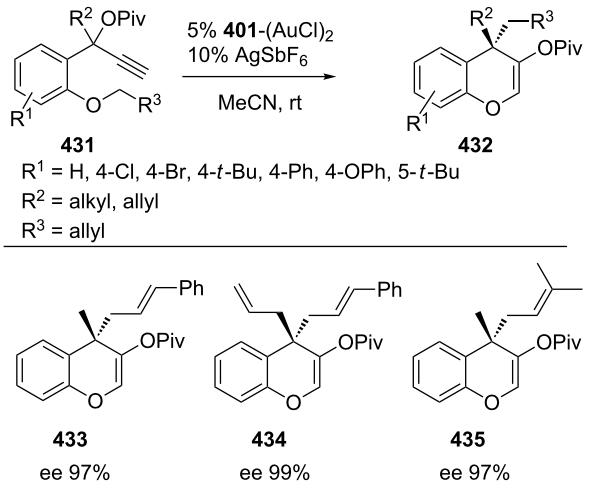


Scheme 69: Gold(I)-catalyzed enantioselective polyene cyclization reaction.

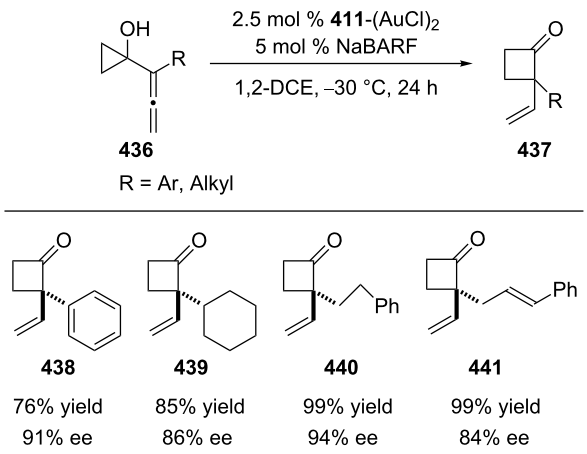
ters with excellent enantioselectivity (Scheme 70) [187]. Kleinbeck and Toste developed a gold(I)-catalyzed enantioselective ring expansion of allenylcyclopropanols **436** with the chiral ligand 3,5-xylyl-MeOBIPHEP **411** to obtain cyclobutanones **437** (including **438**–**441**) (Scheme 71) [188]. Notably, the amount of catalyst could be reduced without significant loss of enantioselectivity or yield.

Conclusion

In this account, we have presented a summary of the recent gold catalysis which involves the addition of X–H (X = O, N, C) bonds to C–C multiple bonds, tandem reactions, and asymmetric additions. The variety of reactions reflects that gold catalysis has become a very innovative synthetic tool in modern organic chemistry. What is particularly worth mentioning is that the design or choice of chiral ligands together with gold catalysts is the key to attaining high asymmetric induction. Up to now, only a small proportion of the chiral ligands have been



Scheme 70: Gold(I)-catalyzed enantioselective synthesis of benzopyrans.



Scheme 71: Gold(I)-catalyzed enantioselective ring expansion of allenylcyclopropanols.

successfully introduced to gold-catalyzed reactions. Consequently, the development of new and efficient chiral ligands or chiral gold complexes is still a major challenge for the future.

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Cationic gold(I) axially chiral biaryl bisphosphine complex-catalyzed atropselective synthesis of heterobiaryls

Tetsuro Shibuya, Kyosuke Nakamura and Ken Tanaka*

Full Research Paper

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Address:
Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

Email:
Ken Tanaka* - tanaka-k@cc.tuat.ac.jp

* Corresponding author

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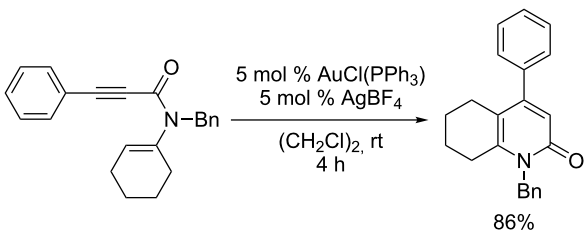
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Abstract

It has been established that a cationic gold(I)/(*R*)-DTBM-Segphos or (*R*)-BINAP complex catalyzes the atropselective intramolecular hydroarylation of alkynes leading to enantioenriched axially chiral 4-aryl-2-quinolinones and 4-arylcoumarins with up to 61% ee.

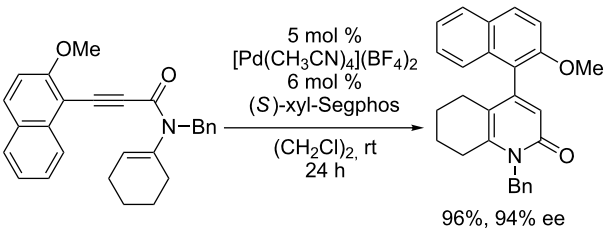
Introduction

Atropselective biaryl synthesis [1-4] has attracted significant interest due to its great utility in asymmetric catalysis and natural product synthesis. In 2004, three research groups, including ours, independently reported transition-metal catalyzed asymmetric [2 + 2 + 2] cycloaddition reactions to produce axially chiral biaryls [5-7]. These reports clearly demonstrated the utility of the asymmetric annulation strategy for the atropselective biaryl synthesis [8]. As an alternative asymmetric annulation method for the atropselective biaryl synthesis, we turned our attention to transition-metal catalyzed hydroalkenylation and hydroarylation reactions [9-15]. In this context, our research group developed the cationic gold(I)/PPh_3-complex catalyzed intramolecular hydroalkenylation of *N*-alkenyl-arylethynylamides leading to 4-aryl-2-pyridones (Scheme 1) [16,17].



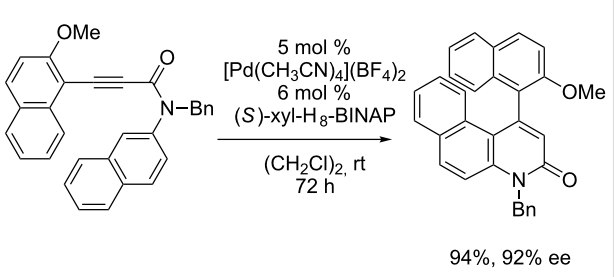
Scheme 1: Cationic gold(I)/PPh_3-complex catalyzed intramolecular hydroalkenylation of alkynes.

The atropselective synthesis of 6-aryl-2-pyridones has already been achieved by rhodium catalyzed [2 + 2 + 2] cycloaddition [18], while the atropselective synthesis of 4-aryl-2-pyridones has not yet been realized. The application of this intramolecular hydroalkenylation reaction to the atropselective synthesis of 4-aryl-2-pyridones from *N*-alkenyl-arylethynylamides was thus investigated. Although cationic gold(I)/axially chiral biaryl bisphosphine complexes [19-31] have been frequently employed in asymmetric variants of cationic gold(I) catalyses [32-38], including 6-*endo*-*dig* and 6-*exo*-*dig* cyclizations [39-41], the use of these gold(I) complexes gave almost racemic products [42]. Fortunately, cationic palladium(II)/axially chiral biaryl bisphosphine complexes were found to be effective catalysts, and a cationic palladium(II)/(*S*)-xyl-Segphos complex showed the highest enantioselectivity (Scheme 2) [42].



Scheme 2: Cationic palladium(II)/(*S*)-xyl-Segphos-complex catalyzed atropselective intramolecular hydroalkenylation of alkynes.

In addition, the cationic palladium(II)/axially chiral biaryl bisphosphine complexes were able to catalyze the asymmetric intramolecular hydroarylation of *N*-aryl-arylethynylamides leading to axially chiral 4-aryl-2-quinolinones, and the cationic palladium(II)/(*S*)-xyl-H_8-BINAP complex showed the highest enantioselectivity (Scheme 3) [43,44].



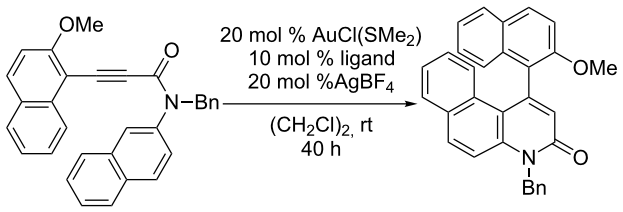
Scheme 3: Cationic palladium(II)/(*S*)-xyl-H_8-BINAP complex-catalyzed atropselective intramolecular hydroarylation of alkynes.

In this paper, we report the use of the cationic gold(I)/axially chiral biaryl bisphosphine complexes in the catalytic asymmetric intramolecular hydroarylation for the synthesis of axially chiral 4-aryl-2-quinolinones and 4-arylcoumarins.

Results and Discussion

The reaction of *N*-benzyl-*N*-(2-naphthyl)propiolamide **1a**, bearing a 2-methoxynaphthyl group at an alkyne terminus, was first investigated in the presence of a cationic gold(I)/(*R*)-BINAP complex (20 mol % Au). Although the reaction proceeded at room temperature in good yield, enantioselectivity was low (Table 1, entry 1). The effect of axially chiral biaryl bisphosphine ligands (Figure 1) on the yield and the enantioselectivity was then investigated. Among the

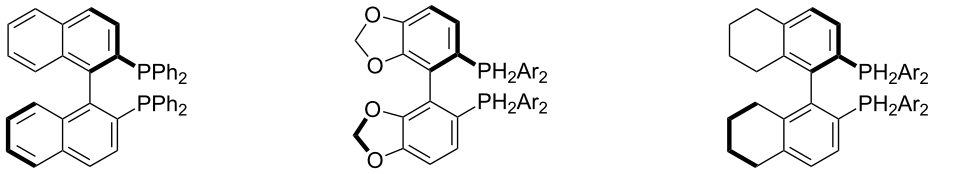
Table 1: Screening of axially chiral biaryl bisphosphine ligands for the cationic gold(I)-complex catalyzed atropselective intramolecular hydroarylation of **1a**.[a]



1a **2a**

Entry	Ligand	Convn (%)[b]	Yield (%)[c]	ee (%)
1	(*R*)-BINAP	81	75	7 (*S*)
2	(*R*)-Segphos	90	81	8 (*R*)
3	(*R*)-H_8-BINAP	94	93	17 (*S*)
4	(*S*)-xyl-H_8-BINAP	100	96	13 (*R*)
5	(*R*)-DTBM-Segphos	100	96	59 (*R*)
6[d]	(*R*)-DTBM-Segphos	71	49	31 (*R*)

[a]$AuCl(SMe_2)$ (0.010 mmol, 20 mol %), $AgBF_4$ (0.010 mmol, 20 mol %), ligand (0.0050 mmol, 10 mol %), **1a** (0.050 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used. [b]Determined by ^1H NMR. [c]Isolated yield. [d]$AuCl(SMe_2)$ (0.010 mmol, 10 mol %), $AgBF_4$ (0.010 mmol, 10 mol %), ligand (0.0050 mmol, 5 mol %), **1a** (0.10 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used. Reaction time: 72 h.



(*R*)-BINAP

(*R*)-Segphos (Ar = Ph)
(*R*)-DTBM-Segphos
(Ar = 4-MeO-3,5-*t*-Bu$_2$C$_6$H$_2$)

(*R*)-H$_8$-BINAP (Ar = Ph)
(*R*)-xyl-H$_8$-BINAP
(Ar = 3,5-Me$_2$C$_6$H$_3$)

Figure 1: Structures of axially chiral biaryl bisphosphine ligands.

bis(diphenylphosphine) ligands examined (Table 1, entries 1–3), the use of (*R*)-H$_8$-BINAP furnished **2a** with the highest enantiomeric excess (Table 1, entry 3). An increase in the steric bulk of the aryl group on the phosphorus atom of H$_8$-BINAP lead to a decrease in the ee (Table 1, entry 4). The use of sterically more demanding (*R*)-DTBM-Segphos as a ligand furnished **2a** in high yield with the highest ee (Table 1, entry 5). Unfortunately, a reduction in the amount of gold to 10 mol % significantly decreased both product yield and enantioselectivity (Table 1, entry 6).

Thus, the scope of the cationic gold(I)-complex catalyzed atropselective intramolecular hydroarylation of alkynes was explored at room temperature, as shown in Table 2. The 2-methoxynaphthalene derivative **1a** (Table 2, entry 1) and the 2-methoxymethoxynaphthalene derivative **1b** (Table 2, entry 2) furnished the desired benzoquinolinones **2a** and **2b**, respectively, in high yields and high ee, using (*R*)-DTBM-Segphos as a ligand. In addition, benzocoumarin **2c** (Table 2, entry 3) was obtained in moderate ee, although the yield was low due to partial deprotection of the methoxymethoxynaphthalene moiety (Table 2, entry 3). The reactions of carbazole and dialkoxybenzene derivatives **1d**–**g**, using (*R*)-DTBM-Segphos as a ligand, furnished the corresponding quinolinone and coumarin derivatives **2d**–**g** in high yields with perfect regioselectivity, while the observed ee values were very low (<10% ee). However, interestingly, the use of (*R*)-BINAP as a ligand improved the enantoselectivity (14–32% ee, Table 2, entries 4–7).

Table 2: Cationic gold(I)-complex catalyzed atropselective intramolecular hydroarylation of **1a**–**g** leading to heterobiaryls **2a**–**g**.[a]

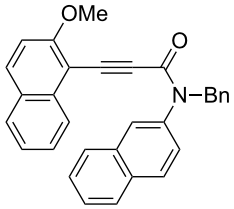
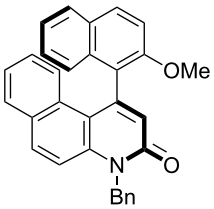
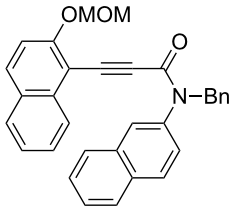
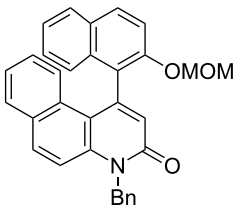
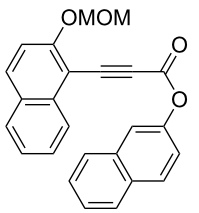
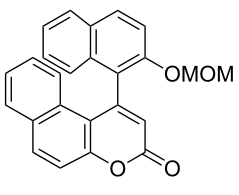
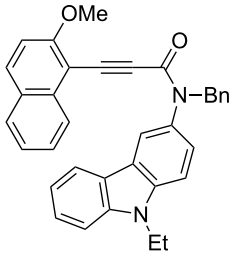
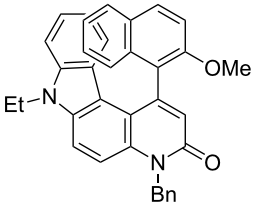
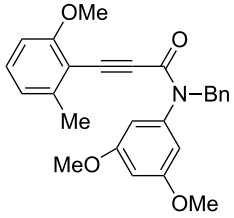
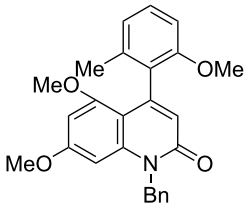
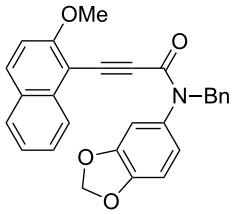
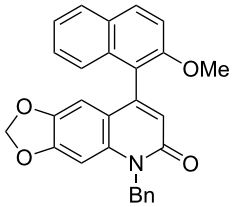
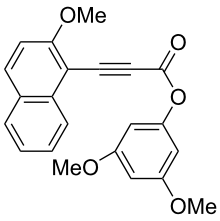
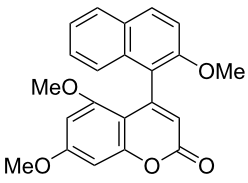
Entry	**1**	Ligand (time)	**2**	% yield[b] (% ee)
1	 **1a**	(*R*)-DTBM-Segphos (40 h)	 (*R*)-(−)-**2a**	96 (59)
2	 **1b**	(*R*)-DTBM-Segphos (72 h)	 (−)-**2b**	87 (61)
3	 **1c**	(*R*)-DTBM-Segphos (40 h)	 (−)-**2c**	33 (49)

Table 2: Cationic gold(I)-complex catalyzed atropselective intramolecular hydroarylation of **1a**–**g** leading to heterobiaryls **2a**–**g**.[a] (continued)

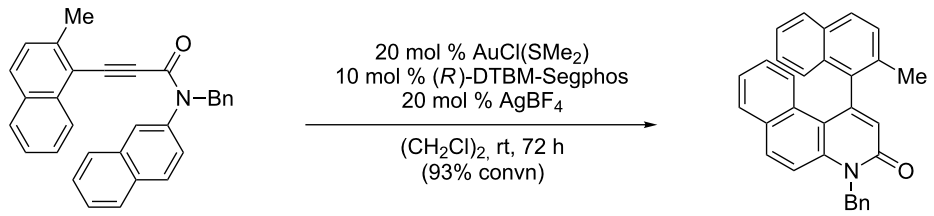
4		**1d**	(*R*)-BINAP (72 h)		(+)-**2d**	82 (28)
5		**1e**	(*R*)-BINAP (40 h)		(−)-**2e**	100 (32)
6		**1f**	(*R*)-BINAP (40 h)		(+)-**2f**	88 (27)
7		**1g**	(*R*)-BINAP (40 h)		(+)-**2g**	93 (14)

[a]Reactions were conducted using $AuCl(SMe_2)$ (0.010 mmol), $AgBF_4$ (0.010 mmol), (*R*)-DTBM-Segphos or (*R*)-BINAP (0.0050 mmol), **1a**–**g** (0.050 mmol), and $(CH_2Cl)_2$ (1.5 mL) at rt. In all entries, 100% convn of substrates **1a**–**g** was observed.
[b]Isolated yield.

In the previously reported cationic palladium(II)/(*S*)-xyl-H_8-BINAP-complex catalyzed atropselective intramolecular hydroarylation of alkynes, the presence of the 2-methoxy-substituted aryl group at the alkyne terminus was important for the realization of both high reactivity and enantioselectivity [40]. Similarly, the reaction of 2-methylnaphthalene derivative **1h** in the presence of the cationic gold(I)/(*R*)-DTBM-Segphos complex furnished the corresponding benzoquinolinone **2h** with lower yield and ee than those of **2a** (Scheme 4).

Conclusion

In conclusion, it has been established that a cationic gold(I)/(*R*)-DTBM-Segphos or (*R*)-BINAP complex catalyzes the atropselective intramolecular hydroarylation of alkynes leading to



Scheme 4: Cationic gold(I)/(*R*)-DTBM-Segphos-complex catalyzed atropselective intramolecular hydroarylation of 2-methylnaphthalene derivative **1h**.

enantioenriched axially chiral 4-aryl-2-quinolinones and 4-aryl-coumarins in up to 61% ee. Although there clearly remains room for improvement in enantioselectivity, the present asymmetric catalysis is a rare example of the utilization of gold(I)/chiral phosphine catalysts for the construction of noncentrochirality [45-47].

Experimental

General: ^{1}H NMR spectra were recorded at 300 MHz (JEOL AL 300). ^{13}C NMR spectra were obtained with complete proton decoupling at 75 MHz (JEOL AL 300). HRMS data were obtained on a Bruker micrOTOF Focus II. Infrared spectra were obtained on a JASCO FT/IR-4100. Optical rotations were obtained on a JASCO DIP-1000. Melting points were obtained on a METTLER MP50. Anhydrous $(CH_2Cl)_2$ (No. 28,450-5) was purchased from Aldrich and used as received. Solvents for the synthesis of substrates were dried over molecular sieves (4 Å, Wako) prior to use. Substrates **1a**, **1b**, **1d**, **1e**, **1f**, and **1h** were prepared according to the literature [43]. Products **2a**, **2b**, **2d**, **2e**, **2f**, and **2h** were already reported [43]. All other reagents were obtained from commercial sources and used as received. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring.

(2-Methoxymethoxynaphthalen-1-yl)propynoic acid naphthalen-2-yl ester (1c): To a stirred solution of 3-[2-(methoxymethoxy)-1-naphthalenyl]-2-propynoic acid [48] (0.256 g, 1.00 mmol), 2-naphthol (0.159 g, 1.10 mmol), and 4-dimethylaminopyridine (12.2 mg, 0.100 mmol) in CH_2Cl_2 (10 mL) was added a solution of dicyclohexylcarbodiimide (0.248 g, 1.20 mmol) in CH_2Cl_2 (3 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h and at room temperature for 18 h. The crude mixture was filtered with CH_2Cl_2. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by a silica gel column chromatography (hexane/EtOAc = 10:1) to give **1c** (0.222 g, 0.580 mmol, 58% yield). Yellow solid; mp 97.3–99.3 °C; IR (KBr): 2203, 1717, 1229, 1149, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15–8.01 (m, 1H), 7.97–7.70 (m, 6H), 7.61–7.31 (m, 6H), 5.36 (s, 2H), 3.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.0, 152.8, 148.1, 134.7, 133.7, 133.4, 131.7, 129.7, 128.8, 128.3, 127.82, 127.79, 126.7, 126.0, 125.1, 124.8, 121.0, 118.8, 115.5, 103.8, 95.1, 89.1, 85.2, 56.6; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{18}O_4Na$, 405.1097; found, 405.1107.

(2-Methoxynaphthalen-1-yl)propynoic acid 3,5-dimethoxyphenyl ester (1g): The title compound was prepared from (2-methoxynaphthalen-1-yl)propynoic acid [49] and 3,5-dimethoxyphenol in 70% yield by the procedure used for **1c**. Yellow solid; mp 102.9–104.7 °C; IR (KBr): 2211, 1714, 1621, 1269, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 6.5 Hz, 1H), 7.42 (dd, *J* = 8.4, 6.5 Hz, 1H), 7.26 (d, *J* = 9.2 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 1H), 4.06 (s, 3H), 3.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 161.1, 152.5, 151.8, 135.0, 133.6, 128.4, 128.3, 128.1, 124.7, 112.1, 101.8, 100.2, 98.7, 89.3, 85.0, 56.5, 55.5; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{22}H_{18}O_5Na$, 385.1046; found, 385.1047.

General procedure for cationic gold(I)/axially chiral biaryl bisphosphine complex-catalyzed atropselective intramolecular hydroarylation of *N*-aryl-arylethynylamides 1: To $AuCl(SMe_2)$ (0.010 mmol) was added a solution of axially chiral biaryl bisphosphine ligand (0.0050 mmol) in $(CH_2Cl)_2$ (0.5 mL), and the mixture was stirred at room temperature for 1 h. To this solution was added $AgBF_4$ (0.010 mmol) in $(CH_2Cl)_2$ (0.5 mL) at room temperature, and the mixture was stirred at room temperature for 0.5 h. To this mixture was added a solution of **1** (0.050 mmol) in $(CH_2Cl)_2$ (0.5 mL) at room temperature. After stirring at room temperature for 40–72 h, the mixture was directly purified on a preparative TLC to afford **2**.

(−)-1-(2-Methoxymethoxynaphthalen-1-yl)benzo[*f*]chromen-3-one [(−)-2c]: Colorless solid; mp 169.4–170.8 °C; $[\alpha]^{25}_D$ −86.1 (*c* 0.28, $CHCl_3$, 49% ee); IR (KBr): 1738, 1510, 1244, 1050, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 9.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.36 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.32 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.97 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 6.45 (s, 1H), 5.04 (dd, *J* = 22.4, 6.9 Hz, 2H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.6, 154.8, 152.5, 150.6, 133.8, 131.6, 131.0, 130.9, 129.8, 129.5, 129.0, 128.2, 127.7, 127.6, 125.4, 124.8, 124.4, 123.8, 122.8, 118.6, 117.8, 115.7, 114.2, 94.2, 56.0; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{18}O_4Na$, 405.1097; found, 405.1085; CHIRALPAK OD-H, hexane/iPrOH = 80:20, 1.0 mL/min, retention times: 14.3 min (major isomer) and 19.0 min (minor isomer).

(+)-5,7-Dimethoxy-4-(2-methoxynaphthalen-1-yl)chromen-2-one [(+)-2g]: Colorless solid; mp 148.8–150.4 °C; $[\alpha]^{25}_D$ +44.9 (*c* 0.24, $CHCl_3$, 14% ee); IR (KBr): 1718, 1618, 1598, 1351, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J* = 9.0 Hz, 1H), 7.85–7.77 (m, 1H), 7.48–7.39 (m, 1H), 7.38–7.27 (m, 3H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.12 (d, *J* = 2.4 Hz, 1H), 6.07 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H) 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.1, 161.2, 158.5, 157.1, 152.4, 151.0, 131.9, 129.3, 128.5, 127.9, 126.6, 124.2, 123.6, 122.9, 114.0, 113.1, 105.0, 95.8, 93.6, 56.7, 55.75, 55.71; HRMS–ESI (*m*/*z*):

$[M + Na]^+$ calcd for $C_{22}H_{18}O_5Na$, 385.1046; found, 385.1036; CHIRALPAK AD-H, hexane/iPrOH = 80:20, 1.0 mL/min, retention times: 8.8 min (minor isomer) and 10.5 min (major isomer).

Supporting Information

Supporting Information File 1

^1H and ^{13}C NMR spectra for new compounds **1c**, **1g**, **2c**, and **2g**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-105-S1.pdf]

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Intramolecular hydroamination of alkynic sulfonamides catalyzed by a gold–triethynylphosphine complex: Construction of azepine frameworks by 7-*exo*-*dig* cyclization

Hideto Ito, Tomoya Harada, Hirohisa Ohmiya and Masaya Sawamura*

Full Research Paper

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Address:
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

Email:
Masaya Sawamura* - sawamura@sci.hokudai.ac.jp

* Corresponding author

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Abstract

The gold-catalyzed, seven-membered ring forming, intramolecular hydroamination of alkynic sulfonamides has been investigated. The protocol, with a semihollow-shaped triethynylphosphine as a ligand for gold, allowed the synthesis of a variety of azepine derivatives, which are difficult to access by other methods. Both alkynic sulfoamides with a flexible linear chain and the benzene-fused substrates underwent 7-*exo*-*dig* cyclization to afford the nitrogen-containing heterocyclic seven-membered rings, such as tetrahydroazepine and dihydrobenzazepine, in good yields.

Introduction

Nitrogen-containing heterocyclic seven-membered rings are found in many biologically active natural products and pharmaceuticals, such as (−)-tuberosutemonin (**1**) [1-6], related *Stemona* alkaloids [7], *Cephalotaxus* alkaloid (−)-cephalotaxine (**2**) [8-12], and SB-462795 (**3**) (Figure 1) [13-16]. Among a number of different approaches for the construction of N-heterocyclic compounds, metal-catalyzed intramolecular hydroamination of unactivated C–C multiple bonds is particularly straightforward and efficient [17,18]. Specifically, gold-catalyzed intramolecular hydroaminations of alkynes, alkenes and allenes show remarkable efficiency [19-28]. Unfortunately, however, the application of these methodologies to the synthesis of the N-heterocyclic seven-membered ring compounds is hampered by the low efficiency of seven-membered ring formations. Despite extensive studies on the gold-catalyzed intramolecular hydroamination of alkynes [19-51], seven-membered

ring formation is rare and is limited to the cases where the substrate is preorganized for cyclization: The substrates must have geminal disubstitution or ring fusion within a linker chain connecting the attacking nitrogen atom and the alkyne moiety. It should be noted, however, that 7-"*endo*"-*dig* cyclizations of (*o*-alkynyl)phenylacetamides and a diynamide were achieved with gold and palladium complexes [39,46,52,53], and the zinc-catalyzed 7-*exo*-*dig* cyclization was reported specifically for a propargyl ether substrate [54].

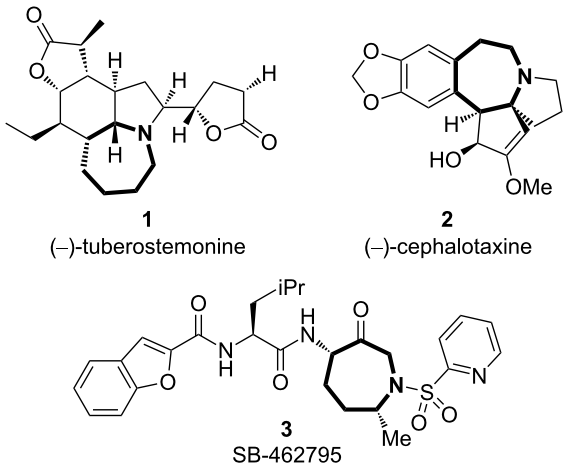


Figure 1: Azepine frameworks found in natural products and pharmaceuticals.

Previously, we reported that semihollow-shaped triethylnylphosphine **L1** (Figure 2) exerted marked acceleration effects in the gold(I)-catalyzed Conia-ene reactions of acetylenic keto esters and enyne cycloisomerizations. The new catalytic system has expanded the scope of the reactions to six- and seven-membered ring formations, which had been difficult with the conventional catalytic systems [55]. Furthermore, we found that **L1**–gold(I) complex efficiently catalyzed the cyclization of internal alkyne substrates, which had also been difficult due to the steric repulsion between a nucleophilic center and a terminal substituent on the alkyne moiety [56]. We proposed that the cavity in the ligand forces the nucleophilic center closer to the gold-bound alkyne, resulting in the entropy-based rate enhancement. Recently, we further developed the gold(I)-catalyzed 7-*exo*-*dig* cyclization of acetylenic silyl enol ethers with **L1** [57].

In this context, we expected that the use of **L1** as a ligand in the gold-catalyzed intramolecular hydroamination of alkynes would enable the construction of nitrogen-containing heterocyclic seven-membered rings, and we applied the triethynylphosphine–gold(I) catalytic systems to the synthesis of azepine derivatives through intramolecular hydroamination of alkynic

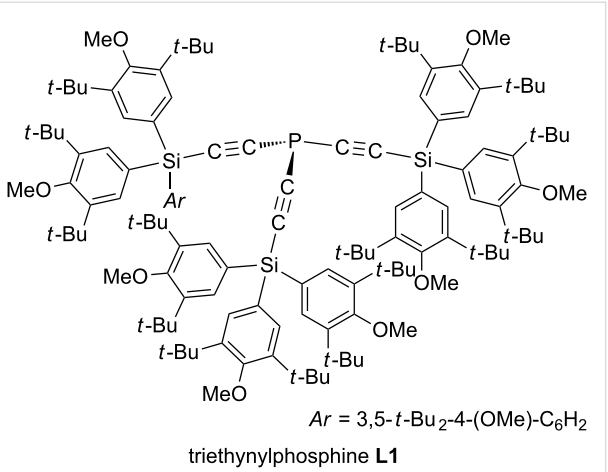


Figure 2: Semihollow-shaped triethynylphosphine **L1**.

sulfonamides. This article describes the results of the optimization of reaction conditions, exploration of substrate scope, and some mechanistic experiments.

Results and Discussion

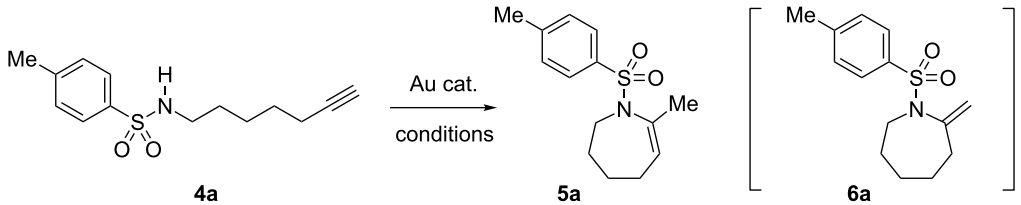
Reaction conditions

The reaction conditions were optimized for the cyclization of *N*-(6-heptyn-1-yl)-*p*-toluenesulfonamide (**4a**) (Table 1). The triethynylphosphine–gold complex [Au(NTf_2)(**L1**)] (0.5 mol %) catalyzed the cyclization of **4a** (0.2 mmol) efficiently in CH_2Cl_2 (1.0 mL) at 25 °C (100% convn. of **4a**) to afford 4,5,6,7-tetrahydroazepine derivative **5a** with 18 h reaction time in 82% isolated yield (Table 1, entry 1). This reaction seemed to proceed through 7-*exo*-*dig* cyclization, but an exomethylene-type cyclic product **6a**, which is a possible product of the 7-*exo*-*dig* cyclization [57], was not observed. The reaction under four-times-diluted conditions did not proceed to full conversion in the same reaction time (Table 1, entry 2). The reaction time was shortened to 9 h by heating at 80 °C, but this caused a slight decrease in the isolated yield of **5a** (79%) (Table 1, entry 3).

Among other solvents examined, toluene gave a result comparable with CH_2Cl_2 (Table 1, entries 1 and 4). On the other hand, polar and potentially coordinating solvents such as THF and MeCN were not effective in this reaction (Table 1, entries 5 and 6). The effect of the counter anion of the cationic gold complex is shown in Table 1, entries 1 and 7–9. While OTf^- was as effective as NTf_2^- (Table 1, entry 7), SbF_6^- and BF_4^- inhibited the reaction completely (Table 1, entries 8 and 9).

The ligand effect is evaluated in Table 1, entries 1 and 10–14. The reaction proceeded slowly, even with a conventional phosphine ligand PPh_3, such that the starting material was not fully consumed even after 24 h and the yield was as low as 26% (Ta-

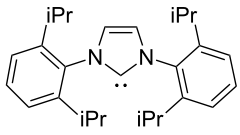
Table 1: Optimization of reaction conditions for the gold-catalyzed intramolecular hydroamination of **4a**.



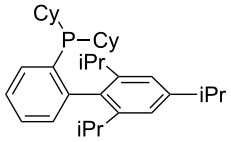
4a
0.2 mmol

5a

6a



IPr



X-Phos

entry	Au cat. (mol %)	solvent (mL)	temp. (°C)	time (h)	convn. (%)[a]	yield orf **5** (%)[a,b]
1	[Au(NTf$_2$)(**L1**)] (0.5)	CH_2Cl_2 (1.0)	25	18	100	90 (82)
2	[Au(NTf$_2$)(**L1**)] (0.5)	CH_2Cl_2 (4.0)	25	18	87	85
3	[Au(NTf$_2$)(**L1**)] (0.5)	DCE (1.0)	80	9	100	83 (79)
4	[Au(NTf$_2$)(**L1**)] (0.5)	toluene (1.0)	25	18	98	97
5	[Au(NTf$_2$)(**L1**)] (0.5)	THF (1.0)	25	18	29	24
6	[Au(NTf$_2$)(**L1**)] (0.5)	MeCN (1.0)	25	18	0	n. d.
7	[Au(OTf)(**L1**)] (0.5)	CH_2Cl_2 (1.0)	25	18	100	90 (80)
8	[Au(SbF_6)(**L1**)] (0.5)	CH_2Cl_2 (1.0)	25	18	14	n. d.
9	[Au(BF_4)(**L1**)] (0.5)	CH_2Cl_2 (1.0)	25	18	7	n. d.
10	[Au(NTf$_2$)(PPh_3)] (0.5)	CH_2Cl_2 (1.0)	25	24	29	22 (26)
11	[Au(NTf$_2$)(PPh_3)] (5.0)	CH_2Cl_2 (1.0)	25	18	100	66 (64)
12	[Au(NTf$_2$){P($OPh)_3$}] (0.5)	CH_2Cl_2 (1.0)	25	18	54	39
13	[Au(NTf$_2$)(X-Phos)] (0.5)	CH_2Cl_2 (1.0)	25	18	41	41
14	[Au(NTf$_2$)(IPr)] (0.5)	CH_2Cl_2 (1.0)	25	18	53	41

[a]Determined by ^{1}H NMR. [b]Isolated yield in parentheses.

ble 1, entry 10). Increasing the catalyst loading of [Au(NTf$_2$)(PPh_3)] to 5.0 mol % caused full consumption of **4a**, but the cyclization product was obtained only in 64% yield (Table 1, entry 11). The low yield relative to the conversion value is probably due to oligomerization and/or product decomposition as suggested by TLC and ^{1}H NMR analysis of the crude mixture. A phosphite ligand P($OPh)_3$, which is comparable to triethynylphosphine **L1** in electron-donor ability [58], was slightly more effective than PPh_3, but was far less effective than **L1** (Table 1, entry 12). Bulky and strongly electron-donating ligands such as X-Phos and IPr were as effective as the electron-deficient ligand P($OPh)_3$ (Table 1, entries 13 and 14). Accordingly, it is concluded that the acceleration effect by **L1** is not due to an electronic effect rather a steric effect.

The time–conversion profiles shown in Figure 3 clearly indicate that the high catalytic efficiency with **L1** is due to the improvement of the reaction kinetics and not the thermal stability of the catalyst. Although it was reported that Au(NTf$_2$)(IPr) was somewhat unstable in the gold-catalyzed intermolecular hydroamination of alkyne under heating conditions [59], the deactivation of the gold catalyst with IPr and X-Phos was not significant under the present reaction conditions: The reactions with X-Phos and IPr ligands reached 100% and 84% conversions after 58 h, respectively (see Supporting Information File 1 for reaction profiles with longer reaction times).

Effect of N-substituents

While alkynic *o*-nitrotoluenesulfonamide **4b** did not react at all with 0.5 mol % of [Au(NTf$_2$)(**L1**)] at room temperature (Table 2, entry 1), this substrate underwent 7-*exo*-*dig* cyclization upon increasing catalyst loading to 2.5 mol % and heating at 80 °C, giving *N*-nosylazepine derivative **5b** in 76% isolated

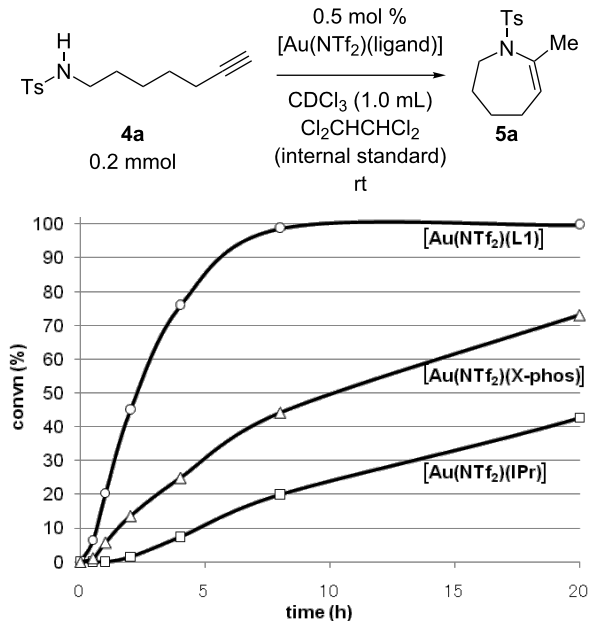


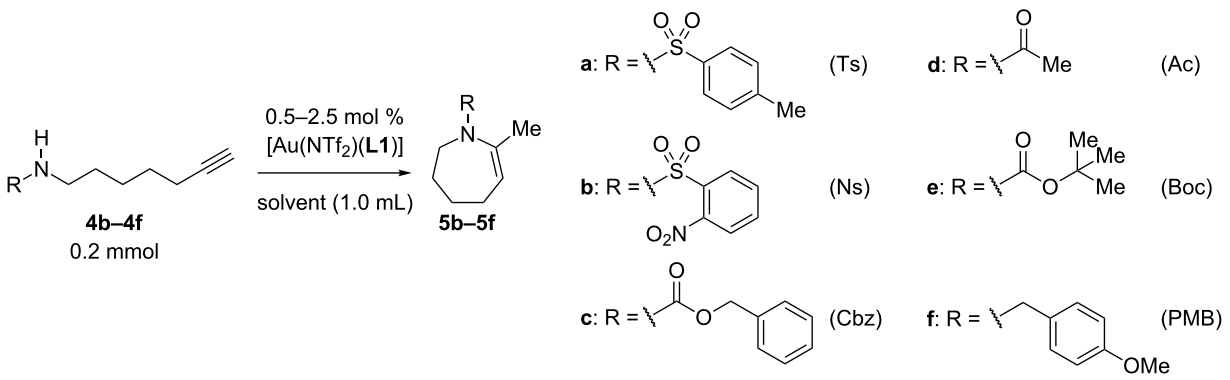
Figure 3: Time–conversion profiles for the gold-catalyzed cyclization of **4a** with **L1**, X-Phos and IPr ligands.

yield (Table 2, entry 2). *N*-Benzyloxycarbonyl (Cbz) and *N*-acetylazepine derivatives **5c** and **5d** were obtained in low yields through the cyclization of substrates **4c** and **4d** (Table 2, entries 3 and 4). On the other hand, the reactions of the substrates bearing *N*-*tert*-butoxycarbonyl (Boc) or *N*-*p*-methoxybenzyl (PMB) groups (**4e**,**f**) did not give the desired products at all (Table 2, entries 5 and 6). It seems that the reactivity of the substrates is affected by the balance between nucleophilicity of the nitrogen atom and acidity of the N–H bond as well as a steric factor.

Effect of substituents in acyclic linkers

Next, we explored the substrate scope by introducing one or two substituents in the acyclic linker chain of the alkynic *N*-tosylsulfonamide **4a** (Table 3). The introduction of the substituents at the α or β positions relative to the alkyne moiety caused a significant decrease in the reactivity, but the cyclization of the substituted alkynic sulfonamide **4g**–**l** proceeded smoothly, with 2.5–5.0 mol % catalyst loading at 80 °C, into full substrate conversion. Specifically, the substrate bearing an α-Me group (**4g**) derived from L-alanine was quantitatively converted into 2,7-dimethyltetrahydroazepine **5g** with 2.5 mol % of [Au(NTf$_2$)(**L1**)] (99% isolated yield, Table 3, entry 1). Although the substitution with bulkier iPr or Bn

Table 2: Effect of N-substitutents.



entry	R	Au cat. (mol %)	solvent	temp. (°C)	time (h)	convn. (%)[a]	yield of **5** (%)[a]
1	Ns (**4b**)	0.5	CH_2Cl_2	25	18	0	n. d.
2	Ns (**4b**)	2.5	DCE	80	18	100	76[b]
3	Cbz (**4c**)	2.5	DCE	80	24	97	33
4	Ac (**4d**)	2.5	DCE	80	24	63	18
5	Boc (**4e**)	2.5	DCE	80	24	17	n. d.
6	PMB (**4f**)	2.5	DCE	80	24	0	n. d.

[a]Determined by ^{1}H NMR. [b]Isolated yield.

groups at the α-position in **4h** and **4i** resulted in even lower reactivities, the corresponding cyclization products **5h** and **5i** were obtained in high or good yields (Table 3, entries 2 and 3). The substrates (**4j**–**l**) with geminal disubstitution at the β-carbon also participated in the 7-*exo*-*dig* cyclization in good yields (Table 3, entries 4–6). Among the cyclization products (**5a**–**l**) described above, only the β,β-diphenyl-substituted sulfonamide **5k** was contaminated with a small amount of exomethylene product **6k** (Table 3, entry 5).

It should be noted that the geminal disubstitution in **4j**–**l** caused a drastic decrease in the ease of the cyclization, which necessitated much more harsh reaction conditions (5 mol % Au, 80 °C, 4–12 h, Table 3, entries 4–6) than those for the reaction of the parent substrate **4a** (0.5 mol % Au, 25 °C, 18 h, Table 1, entry 1). This means that the Thorpe–Ingold effect did not operate in the present case and that the substituents caused steric repulsion hindering the cyclization.

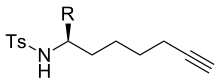
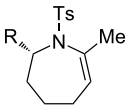
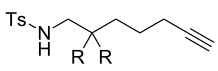
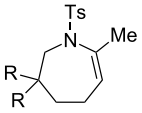
Construction of bicyclic frameworks

Next, we applied the gold(I)–triethynylphosphine **L1** complex to the construction of bicyclic frameworks such as benzazepine (Table 4). The cyclization of *o*-alkynyl benzylsulfonamide **4m** proceeded with both [Au(NTf$_2$)(**L1**)] and [Au(NTf$_2$)(IPr)] to give a benzazepine derivative **5m** (Table 4, entries 1 and 2). Although the starting material was fully consumed after 3 h or 6 h, using the respective catalysts, **L1** was superior to IPr with respect to both reaction time and product yield. The reaction of *N*-tosylbenzamide **4n** with **L1** afforded the benzene-fused ε-caprolactam **6n** within an exomethylene structure in 97% yield in an isomerically pure form (vide infra for discussion) (Table 4, entry 3). Sulfonamide **4o**, with a cyclohexane-fused linker, also participated in the cyclization to form azabicylo[5.4.0]decene **5o** in 76% yield along with a small amount of exomethylene isomer **6o** (**5o**/**6o** 98:2, Table 4, entry 4).

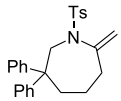
Effect of ring sizes

We also evaluated the triethynylphosphine **L1**, X-Phos, and IPr for an acceleration effect in the six-membered, ring forming, gold-catalyzed hydroamination of *N*-(5-hexyn-1-yl)-*p*-toluenesulfonamide **7**. As expected from entropy considerations, the six-membered ring formations of **7** with these ligands were generally much faster than the seven-membered ring formations of **4**: The reaction with 0.5 mol % catalyst loading at room temperature completed within 1 h irrespective of the ligand used. When the catalyst loading was reduced to 0.1 mol %, however, the superiority of **L1** to X-Phos and IPr became significant, as shown in Table 5. The reaction with **L1** at room temperature afforded the six-membered ring product **8** in 91%

Table 3: Cyclization of alkynic sulfonamides with an acyclic linker.[a]

entry	substrate	Au cat. (mol %)	time (h)	convn. (%)[b]	product	yield (%)[c]
						
1	R = Me (**4g**)	2.5	8	100	R = Me (**5g**)	99
2	R = iPr (**4h**)	5.0	12	100	R = iPr (**5h**)	88
3	R = Bn (**4i**)	5.0	12	100	R = Bn (**5i**)	71
						
4	R = Me (**4j**)	5.0	4	100	R = Me (**5j**)	77
5	R = Ph (**4k**)	5.0	4	100	R = Ph (**5k**)	69[d]
6	R = –(CH$_2$)$_5$– (**4l**)	5.0	12	100	R = –(CH$_2$)$_5$– (**5l**)	66

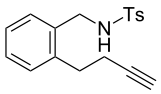
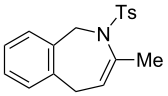
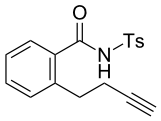
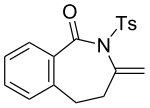
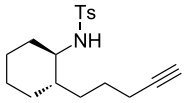
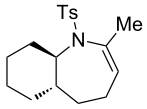
[a]Reaction conditions: **4**, 0.1 mmol; [Au(NTf$_2$)(**L1**)], 2.5 or 5 mol %; DCE, 1.0 mL; 80 °C.
[b]Determined by ^{1}H NMR.
[c]Isolated yield.



6k

[d]Mixture of **5k** and **6k** in 92:8 ratio.

Table 4: Cyclization of alkynic sulfonamide with a ring-fused linker.[a]

entry	substrate	Au cat. (mol %)	time (h)	convn. (%)[b]	product	yield (%)[c]
1	 **4m**	[Au(NTf$_2$)(**L1**)] (2.5)	3	100	 **5m**	86
2	**4m**	[Au(NTf$_2$)(IPr)] (2.5)	6	100	**5m**	58
3	 **4n**	[Au(NTf$_2$)(**L1**)] (5.0)	3	100	 **6n**	97
4	 **4o**	[Au(NTf$_2$)(**L1**)] (2.5)	17	100	 **5o**	76[d]

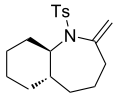
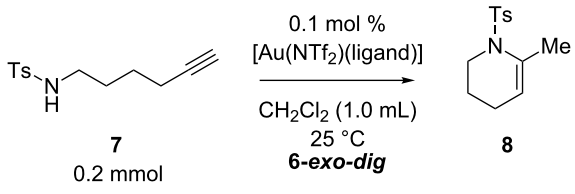
[a]Reaction conditions: **4**, 0.1 mmol; DCE, 1.0 mL; 80 °C.
[b]Determined by ^{1}H NMR.
[c]Isolated yield.
[d]Mixture of **5o** and **6o** in 98:2 ratio.  **6o**

Table 5: 6-*exo-dig* cyclization of sulfonamide **7**.

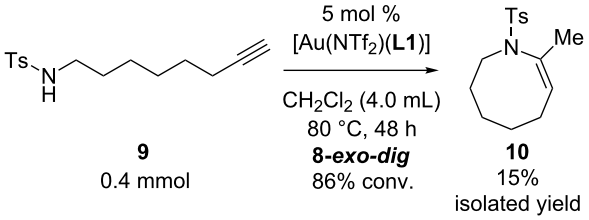


7
0.2 mmol

8

entry	Ligand	time (h)	convn. (%)[a]	yield of **8** (%)[a,b]
1	**L1**	2	100	100 (91)
2	X-Phos	12	76	76 (70)
3	IPr	12	68	67 (58)

[a]Determined by ^{1}H NMR. [b]Isolated yield in the parentheses.



9
0.4 mmol

10
15%
isolated yield

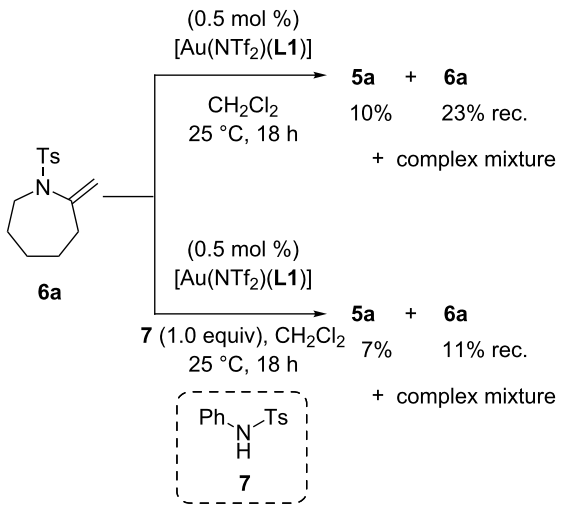
Scheme 1: 8-*exo-dig* cyclization of sulfonamide **9**.

isolated yield after 2 h (Table 1, entry 1). On the other hand, the reaction with X-Phos did not reach full conversion (76% convn.) even after 12 h and gave **8** in only 70% yield (Table 5, entry 2). The use of IPr ligand resulted in even lower conversion (68%) and isolated yield (58%) (Table 5, entry 3).

The triethynylphosphine ligand **L1** was also evaluated for the eight-membered ring formation of sulfonamide **9**, which is much more challenging than the seven-membered ring formation of **4**. The reaction required 5 mol % catalyst loading under heating conditions (80 °C) in 1,2-dichloroethane for a reasonable conversion rate to afforded an eight-membered ring azocine derivative **10** in 15% isolated yield (Scheme 1). It should be noted that the reaction produced significant amounts of unidentified oligomeric side products.

Alkene isomerization

We carried out alkene isomerization experiments to clarify how tetrahydroazepines **5** formed via the 7-*exo-dig* cyclization of **4**. One possible reaction pathway is the alkene isomerization of an exomethylene product **6**. To test this possibility, we synthesized **6a** through another route (see Supporting Information File 1) and subjected it to the standard reaction conditions of the gold–triethynylphosphine-catalyzed cyclization of alkynic sulfonamide with or without *N*-tosyl aniline **7** as an external



Scheme 2: Isomerization experiments of **6a**.

proton source (Scheme 2). Although **6a** was indeed isomerized into **5a** to some extent in both cases, the main reaction was decomposition to give complex mixtures. The exomethylene substrate **6a** appeared to be unstable at room temperature even in the absence of the gold-catalyst.

According to these results, the formation of exomethylene compound **6** and subsequent alkene isomerisation should not be a major pathway to **5**. Instead, a possible reaction pathway from **4a** to **5a** is illustrated in Figure 4. First, the cationic gold center coordinates with **4a** to form the gold–alkyne complex **A**. Intramolecular nucleophilic attack of the nitrogen atom affords the 7-*exo-dig* cyclization product **B** with an exocyclic C–C double bond. The protonated *N*-sulfonylenamide **B** tautomerizes to iminium ion **C** through 1,3-proton shift, or through an alternative pathway via a gold(I)–carben intermediate (**D**). Then, re-tautomerization affords the protonated *N*-sulfonylenamide **E** with an endocyclic C–C double bond. Finally, protodemetalation of **E** give the *N*-sulfonylenamide **5a**, which is thermodynamically more stable than **6a**.

It should be noted that the reaction of the *N*-tosylbenzamide **4n** afforded exceptionally the exomethylene isomer **6n**. One conceivable reason is that the alkene isomerisation was prevented due to a ring strain in the seven-membered ring of **5n**, of which six out of seven atoms are sp^2-hybridized.

Conclusion

We demonstrated that the 7-*exo-dig* intramolecular hydroamination of ω-alkynic *N*-alkyl-*N*-sulfonamides is efficiently catalyzed by a gold(I) complex coordinated with the semi-hollow-shaped triethynylphopshine ligand **L1**, and that the cyclization protocol provides a new efficient route to N-containing seven-membered ring compounds. The protocol is applicable to the reaction of alkynic sulfonamides with an acyclic or ring-fused linker chain with various substitution patterns. Evaluation of the ligand effect in the gold catalysis

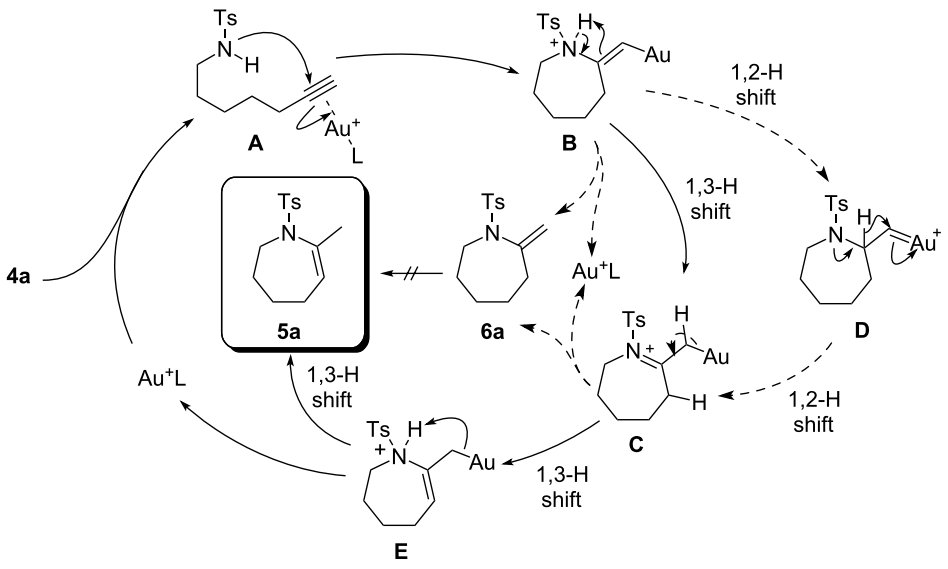


Figure 4: Possible pathway for the gold-catalyzed conversion of **4a** into **5a**.

with different ligands and substrates strongly suggested that the rate enhancement by the triethynylphosphine would be due to a steric factor which enforces a nucleophilic center close to a gold-activated alkyne moiety.

Experimental

Preparation of [Au(NTf$_2$)(L1)]

[AuCl(**L1**)] (1 equiv) was placed in an open vial and was dissolved in CH_2Cl_2 (ca. 0.1 M). $AgNTf_2$ (>1.5 equiv) was added, and the mixture was stirred at 25 °C for 10 min. The resulting white suspension was filtered through celite into a screw vial. The resulting colorless solution was first concentrated with a stream of Ar gas and then dried in vacuo to give [Au(NTf$_2$)(**L1**)] as a white solid. (See also [55].)

General procedure for gold-catalyzed intramolecular hydroamination of alkynic sulfonamide **4a**

[Au(NTf$_2$)(**L1**)] (2.6 mg, 1.0 μmol, 0.5 mol %) and a magnetic stirring bar were placed in an open vial. Separately, the alkynyl sulfonamide **4a** (55 mg, 0.20 mmol) was weighted into a micro tube. The tubes were placed in a glove box. The gold complex and **4a** were dissolved in degassed dry CH_2Cl_2 (0.25 mL), in their respective tubes. The solution of **4a** was transferred to the solution of the catalyst with a syringe. The remaining solutions in the micro tube and the syringe were washed with CH_2Cl_2 (2 × 0.25 mL) and, the washings were added to the reaction mixture. The tube was sealed with a cap equipped with a Teflon-coated silicon rubber septum. The tube was taken from the glove box, and was placed in a water bath (25 °C). After the reaction was complete (as monitored by TLC), the reaction mixture was passed through a pad of silica gel and was concentrated to dryness. Purification by flash chromatography on silica gel gave the cyclization product **5a** (45 mg, 82%) as a white solid; mp 65.8–66.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32–1.53 (m, 6H), 1.94 (t, J = 2.7 Hz, 1H), 2.14 (td, J = 6.9, 2.7 Hz, 2H), 2.44 (s, 3H), 2.95 (q, J = 6.9 Hz, 2H), 4.34 (br s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.94, 21.29, 25.34, 27.59, 28.75, 42.80, 68.35, 84.05, 127.06, 129.90, 136.85, 143.34; Anal. calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28; found: C, 63.29; H, 7.16; N, 5.21.

Supporting Information

Supporting Information File 1

Experimental procedures and NMR spectra for **4a**–**o** and **5a**, **b**, **g**–**m**, **o**, **6a**, **n**, **7**, **8**, **9**, **10**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-106-S1.pdf]

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Chiral gold(I) vs chiral silver complexes as catalysts for the enantioselective synthesis of the second generation GSK-hepatitis C virus inhibitor

María Martín-Rodríguez[1], Carmen Nájera[*1,§], José M. Sansano[*1,§], Abel de Cózar[2] and Fernando P. Cossío[*2,¶]

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Address:
[1]Departamento de Química Orgánica e Instituto de Síntesis Orgánica, Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain and [2]Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, Apdo. 1072, E-20018 San Sebastián, Spain

Email:
María Martín-Rodríguez - mmartin@ua.es; Carmen Nájera* - cnajera@ua.es; José M. Sansano* - jmsansano@ua.es; Fernando P. Cossío* - fp.cossio@ua.es

* Corresponding author
§ Corresponding author for experimental details
¶ Corresponding author for computational data

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Abstract

The synthesis of a GSK 2nd generation inhibitor of the hepatitis C virus, by enantioselective 1,3-dipolar cycloaddition between a leucine derived iminoester and *tert*-butyl acrylate, was studied. The comparison between silver(I) and gold(I) catalysts in this reaction was established by working with chiral phosphoramidites or with chiral BINAP. The best reaction conditions were used for the total synthesis of the hepatitis C virus inhibitor by a four step procedure affording this product in 99% ee and in 63% overall yield. The origin of the enantioselectivity of the chiral gold(I) catalyst was justified according to DFT calculations, the stabilizing coulombic interaction between the nitrogen atom of the thiazole moiety and one of the gold atoms being crucial.

Introduction

The prevalence of chronic hepatitis C virus (HCV) infection is such that it is estimated to be suffered by around 200 million people worldwide [1]. This enveloped single-stranded RNA virus (belonging to the *Flaviviridae* family) is present in six major genotypes in the world's industrialized nations, genotype 1 being the most prevalent, followed by genotype 2

and 3. Due to the poor toleration of the current therapy, and the lack of an appropriate vaccine, researchers working on strategies for developing antivirals have tried to attack viruses at every stage of their life cycles, namely attachment to a host cell, replication of viral components, assembly of viral components into complete viral particles and release of viral particles able to infect new hosts cells. Inside the infected hepatocytes, structural E1 and E2 and non-structural proteins such as NS2, NS3 (which bear serine proteinase, helicase, and NTPase activities), NS4A, NS4B, NS5A (regulators of RNA replication), and NS5B (the RNA-dependent RNA polymerase) are generated [2,3] and, in fact, constitute the main targets. At the moment, there are many drugs under clinical trial evaluation, the compounds targeting HCV replication being the most promising candidates to achieve a sustained virological response [1,4]. Several years ago, a high-throughput screening of the GlaxoSmithKline compound collection identified a series of small pyrrolidine molecules, e.g., **1** (Figure 1), able to inhibit the RNA-dependent RNA polymerase of the virus responsible for hepatitis C (genotype 1g) [5]. Thus, their high replication rates (billions of copies per day) can be drastically suppressed by the inhibition of the NS5B RNA-dependent RNA polymerase enzyme, which is the primary target for oral antiviral agents [6,7]. In further studies, a second generation of antiviral agents **2** and **3** (Figure 1), offering a greater dynamic range even for HCV genotype 1b, was published [5,8,9]. These molecules incorporated a 2-thiazole heterocycle instead of the 2-thienyl group, together with a more hydrophobic environment at the amido group [9-12]. However, the design of improved broader spectrum compounds, capable of effective inhibition of genotypes 1a and 1b, is desirable. In this sense, GSK625433 (**4**) (Figure 1) has exhibited a good pharmacokinetic profile in preclinical animal species [13].

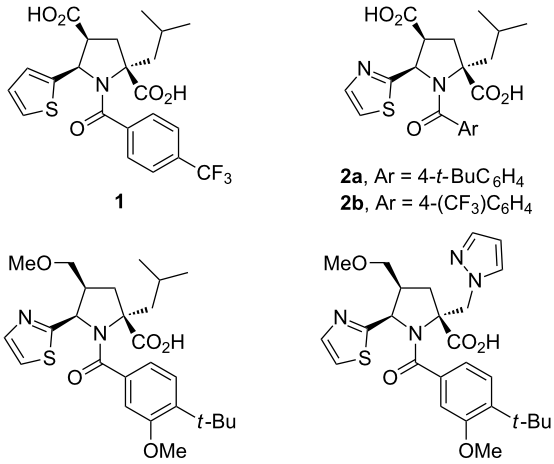
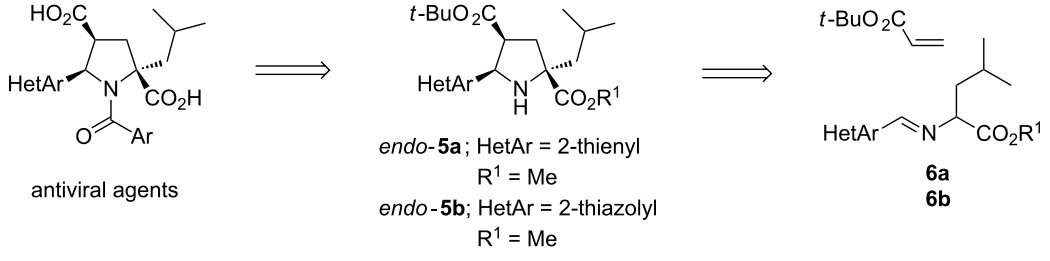


Figure 1: More active GSK HCV inhibitors.

The synthesis of the *endo*-pyrrolidine core of **5** is the key step for the preparation of these antiviral agents, and can be efficiently achieved by a 1,3-dipolar cycloaddition (1,3-DC) between the corresponding azomethine ylide and an alkyl acrylate [14-18] (Scheme 1). The first synthesis of racemic product **1**, and other derivatives including compounds **2**, was achieved in several steps using, as the key reaction, the silver(I) or lithium(I)-metalloazomethine ylide, under basic conditions, and *tert*-butyl acrylate. The enantiomeric samples were isolated by semi-preparative chiral HPLC [9,10]. The first *endo*-diastereoselective synthesis of the key precursor **5a** (HetAr = 2-thienyl), of the antiviral agent **1** (96% de), was achieved by our group from imine **6a** (HetAr = 2-thienyl; R^1 = Me) in the presence of the acrylate derived from (*R*)-methyl lactate [19]. However, the most straightforward, and also faster, approach to the enantiomeric formation of this non-nucleosidic antiviral agent **1** is based on a catalytic enantioselective 1,3-DC [20-24]. The first reported enantioselective overall synthesis of the structure **1** was catalyzed by a chiral phosphoramidite and $AgClO_4$ [25,26], although the synthesis of the five-membered core has also been published using chiral calcium complexes [27,28].

In addition, for the second generation antivirals **2** or **3**, the efficiency of the Lewis acid-catalyzed 1,3-DC, following the route shown in Scheme 1, was combined with hydroquinine as chiral



Scheme 1: Retrosynthetic analysis of antiviral structures.

base (6 mol %) together with silver acetate (3 mol %), and this afforded moderate enantioselectivities (70–74%) of **5b**, in such a way that a further 1,1'-binaphthyl-2,2'-dihydrogen phosphate assisted chiral resolution was required to increase the optical purity of the target molecule [11]. Chiral calcium(II) complexes have been used for the synthesis of a similar key molecule **5b** (R^1 = *t*-Bu, 88% ee), but the overall synthesis of the antiviral drug was not reported [27,28].

In this article, we describe the full study concerning the enantioselective synthesis of product **5b** using silver(I) or gold(I) complexes, generated from chiral phosphoramidites or BINAP as ligands, in order to prepare antiviral agent **2a**.

Results and Discussion

The efficiency of the chiral phosphoramidite/silver(I) salts [25,26,29] and BINAP/Ag(I) salts [30,31] in 1,3-DC, following the general pattern shown in Scheme 1, has been demonstrated by our group, establishing a wider scope and sensibly higher enantioselectivities for the reactions performed in the presence of chiral phosphoramidite/silver(I) complexes [24]. Concerning enantioselective gold(I)-catalyzed 1,3-DC, the classical cycloaddition starting from iminoesters **6** has not been so extensively explored. Reports of chiral transformations involving azlactones [32,33] and iminoesters **6** [34], which employed chiral diphosphines and gold(I) salts, have been published showing very good *endo*-diastereoselectivities and moderate to excellent enantioselectivities. However, the use of acrylates as dipolarophiles has only been explored with the 2-thienyliminoesters **6a**.

Therefore, based on our experience of silver(I)- and gold(I)-catalyzed 1,3-DC involving azomethine ylides derived from α-iminoester **6b** and *tert*-butyl acrylate, we selected a series of known chiral phosphoramidite ligands (Figure 2), which were prepared according to the literature [35]. The chiral phosphoramidite/silver(I) complexes were generated in situ by mixing equimolar amounts of both components at room temperature for 30 min. Chiral phosphoramidite/AuCl complexes were generated according to the literature [36] and, finally, underwent anion interchange in the presence of the corresponding silver salt. The precipitate was filtered through a celite pad and used without any other additional treatment.

All of the reactions were performed at room temperature, employing a 5 mol % of both catalyst and base, for 17 h (Scheme 1). Reactions between iminoester **6b** and *tert*-butyl acrylate, which employed silver complexes derived from Monophos (S_a)-**7** ligand, afforded racemic *endo*-cycloadduct **5b** (Table 1, entries 1–3). The analogous reaction catalyzed by chiral phosphoramidite **7**/gold(I) complexes did not occur at all

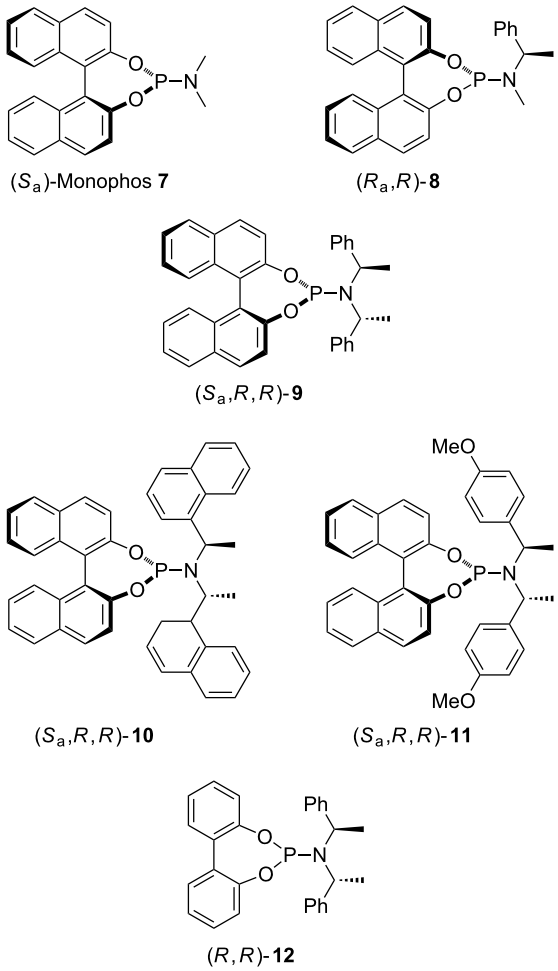


Figure 2: Chiral phosphoramidites tested in this study.

when $AgClO_4$ or $AgSbF_6$ were employed as anion interchange agents. Just a small conversion, with some side products, and null enantioselectivity was observed in the crude reaction mixtures obtained when using (S_a)-**7**/AuTFA (Table 1, entry 4). When the reaction was carried out in the presence of chiral ligand (R_a,*R*)-**8** the enantioselectivities were low or moderate in the examples concerning $AgClO_4$ and AgTFA (TFA = trifluoroacetate anion), respectively (Table 1, entries 5 and 7). Surprisingly, the reaction involving this chiral ligand **8** combined with $AgSbF_6$ afforded a good yield of the enantiomerically pure cycloadduct **5b** (Table 1, entry 6). Attempts to increase the enantioselectivity, in the example run with AgTFA, by replacing triethylamine by diisopropylethylamine (DIPEA) were not successful, and only a slight increment of enantiomeric excess was observed (Table 1, entry 8). Again, the gold complex (R_a,*R*)-**8**/AuTFA did not give the expected reaction product (Table 1, entry 9). The employment of this matched combination with (R_a,*R*)-**8** was justified by the low

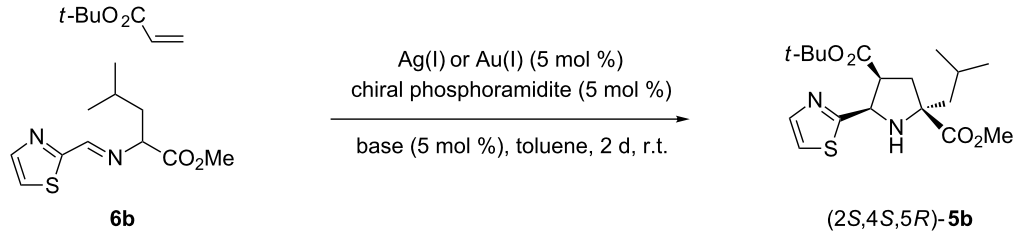
enantioselectivity achieved through the use of (R_a,S)-**8** in the same transformation (not shown in Table 1). The widely used chiral ligand (S_a,*R*,*R*)-**9** has also been similarly studied. In this case, the matched combination was determined in previous works that investigated the scope of enantioselective silver(I)-catalyzed 1,3-DC of azomethine ylides and dipolarophiles [25,29]. The enantioselectivities were moderate, even when using $AgSbF_6$, and the effect of the added base was negligible (Table 1, entries 10–14). The process catalyzed by the (S_a,*R*,*R*)-**9**/AuTFA was not suitable (Table 1, entry 15). The more sterically hindered chiral phosphoramidite (S_a,*R*,*R*)-**10** did not afford any interesting results because the conversions were extremely low after 2 days reaction, and the crude reaction mixture was very complex (^{1}H NMR analysis) (Table 1, entries 16–18). However, a good result was obtained when phosphoramidite (S_a,*R*,*R*)-**11** was tested together with $AgClO_4$. The high enantioselectivity achieved for **5b** (86% ee) is in contrast to the racemic samples identified when either $AgSbF_6$ or AgTFA were employed as co-catalysts (Table 1, entries 19–21). Biphenol derived ligand (*R*,*R*)-**12** generally furnished good yields of the cycloadduct **5b** but with a low enantiodiscrimination (Table 1, entries 22–24). In many examples, although the reactions were performed at lower temperatures (0 or −20 °C, not shown in Table 1) the resulting enantioselectivities did not suffer noticeable variations. In all of the cases given in Table 1, the *endo*-cycloadduct was exclusively generated, and the absolute configuration of **5b** was established by extrapolation with the results previously obtained for each chiral catalyst [25,26,28-30,33]. According to these results the combination of chiral phosphoramidite and silver(I) salt is much more appropriate than the analogous one made with gold(I) salts. Especially useful is the reaction of (R_a,*R*)-**8**/$AgSbF_6$ catalytic complex affording enantiomerically pure cycloadduct *endo*-**5b**. It is worth mentioning that chiral phosphoramidite/gold(I) complexes, formed by anion interchange of the corresponding phosphoramidite/AuCl complex and $AgSbF_6$ [36] or $AgBF_4$ [37,38], have been successfully employed in enantioselective cycloaddition of allenedienes [36,37] or allenenes [38] under very mild reaction conditions (0 ºC to r.t.). Despite these described opportunities provided by chiral phosphoramidite ligands as a part of gold(I) complexes, their activity (see Table 1) was negligible, until now, when applied in the 1,3-DC represented in Scheme 2.

Table 1: Optimization of the 1,3-dipolar cycloaddition of **6b** and *tert*-butyl acrylate using chiral phosphoramidite ligands.

Entry	Catalyst[a]	Base	Yield[b] (%)	ee[c] (%)
1	(S_a)-**7**/$AgClO_4$	Et_3N	—[d]	*rac*
2	(S_a)-**7**/$AgSbF_6$	Et_3N	—[d]	*rac*
3	(S_a)-**7**/AgTFA	Et_3N	—[d]	*rac*
4	(S_a)-**7**/AuTFA	DIPEA	—[d]	—[d]
5	(S_a,*R*)-**8**/$AgClO_4$	Et_3N	82	20
6	(S_a,*R*)-**8**/$AgSbF_6$	Et_3N	82	99
7	(S_a,*R*)-**8**/AgTFA	Et_3N	82	60
8	(S_a,*R*)-**8**/AgTFA	DIPEA	82	64
9	(S_a,*R*)-**8**/AuTFA	DIPEA	—[d]	—[d]
10	(S_a,*R*,*R*)-**9**/$AgClO_4$	DIPEA	86	30
11	(S_a,*R*,*R*)-**9**/$AgSbF_6$	Et_3N	72	40
12	(S_a,*R*,*R*)-**9**/$AgSbF_6$	DIPEA	82	40
13	(S_a,*R*,*R*)-**9**/AgTFA	Et_3N	82	50
14	(S_a,*R*,*R*)-**9**/AgTFA	DIPEA	82	40
15	(S_a,*R*,*R*)-**9**/AuTFA	DIPEA	—[d]	—[d]
16	(S_a,*R*,*R*)-**10**/$AgClO_4$	Et_3N	—[d]	*rac*
17	(S_a,*R*,*R*)-**10**/AgTFA	Et_3N	—[d]	*rac*
18	(S_a,*R*,*R*)-**10**/$AgSbF_6$	Et_3N	—[d]	*rac*
19	(S_a,*R*,*R*)-**11**/$AgClO_4$	Et_3N	72	86
20	(S_a,*R*,*R*)-**11**/$AgSbF_6$	Et_3N	—[d]	*rac*
21	(S_a,*R*,*R*)-**11**/AgTFA	Et_3N	—[d]	*rac*
22	(*R*,*R*)-**12**/$AgClO_4$	Et_3N	79	30
23	(*R*,*R*)-**12**/AgTFA	Et_3N	87	40
24	(*R*,*R*)-**12**/$AgSbF_6$	Et_3N	86	30

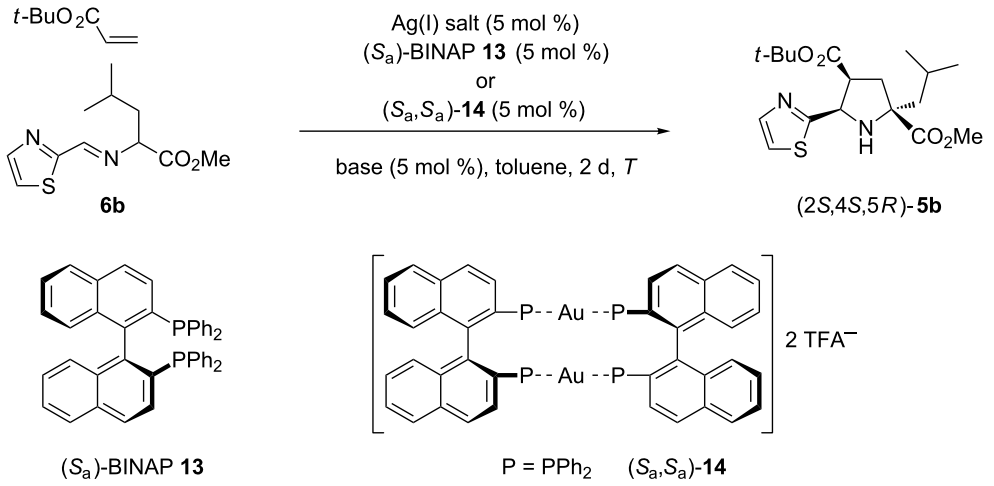
[a]The generation of silver catalysts was achieved by mixing equimolar amounts of silver(I) or gold(I) salt and the corresponding phosphoramidite. [b]After flash chromatography (silica gel). The observed *endo*:*exo* ratio was always >98:2 (^{1}H NMR). [c]Determined by using analytical chiral HPLC columns (Daicel, Chiralpak AS). [d]Not determined.

The chiral ligand (S_a)-BINAP (**13**) was also tested in the standard reaction to access key molecule *endo*-**5b** (Scheme 3).



6b (2*S*,4*S*,5*R*)-**5b**

Scheme 2: Optimization of the reaction conditions for the synthesis of the key intermediate **5b**.



Scheme 3: Preparation of the enantiomerically enriched **5b**.

$AgClO_4$ was found to be the most appropriate silver salt to achieve the highest enantioselectivity (88% ee) compared to the results obtained when other silver salts were employed (Table 2, entries 1, 3, and 4). In agreement with the previous results, the reaction with chiral silver complexes at lower temperatures did not improve the enantioselectivity. According to our previous work, dimeric chiral gold(I) catalyst $[(S_a)$-BINAPAuTFA$]_2$ (S_a,S_a)-**14** was very efficient in 1,3-DC compared to other catalysts with different stoichiometry or anion nature. The gold complex (S_a,S_a)-**14** was prepared according to the literature [39] and immediately used in the cycloaddition in the absence of base because of its bifunctional behaviour, namely the activation of the basic character of the dipole [34]. However, no reaction occurred under these conditions (Table 2, entry 5). Therefore, the presence of the base was crucial for the evolution of the reaction, as can be seen in entries 6 and 7 of Table 2. Triethylamine promoted the reaction affording good yield and good enantioselectivity (78% ee). However, DIPEA-mediated cycloaddition did not improve the enantioselectivity of the resulting *endo*-cycloadduct **5b**. Unlike the results obtained with silver(I) catalytic complexes at lower temperatures (0 or −20 °C), the gold(I)-catalyzed cycloaddition could be successfully carried out at 0 °C resulting in excellent enantiodiscrimination (99% ee) to the detriment of the reaction time, which had to be increased to 3 days (Table 2, entry 8). The result obtained in this last example was excellent but the enantiomeric excess achieved at room temperature in the reaction performed with (S_a)-**13**/$AgClO_4$ complex is also valuable.

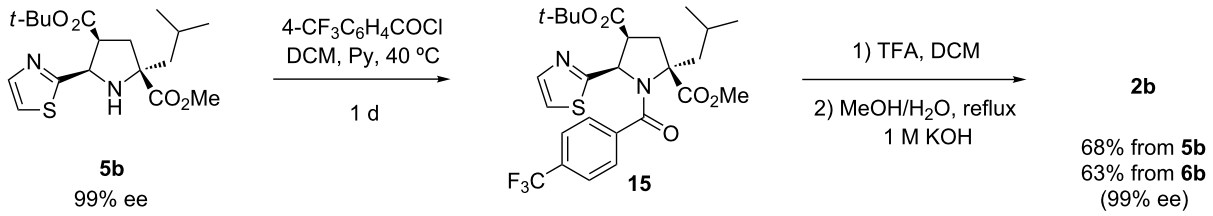
With the most enantiomerically enriched cycloadduct **5b**, the synthesis of the antiviral agent **2a** could be accomplished in two conventional steps involving an amidation reaction and a double ester hydrolysis. The latter step consisted of a first stage TFA-mediated hydrolysis of the *tert*-butyl ester followed by a basic stage employing a refluxing solution of KOH/MeOH (Scheme 4). The final product **2b** was finally isolated in 68% overall yield (from pyrrolidine **5b**) and with 99% ee, or alternatively in 63% overall yield from iminoester **6b**.

Table 2: Optimization of the 1,3-dipolar cycloaddition of **6a** and *tert*-butyl acrylate using chiral (S_a)-BINAP (**13**) ligand.

Entry	Catalyst[a]	Base	Yield[b] (%)	ee[c] (%)
1	(S_a)-**13**/$AgClO_4$	Et_3N	78	88
2	(S_a)-**13**/$AgClO_4$	Et_3N[d]	75	85
3	(S_a)-**13**/$AgSbF_6$	Et_3N	79	72
4	(S_a)-**13**/AgTFA	Et_3N	82	40
5	(S_a,S_a)-**14**	—	—[e]	—[e]
6	(S_a,S_a)-**14**	Et_3N	90	78
7	(S_a,S_a)-**14**	DIPEA	87	70
8	(S_a,S_a)-**14**	Et_3N[d,f]	92	99

[a]The generation of silver catalysts was achieved by mixing equimolar amounts of silver(I) and (S_a)-BINAP. [b]After flash chromatography (silica gel). The observed *endo*:*exo* ratio was always >98:2 (^{1}H NMR). [c]Determined using analytical chiral HPLC columns (Daicel, Chiralpak AS). [d]Reaction performed at 0 °C. [e]Not determined. [f]After 3 days reaction.

Although the study of the enantioselectivity exhibited by chiral phosphoramidite/silver(I) complexes employing DFT calculations was confirmed by our group [25], an explanation for the excellent results obtained employing the gold complex (S_a,S_a)-**14** (Table 2, entry 8) was needed. In a previous work, we demonstrated that the stereoselectivity of the 1,3-DC employing chiral metallic Lewis bases arises from the blockage of one of



Scheme 4: Total synthesis of antiviral agent **2b**.

the prochiral faces [40]. In this way, our results (in terms of DFT calculations) show that there is only one energetically accessible conformation due to the high substitution of the leucine-derived ylide (Figure 3). In this reactive complex there is an effective blockage of the (2*re*,5*si*) prochiral face of the ylide. Therefore, the predicted stereochemical outcome corresponds to the exclusive formation of the (2*S*,4*S*,5*R*)-**5b** cycloadduct, the same as that obtained experimentally.

As shown in Figure 3, the reaction proceeds to a concerted but highly asynchronous cycloaddition in which the *endo*-approach of the dipolarophile is favoured due to a stabilizing interaction of the carboxylic group and the metallic centre. The computed activation Gibbs free energy barrier associated with the formation of (2*S*,4*S*,5*R*)-**5b** is 23.4 kcal mol^{-1}, which means that the process is feasible at the reaction temperature. It is worth noting that there is a stabilizing coulombic interaction between the nitrogen atom of the thiazole moiety (N_7) and one of the gold atoms of the catalyst, both in the TS and the ylide complex. This interaction fixes the planar conformation of the ylide moiety and minimizes the possible steric hindrance with the bulky *tert*-butyl group of the dipolarophile. When a phenyl substituent is placed to the imino group this planar conformation does not exist and, in consequence, a more steric interaction avoids the approach of the mentioned dipolarophile.

Conclusion

In this work the complexity of the 1,3-DC reaction of azomethine ylides and dipolarophiles (in this case acrylates) was demonstrated. There are many parameters to control and a small variation can cause a dramatic effect in the overall enantiodiscrimination of the process. The temperature does not equally affect silver(I) and gold(I) catalysts. The effect of the heterocycle remains crucial in these transformations because, originally, the enantioselectivity of the reaction between methyl benzylideneiminoglycinate and alkyl acrylates failed in the presence of the silver(I) or the dimeric gold(I) complexes derived from chiral BINAP. The metal cation and the counterion are also important in the final result and, in certain cases, their position with respect to the reaction centre can modify the

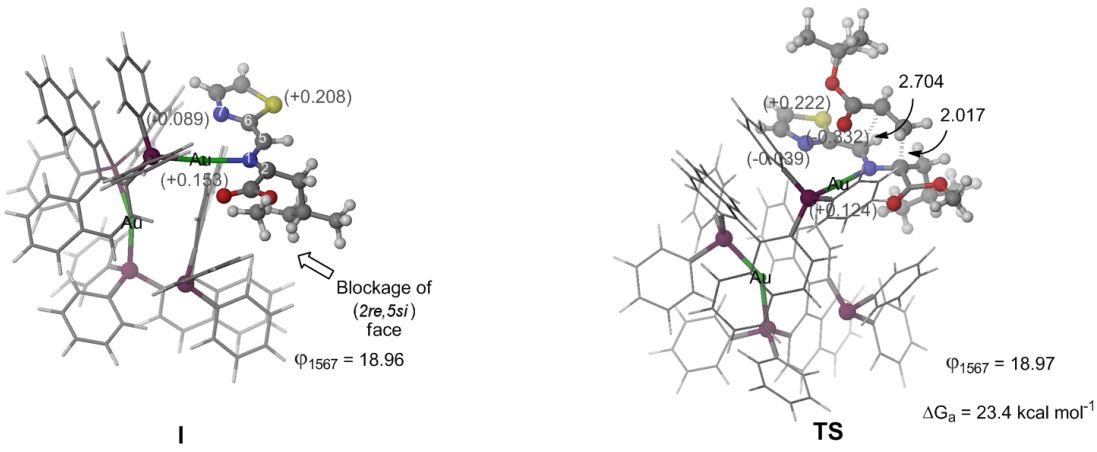


Figure 3: Gibbs activation energy and main geometrical features of the computed ylide and transition structures (TS) corresponding to the 1,3-DC of the Au(I)–ylide complex and *tert*-butyl acrylate computed at ONIOM(B3LYP/LanL2DZ:UFF) level of theory. High-level and low-level layers are represented as ball & stick and wireframe models, respectively. Grey numbers in parentheses represent Mulliken charges. Distances are in Å.

overall reaction and consequently alter the enantioselectivity of the process. To date, the best reaction conditions to access GSK 2nd generation antiviral drugs **2a** are: The employment of chiral phosphoramidite (R_a,*R*)-**8**/$AgSbF_6$ and Et_3N (both in 5 mol % amount) at r.t. for 2 h, or chiral (S_a,S_a)-**14** gold complex and Et_3N (both in 5 mol % amount) at 0 °C for 3 days. Whilst phosphoramidite complexes operated exclusively in the presence of silver salts, the most versatile chiral BINAP ligand could work efficiently with both silver(I) or gold(I) cations. The stabilizing coulombic interaction between the nitrogen atom of the thiazole moiety and one of the gold atoms of the catalyst both in the TS and the ylide complex is the explanation for the success of the gold-catalyzed cycloaddition, in constrast to the observed TS involving methyl benzylideneiminoleucinate.

Experimental

General. All reactions were carried out in the absence of light. Anhydrous solvents were freshly distilled under an argon atmosphere. Aldehydes were also distilled prior to use for the elaboration of the iminoesters. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet 510 P-FT and on a Jasco FTIR 4100) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a JASCO 2000-series equipped with a chiral column (detailed for each compound in the main text), using mixtures of *n*-hexane/isopropyl alcohol as mobile phase, at 25 °C. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized under UV light (λ = 254 nm). For flash chromatography we employed Merck silica gel 60 (0.040–0.063 mm). Ligands **7**–**12** were prepared according to the reported procedure (see text). All of the transformations performed with silver catalysts were performed in the absence of light. The synthesis of the already characterized chiral complex (S_a,S_a)-**14** was performed according to the published procedure [39].

Computational methods. Hybrid QM/MM calculations for optimizations of saddle points were performed in terms of ONIOM [41-43] method implemented in GAUSSIAN09 suite of programs [44]. Ball & stick model in Figure 3 shows atoms included in the high-level layer, and a wire model is used to represent atoms included in the low-level layer. In the high-level layer, the electron correlation was partially taken into account by using the hybrid functional B3LYP [45-50] combined with Hay-Wadt small core effective potential (ECP) [51] basis set. UFF [52] molecular mechanics force field was employed in the low-level layer. Thermal corrections of Gibbs free energies were computed at the same level of theory and were not scaled. All stationary points were characterized by harmonic analysis. Reactant intermediates and cycloadducts have positive definite Hessian matrices. Transition structures show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration.

1,3-Dipolar cycloaddition of iminoester 6b and *tert*-butyl acrylate. General procedure. To a solution of the in situ prepared chiral gold complex or chiral silver complex (0.05 mmol) in toluene (2 mL) was added, at r.t., a solution of the iminoester **6b** (120 mg, 0.5 mmol) and *tert*-butyl acrylate (109 μL, 0.75 mmol) in toluene (2 mL). In some cases DIPEA or triethylamine (0.05 mmol) was added (see Tables) and the mixture stirred at r.t. or 0 °C for 2 or 3 days (see Tables). The reaction mixture was filtered off through a celite pad, the organic filtrate was directly evaporated and the residue was purified by recrystallization or by flash chromatography, yielding pure *endo*-cycloadduct **5b**.

(2*S*,4*S*,5*R*)-4-*tert*-Butyl-2-methyl-2-isobutyl-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (**5b**): Colourless solid; mp >195 °C dec (*n*-hexane/ethyl acetate); $[\alpha]_D^{20}$ +43 (*c* 1.00, CH_2Cl_2, 99% ee by HPLC); IR (neat) ν_{max}: 3330, 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70, 7.27 (2 × d, *J* = 3.4 Hz, 2H, C*H*C*H*S), 4.83 (d, *J* = 7.5 Hz, 1H, CHCS), 3.73 (s, 3H, OCH_3), 3.41 (q, *J* = 7.8 Hz, 1H, C*H*CHN), 3.25 (br. s, 1H, NH), 2.79, 2.10 (2 × dd, *J* = 13.5, 7.9 Hz, 2H, CH_2CCO), 1.76–1.69 (m, 2H, CH_2CH), 1.54–1.48 (m, 1H, CH_2CH), 1.17 (s, 9H, $(CH_3)_3$), 0.94, 0.85 (2 × d, *J* = 6.2 Hz, 6H, 2 × CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 170.8, 170.6 (2 × CO and CSN), 142.4, 118.8 (CHCHS), 80.6 (*C*$(CH_3)_3$), 68.3 (CO*C*N), 61.7 (*C*HCS), 52.2 (OCH_3), 49.6 (*C*HCO), 49.3 (CH_2CCO), 39.5 (CH_2CH), 27.6 ($(CH_3)_3$), 25.0 ($C(CH_3)_2$), 24.3, 22.9 (2 × CH_3C); EIMS *m/z* (% relative intensity): 368 (M^+, 1), 310 (51), 295 (16), 255 (23), 254 (14), 253 (100); HRMS calcd for $C_{18}H_{28}N_2O_4S$, 368.1770; found, 368.1761; HPLC (Chiralpak AD-H), *n*-hexane:iPrOH 95/5, 1 mL/min, λ = 225 nm, $t_{R,maj}$ = 12 min, $t_{R,min}$ = 18 min.

Synthesis of the antiviral agent 2b. Compound (2*S*,4*S*,5*R*)-**5b** (1.2 mmol, 441 mg) was dissolved in dichloromethane (25 mL), and pyridine (2.4 mmol, 174 μL) and 4-(trifluoromethyl)-

benzoyl chloride (1.2 mmol, 182 μL) were slowly added at 0 °C. The resulting mixture was refluxed for 1 day and the solvent was removed under vacuo (15 Torr). Crude compound (2*S*,4*S*,5*R*)-**15**, was allowed to react with trifluoroacetic acid/dichloromethane mixture (9.6 mL/18 mL). The resulting mixture was stirred at r.t. overnight and the solvent evaporated under vacuo. The residue was dissolved in a 1 M solution of KOH in a 4/1 MeOH/H_2O (50 mL) and refluxed for 16 h. Methanol was evaporated and aqueous HCl (0.5 M, 20 mL) and ethyl acetate were added (2 × 20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated, yielding the crude compound (2*S*,4*S*,5*R*)-**2b**, which was recrystallized from a mixture containing *n*-hexane/ethyl acetate.

(2*S*,4*S*,5*R*)-2-Isobutyl-5-(thiazol-2-yl)-1-[4-(trifluoromethyl)-benzoyl]pyrrolidine-2,4-dicarboxylic acid (**2b**): Pale brown solid; mp >130 °C dec (*n*-hexane/ethyl acetate); $[\alpha]_D^{20}$ +35 (*c* 0.3, toluene, 99% ee); IR (neat) ν_{max}: 3100, 1731, 1693 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 8.15 (d, *J* = 7.5 Hz, 2H, ArH), 7.80–7.64 (m, 3H, ArH and C*H*CHS), 7.29 (d, *J* = 3.4 Hz, 1H, CHC*H*S), 5.85 (d, *J* = 8.7 Hz, 1H, CHNS), 4.01–3.81 (m, 1H, CHCO), 2.84 (t, *J* = 13.3 Hz, 1H, CH_2CCO), 2.34 (dd, *J* = 13.2, 6.5 Hz, 1H, CH_2CCO), 1.28 (m, 4H, CH_2CH and 2 × OH), 1.14–1.06 (m, 1H, CH_2CH), 0.85 (m, 6H, 2 × CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 169.1, 168.9, 167.4 (3 × CO and CNS), 141.1, 134.2, 134.1, 130.2, 126.9, 125.4, 120.9, (ArC, CF_3, and CHCHS), 69.7 (CO*C*N), 65.3 (N*C*H), 51.39 (CHCO), 42.3 (CH_2CCO), 35.3 (CH_2CH), 25.7 ($CH(CH_3)_2$), 24.4, 24.2 ($CH(CH_3)_2$); ESIMS *m/z* (% relative intensity) 470 (M^+, 2); HRMS calcd for $C_{21}H_{21}F_3N_2O_5S$, 470.4620; found, 470,4631; HPLC (Chiralpak AD-H), *n*-hexane:iPrOH 85/15, 0.1 mL/min, λ = 250 nm), $t_{R,maj}$ = 12.5 min, $t_{R,min}$ = 15.5 min.

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One-pot Diels–Alder cycloaddition/gold(I)-catalyzed 6-*endo-dig* cyclization for the synthesis of the complex bicyclo[3.3.1]alkenone framework

Boubacar Sow, Gabriel Bellavance, Francis Barabé and Louis Barriault*§

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Address:
Department of Chemistry, 10 Marie Curie, University of Ottawa, Ottawa, Canada, K1N 6N5

Email:
Louis Barriault* - lbarriau@uottawa.ca

* Corresponding author
§ Phone: 1-613-562-5800; Fax 1-613-562-5170

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Abstract

The rapid synthesis of bicyclo[*m.n.*1]alkanone cores possessing quaternary carbon centers adjacent to a bridged ketone represents a significant synthetic challenge. This type of architectural feature is embedded in various complex biologically active compounds such as hyperforin and garsubellin A. Herein, we report a highly diastereoselective one-pot Diels–Alder reaction/Au(I)-catalyzed carbocyclization to generate bicyclo[3.3.1]alkanones in yields ranging from 48–93%.

Introduction

Highly oxygenated and densely substituted carbon-bridged medium sized rings such as **1** are commonly found in nature as structural frameworks of many important bioactive natural products, and in particular, polycyclic polyprenylated acetylphloroglucinols (PPAPs) (Figure 1) [1]. In the past decades, more than 100 PPAPs exhibiting a wide variety of biological activities (antibiotic, anti-HIV, anti-oxidant, etc.) have been isolated from *Guttiferrea* plants such as hyperforin (**2**) [2-6] and garsubellin A (**3**) [7,8]. The challenging synthesis of PPAP structures combined with their promising therapeutic potential has drawn attention from several research groups [9-12].

In 2009, we reported a mild and highly efficient method to generate carbon-bridged frameworks of various sizes through a gold(I)-catalyzed carbocyclization [13]. Although the cyclization of enol ether **5** can produce 5-*exo* and 6-*endo* products, we found that gold complexes **6**, having bulky phosphine ligands such as 2-bis(*tert*-butylphosphino)biphenyl, gave exclusively the 6-*endo-dig* cyclized products **7** (Scheme 1). In the course of

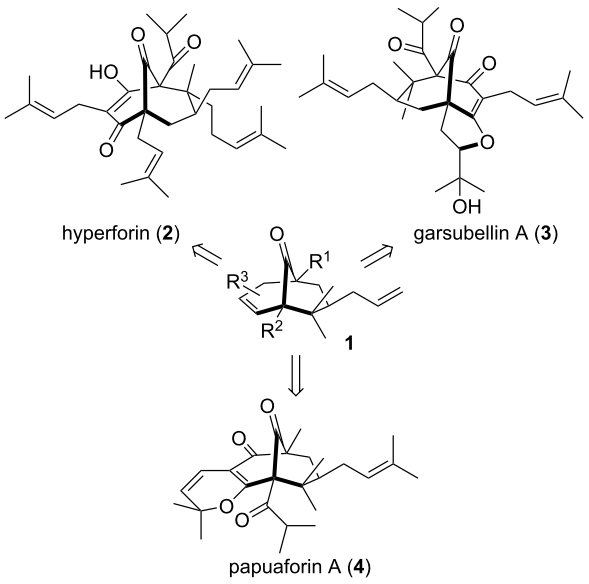
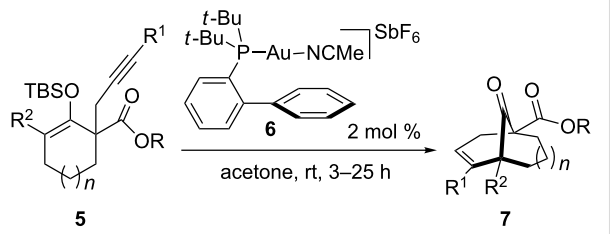


Figure 1: Structures of naturally occurring PPAPs.

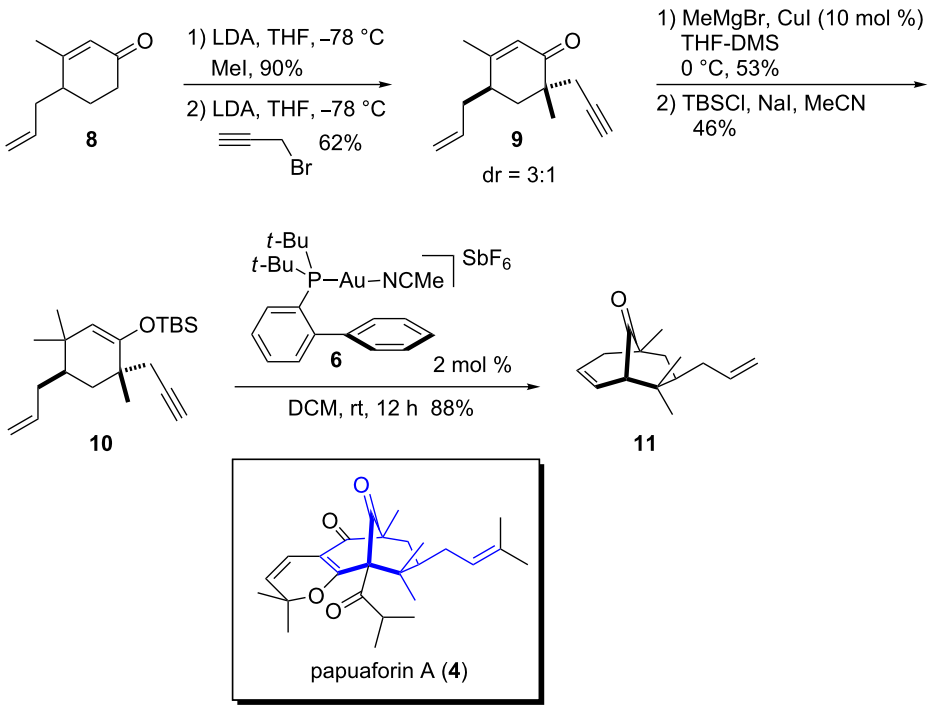
our studies directed towards the synthesis of naturally occurring PPAPs and related carbon-bridged ketone scaffolds, we envisioned that PPAP framework **1** could be generated via a Au(I)-catalyzed cyclization [14-22].



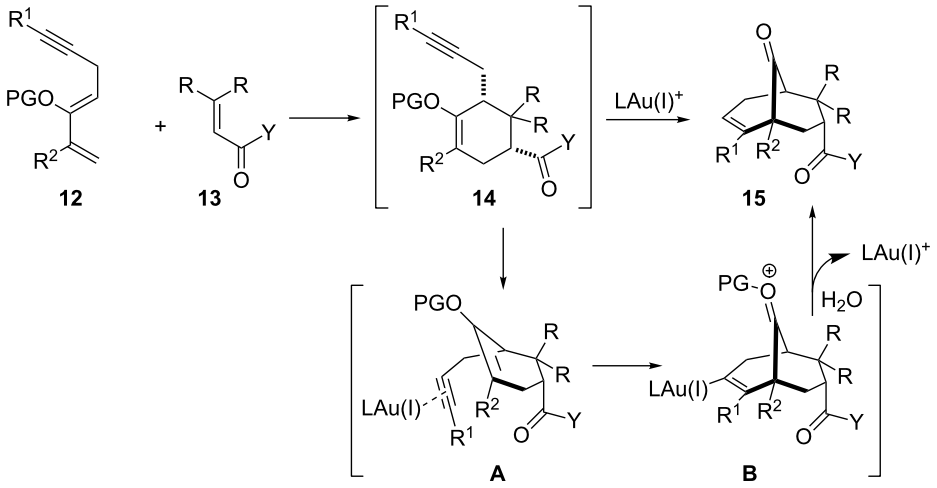
Scheme 1: Gold(I)-catalyzed 6-*endo-dig* cyclization.

Results and Discussion

The synthesis began by a *C*-alkylation of enone **8** [23] using LDA and MeI to give the corresponding ketone in 90% yield (Scheme 2). A second alkylation to add the propargyl chain was carried out using LDA and propargyl bromide to afford **9** in 62% yield as an inseparable mixture of diastereomers (dr = 3:1). Subsequently, conjugate addition of methylmagnesium bromide in the presence of a catalytic amount of CuI provided the corresponding ketone in 53% yield. The ketone was then treated with TBSCl, NaI and triethylamine to give the desired silylenol ether **10** in 46% yield, which upon exposure to the Au(I) complex **6** (2 mol %) provided the desired bicyclo[3.3.1]nonenone **11** in 88% yield. It is important to note



Scheme 2: Synthesis of papuaforin A core **4**.

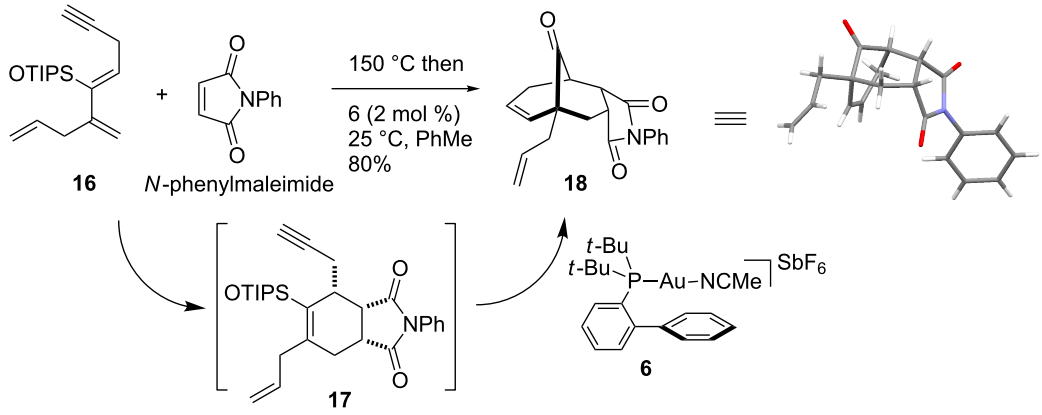


Scheme 3: Proposed domino Diels–Alder reaction/gold(I)-catalyzed cyclization.

that the Au(I)-catalyzed cyclization proceeds in high yields in a sterically congested environment. The synthesis of the core of papuaforin (**11**) was achieved in five steps from enone **8**.

However, one might recognize that the low chemical yields encountered in some steps undermine the efficacy of the Au(I)-catalyzed cyclization approach. In order to solve this issue, we assumed that bicyclo[3.3.1]nonenone scaffolds can be directly obtained through an intermolecular Diels–Alder reaction/Au(I)-catalyzed 6-*endo*-*dig* carbocyclization (Scheme 3). Cycloaddition between diene **12** and dienophile **13** should provide the endo cycloadduct **14**, which, in the presence of a gold(I) catalyst, would form the gold complex **A**. This undergoes a carbocyclization of enol ether [24-31] to afford intermediate **B**, which after proto-deauration and hydrolysis affords the bridgehead ketone **15**. The attractive feature of this process resides in the ability to generate four new stereogenic centers and three new C–C bonds in one single operation.

To validate the above hypothesis, diene **16** (*Z*-isomer) was heated with *N*-phenylmaleimide in toluene at 150 °C, for two hours, by microwave irradiation (Scheme 4) (see Supporting Information File 1 for experimental procedures). The solution containing the Diels–Alder adduct **17** was cooled down to room temperature and 2 mol % of Au(I) complex **6** was added. The bridgedhead ketone **18** was obtained in 80% yield as a single diastereomer. The relative stereochemistry of **18** was unambiguously established by X-ray analysis (see Supporting Information File 2). With this result in hand, we explored the scope of this sequential reaction (Table 1).



Scheme 4: One-pot Diels–Alder cycloaddition/gold(I) catalyzed carbocyclization.

Table 1: Results of the one-pot Diels–Alder reaction/Au(I)-catalyzed cyclization.

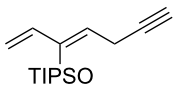
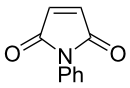
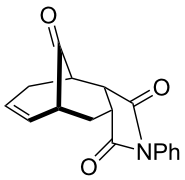
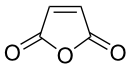
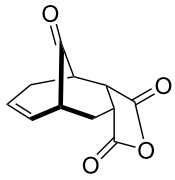
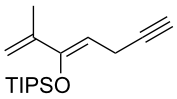
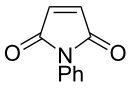
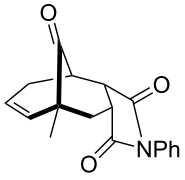
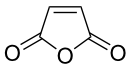
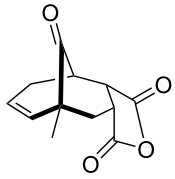
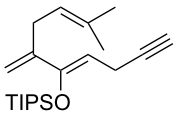
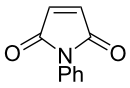
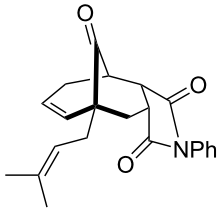
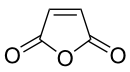
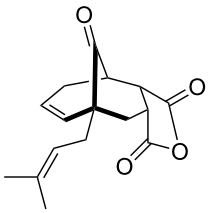
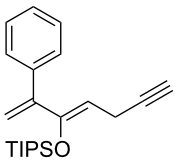
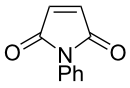
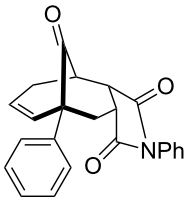
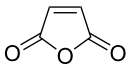
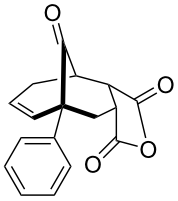
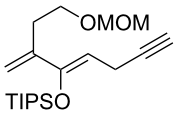
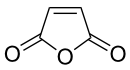
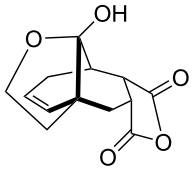
entry	diene	dienophile	product (yield)[a]
1	 **19**		 **24** (93%)
2	**19**		 **25** (51%)
3	 **20**		 **26** (88%)
4	**20**		 **27** (50%)
5	 **21**		 **28** (81%)

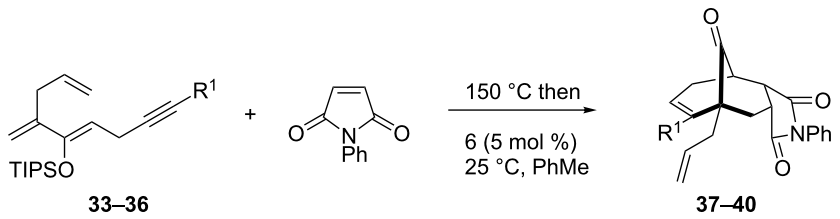
Table 1: Results of the one-pot Diels–Alder reaction/Au(I)-catalyzed cyclization. (continued)

6	**21**		 **29** (78%)
7	 **22**		 **30** (77%)
8	**22**		 **31** (48%)
9	 **23**		 **32** (56%)

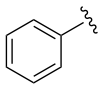
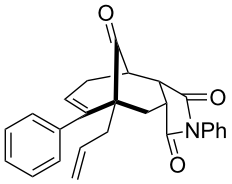
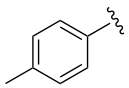
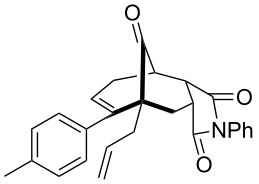
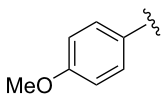
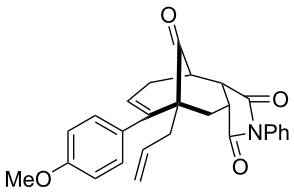
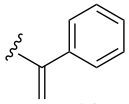
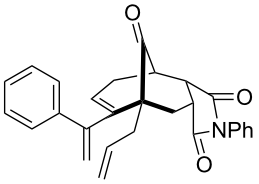
[a]Isolated yield and dr > 25:1 in all cases.

One-pot cycloaddition/cyclization of dienes **19** and **20** (*Z*/*E* = 6:1 ca.) with *N*-phenylmaleimide gave ketones **24** and **26** in 93 and 88% yield, respectively, as the sole diastereomers (Table 1, entries 1 and 3). The use of maleic anhydride as the dienophile also provided the desired products **25** and **27**, albeit in lower yields of 51 and 50%, respectively (Table 1, entries 2 and 4). Prenylated diene **21** was smoothly converted to ketones **28** and **29** in 81 and 78% yield, respectively (Table 1, entries 5 and 6). Table 1, entries 7 and 8 reveal that the diene **22**, bearing a phenyl group at C2, can be stereoselectively transformed into the desired bridgehead ketones **30** and **31** in 77 and 48% yields, respectively. Interestingly, hemiketal **32** was isolated in 56% yield, which suggests that the MOM group was cleaved during the Au(I)-catalyzed carbocyclization. It is important to note that the *E*-isomer of dienes **19**–**23** (minor compound) do not react with the dienophiles, but rather isomerized to the *Z*-form under the reaction conditions, thus, ensuring the formation of a single diastereomer.

Table 2: One-pot Diels–Alder cycloaddition/Au(I)-catalyzed carbocyclization of internal alkynes.



33–36 **37–40**

entry	substituent R^1	product	yield (%)[a]
1	 **33**	 **37**	68
2	 **34**	 **38**	91
3	 **35**	 **39**	74
4	 **36**	 **40**	79

[a]Isolated yield and dr >25:1 in all cases.

To extend the scope of the reaction, other dienes possessing internal alkynes were also investigated (Table 2). It can be seen that large substituents at the alkyne terminal position did not affect the efficacy of the reaction. Intermolecular cycloaddition/Au(I)-catalyzed cyclization of aryl acetylene dienes **33**–**35** provided the desired ketones **37**–**39** in yields ranging from 68 to 91% (Table 2, entries 1–3). Remarkably, enyne **36** was converted to **40** in 79% yield (Table 2, entry 4).

Conclusion

In summary, we have developed an efficient stereoselective method for the construction of bicyclic[3.3.1]nonenone frameworks. This one-pot Diels–Alder/Au(I)-catalyzed carbocyclization process provides access to synthetically useful motifs that are found in numerous naturally occurring PPAPs. In addition, the Au(I)-catalyzed cyclization proved to be tolerant of a sterically crowded environment. Further studies to develop an

enantioselective version of this reaction and its application to the total synthesis of hyperforin (**2**) and garsubellin A (**3**) are underway and will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, ^{1}H NMR and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-114-S1.pdf]

Supporting Information File 2

X-ray data of compound **18**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-114-S2.cif]

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Triazole–Au(I) complex as chemoselective catalyst in promoting propargyl ester rearrangements

Dawei Wang, Yanwei Zhang, Rong Cai and Xiaodong Shi*

Letter

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Address:
Department of Chemistry, West Virginia University, Morgantown, WV 26506, USA

Email:
Xiaodong Shi* - Xiaodong.Shi@mail.wvu.edu

* Corresponding author

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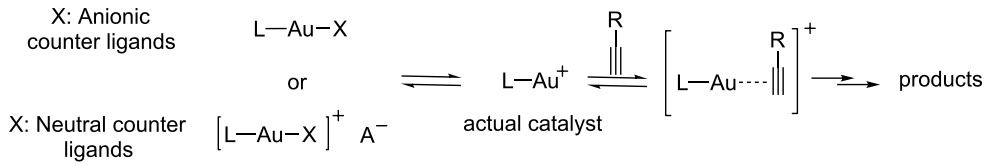
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Abstract

Triazole–Au (TA–Au) catalysts were employed in several transformations involving propargyl ester rearrangement. Good chemoselectivity was observed, which allowed the effective activation of the alkyne without affecting the reactivity of the allene ester intermediates. These results led to the investigation of the preparation of allene ester intermediates with TA–Au catalysts under anhydrous conditions. As expected, the desired 3,3-rearrangement products were obtained in excellent yields (generally >90% yields with 1% loading). Besides the typical ester migrating groups, carbonates and carbamates were also found to be suitable for this transformation, which provided a highly efficient, practical method for the preparation of substituted allenes.

Introduction

The past decade has seen rapid growth in the use of homogeneous gold catalysis for conducting powerful organic transformations [1-9]. Like many other transition metal complexes, the reactivity of gold catalysts greatly depends on the nature of the ligands coordinating with the metal cations [10-15]. Of the two typical oxidation states, Au(I) and Au(III), more studies have been focused on the former cation due to the easier preparation of the catalyst and better pre-catalyst stability. It is currently accepted by the research community that Au(I) complexes adopt one of two coordination sites with 180° linear geometry (Scheme 1) (although some exceptions exist). The actual catalysts involved in alkyne and alkene activation are of the type $[L–Au]^+$, with the open coordination site on the opposite side of the ligand (L) for substrate binding [5,6]. The recent success in obtaining the complexes of the alkyne-coordinated $[L–Au]^+$, reported by Toste and coworkers, greatly supported this mechanistic model [16]. Generally, the PR_3 compounds can be applied as the ligand in Au(I) catalysis. The recent development of N-heterocyclic carbene (NHC) derivatives has significantly expanded the choice of ligands by improving the catalyst stability through metal-ligand backbonding [17-20]. To access the active catalyst $[L–Au]^+$, stable precursors L–Au–X or



Scheme 1: The counter ligands, an important factor in Au(I) catalysis.

$[L–Au–X]^+·A^-$ were typically used. While the ligands (L) are certainly considered critical in gold catalysis, more and more attention have been paid to the evaluation of whether the choice of counter ligand "X" can be used to adjust the overall catalyst reactivity.

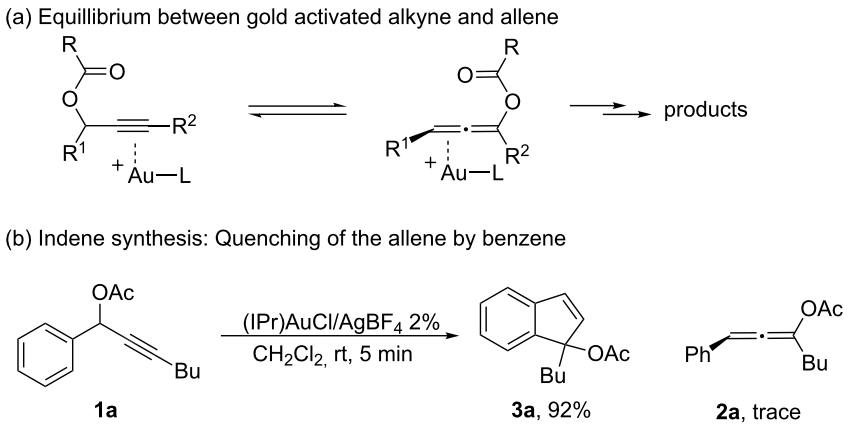
The propargyl ester rearrangement was considered as one of the most important reaction modes in the Au(I) promoted transformation [21-31]. Recent experimental and computational mechanistic studies revealed the 3,3-rearrangement to form the allene ester intermediate [32,33] as the key step in this transformation (Scheme 2a) [34]. Both experimental and theoretical investigations confirmed the reversibility between allene and propargyl ester due to effective activation of both functional groups by the Au(I) catalysts. As a result, it was extremely challenging to obtain the allene intermediates with good yields. Many strategies have been developed to make the Au(I)-activated allene esters react with other proper substrates, forming interesting new products in a cascade fashion. The indene synthesis (Scheme 2b), reported by Nolan and coworkers, is one good example highlighting the importance of the cascade process [35].

As shown in Scheme 2b, with the $[IPr–Au]^+$ catalyst, only trace amount of the allene **2a** was obtained. The major product derived from the Friedel–Crafts addition of the aromatic ring to the gold activated allene. Therefore, selective activation of the alkyne over the allene was considered as a significant challenge in gold catalysis.

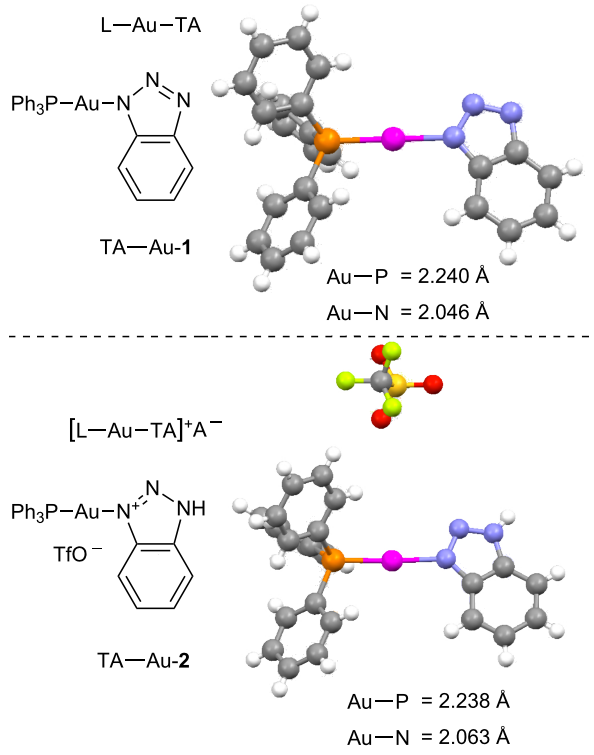
Results and Discussions

Recently, our group reported the synthesis and characterization of the 1,2,3-triazole [36-40] coordinated gold(I) complexes. As revealed by the X-ray crystal structures (Scheme 3), both neutral and anionic triazoles can coordinate with Au(I) cation, forming stable TA–Au complexes [41].

The preparation of these complexes was very straightforward. Simply treating the NH-triazoles with PPh_3AuCl in methanol under basic conditions (K_2CO_3, 1 equiv) at room temperature gave the neutral TA–Au-**1** in >90% yield. The "cationic" complex TA–Au-**2** was prepared either from the addition of HOTf to TA–Au-**1** or by the reaction between $PPh_3Au–OTf$ (prepared from $PPh_3–Au–Cl$ and AgOTf) and benzotriazole. Both complexes were stable and could be further purified by recrystallization to ensure no extra Ag^+ or acid in the catalysts. The crystal structures revealed nearly identical Au–P bond length for both the anionic and neutral triazole coordinated Au(I) complexes. The longer Au–N bond in TA–Au-**2** implies that the neutral triazole dissociates more easily to release the coordination site for substrate activation. This new class of compounds offers improved thermal stability and substrate stability in the



Scheme 2: The challenge of the synthesis of allenes through gold activated alkynes.



Scheme 3: X-ray crystal structures of the two different types of 1,2,3-triazole–Au complexes.

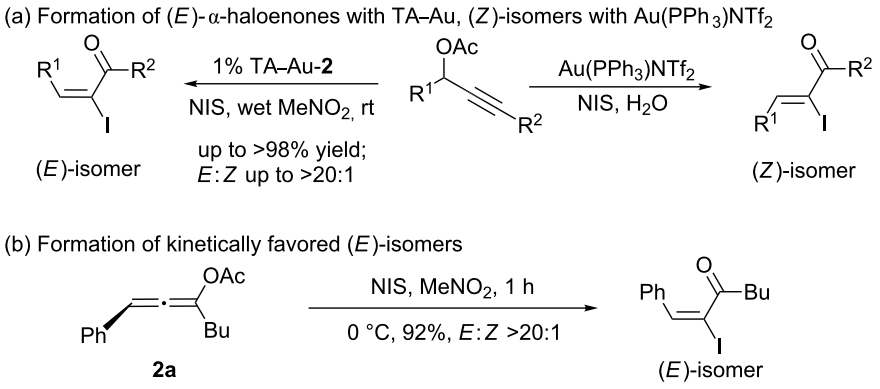
gold(I) promoted hydroamination and Hashmi phenol synthesis [42], which makes them interesting novel catalysts in the field of gold catalysis. One particular new development of the TA–Au catalysis that attracted our attention was the synthesis of α-iodoenone from propargyl esters (Scheme 4a) [43].

As indicated in Scheme 4a, the typical $[L–Au]^+$ catalyst promoted the sequential rearrangement and iodination, giving the thermally, dynamically stable (*Z*)-isomer [44-46]. The cationic TA–Au catalyst, on the other hand, produced the kinetically favored (*E*)-isomer. Notably, treating the allene ester **2a** with NIS gave the (*E*)-isomer as the dominant product. These results imply that the allene iodination should favor the formation of the (*E*)-isomer (Scheme 4b). The typical $[L–Au]^+$ catalyst not only promoted the propargyl ester 3,3-rearrangement, but also influenced the allene reactivity, probably through gold catalyzed allene activation. The fact that TA–Au gave the dominant (*E*)-isomers strongly suggests that these complexes may be applied as the chemoselective catalyst in alkyne activation over allene. The reactions of propargyl ester **1a** with TA–Au catalysts were then investigated as shown in Figure 1.

As expected, with the cationic catalyst TA–Au-**2** or TA–Au-**3**, the allene ester **2a** was formed in excellent yields (1% loading, 91% yield). It is important to note here, that indene **3a** was not observed even after 48 h reaction time, thus indicating excellent chemoselectivity of the triazole coordinated gold complexes. Various propargyl esters were synthesized to test the reaction substrate scope. The results are summarized in Table 1.

As shown in Table 1, the transformation proceeded smoothly with substrates having both an aromatic group on the propargyl side and an aliphatic group on the alkyne side (entries 1–6). The desired allene products were formed in excellent yields, with 1% catalyst loading. The electronic density on the aromatic ring did not have a strong impact on the transformation: Both electron donating and electron-withdrawing groups were suitable for the reaction. Again, no indene by-products were observed in any of the tested cases, even with the electron-enriched *p*-OMe substituted alkyne **1d**. These results highlighted the excellent chemoselective nature of the TA–Au catalyst.

The terminal alkyne **1i** did not give any product when treated with TA–Au catalyst, even after an extended reaction time



Scheme 4: Synthesis of α-iodoenone compounds from propargyl esters.

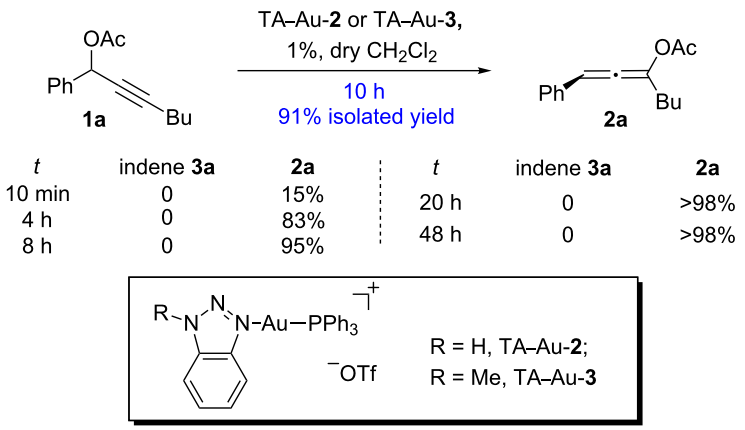
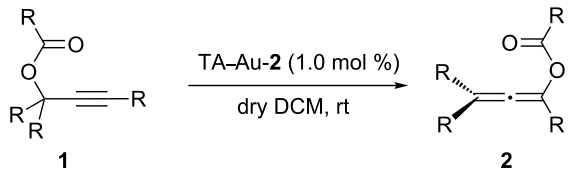


Figure 1: Chemoselective activation of alkyne over allene by the TA–Au catalysts.

Table 1: The reaction substrate scope.[a]



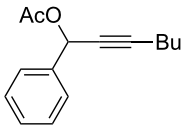
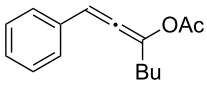
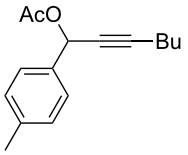
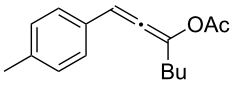
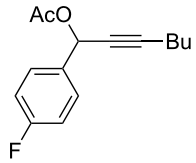
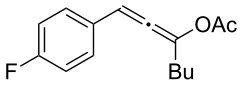
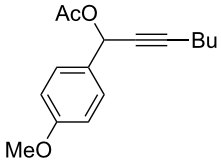
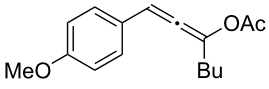
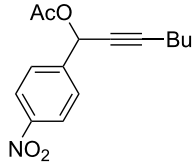
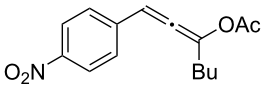
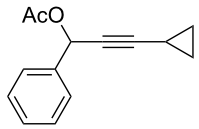
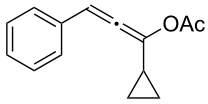
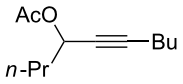
Entry	Substrate		Product		Yield
1		**1a**		**2a**	91%
2		**1b**		**2b**	90%
3		**1c**		**2c**	87%
4		**1d**		**2d**	89%
5		**1e**		**2e**	89%

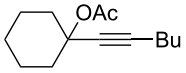
Table 1: The reaction substrate scope.[a] (continued)

6		**1f**		**2f**	85%

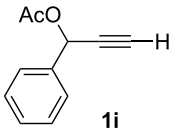
Substrates that did not form the desired allenes[b]



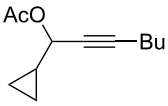
1g



1h



1i



1j

[a]General reaction conditions: **1** (0.25 mmol) and TA–Au-**2** (1.0 mol %) in dry DCM (2.5 mL), the reactions were monitored by TLC (2–10 h), rt.
[b]TA–Au-**1**, TA–Au-**2** and TA–Au-**3** did not catalyze the reaction under the standard conditions.

(24 h). This was probably caused by the preferred 1,2-rearrangement with the formation of a vinyl–Au intermediate. The aliphatic propargyl esters (**1g**, **1h**) also did not give any desired allene products (enones from hydrations were produced after a long reaction time, 24–48 h; the crude NMR of the reaction mixtures did not show any allene products). This may be caused by the high reactivity of the corresponding aliphatic allenes under the reaction conditions (activated by TA–Au) and the overall better stability of the propargyl ester compared to the aliphatic substituted allenes (equilibrium favored the starting material). The reaction of cyclopropyl substituted propargyl ester **1j** with the TA–Au catalyst gave a complex reaction mixture, which suggests possible ring opening and sequential cyclization as reported previously [47]. Overall, this study suggests that the propargyl ester rearrangement to form allene is highly substrate dependent. This could either be due to the similar reactivity of the alkyne and the allene (giving an equilibrium state favoring the alkyne over the allene) or it be could be due to a preferred alternative migration path (2,3-migration versus 3,3-migration). In any case, the TA–Au catalyst clearly displayed the interesting chemoselectivity, if the reaction could occur. To study the feasibility of this migration, we then investigated migrating groups other than esters. The results are summarized in Table 2.

As indicated in Table 2, carbonates (entries 1–5) and carbamate (entry 6) were also suitable for this transformation. Compared to the allene-acetates, the allene-carbonates and allene-carba-

Table 2: Different migrating groups.[a]

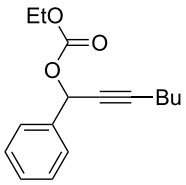
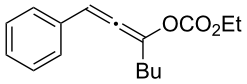
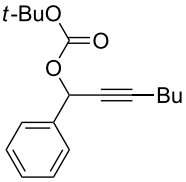
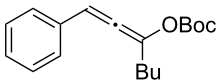
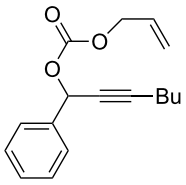
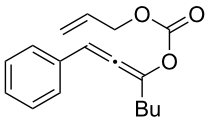
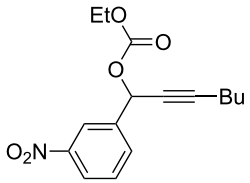
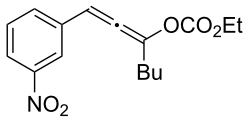
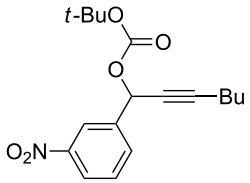
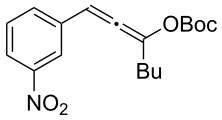
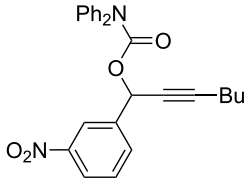
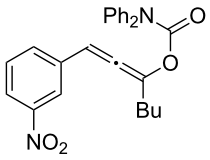
Entry	Substrate		Product		Yield
1		**4a**		**5a**	92%
2		**4b**		**5b**	91%
3		**4c**		**5c**	88%

Table 2: Different migrating groups.[a] (continued)

4		**4d**		**5d**	92%
5		**4e**		**5e**	89%
6		**4f**		**5f**	85%

[a]General reaction condition: **4** (0.25 mmol) and TA–Au-**2** (1.0 mol %) in dry DCM (2.5 mL), the reactions were monitored by TLC (2–10 h), rt.

mates were more stable in water. Notably, although the alkene was considered as a readily reactive functional group in gold catalysis, the substrate **4c** was suitable for this transformation, giving the desired allene-ene **5c** in excellent yield.

Conclusion

In this letter, we reported the application of triazole-coordinated gold(I) complexes as the effective catalysts for the promotion of the propargyl ester, carbonate and carbamate 3,3-rearrangement for the synthesis of the corresponding substituted allene derivatives. The chemoselective nature of the TA–Au catalysts was clearly demonstrated, which makes them an interesting class of new catalysts for promoting organic transformations. The application of the allene-carbonates and allene-carbamates as building blocks for development of new synthetic methodologies is currently underway in our group.

Supporting Information

Supporting Information File 1

General methods, characterization data and NMR spectra of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-115-S1.pdf]

Acknowledgements

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Asymmetric Au-catalyzed cycloisomerization of 1,6-enynes: An entry to bicyclo[4.1.0]heptene

Alexandre Pradal, Chung-Meng Chao, Patrick Y. Toullec and Véronique Michelet*

Full Research Paper

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Address:
Laboratoire Charles Friedel, UMR 7223, Ecole Nationale Supérieure de Chimie de Paris, Chimie ParisTech, 11 rue P. et M. Curie, F-75231 Paris Cedex 05, France

Email:
Véronique Michelet* - veronique-michelet@chimie-paristech.fr

* Corresponding author

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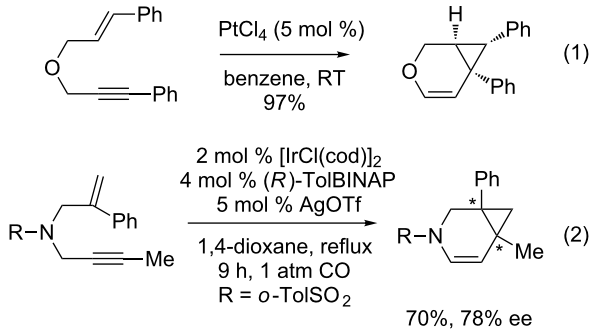
Abstract

A comprehensive study on the asymmetric gold-catalyzed cycloisomerization reaction of heteroatom tethered 1,6-enynes is described. The cycloisomerization reactions were conducted in the presence of the chiral cationic Au(I) catalyst consisting of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP-(AuCl)$_2$ complex and silver salts (AgOTf or AgNTf$_2$) in toluene under mild conditions to afford functionalized bicyclo[4.1.0]heptene derivatives. The reaction conditions were found to be highly substrate-dependent, the best results being obtained in the case of oxygen-tethered enynes. The formation of bicyclic derivatives, including cyclopropyl pentasubstituted ones, was reported in moderate to good yields and in enantiomeric excesses up to 99%.

Introduction

Metal-catalyzed cycloisomerization reactions of 1,*n*-enynes have emerged as efficient processes that contribute to sustainable development and atom economy concepts [1-8]. In the last ten years, they have provided extremely efficient access to cyclic skeletons with a broad range of functional moieties. Among them, the synthesis of oxa- and azabicyclo[4.1.0]heptenes starting from heteroatom-linked 1,6-enynes has been recently a field of high interest considering the fundamental skeleton rearrangement research of 1,*n*-enynes [1-11] and the potential applications in biological active and natural products [12,13]. In 1995, Blum et al. described a novel $PtCl_4$-catalyzed cycloisomerization reaction of allyl propynyl ethers leading to oxabicyclo[4.1.0]heptenes [14] (Scheme 1, reaction 1). The group of Murai observed a similar reactivity in the presence of $PtCl_2$, although in a lower yield [15]. These seminal contributions were then followed by several comprehensive studies involving carbophilic complexes such as platinum or gold [16-22] that led to the formation of complex

bicyclic and tricyclic compounds [23-40]. The first asymmetric version was described by Shibata's group in 2005 in the presence of a chiral iridium catalyst [41] (Scheme 1, reaction 2). We and others recently pursued the improvement and development of this enantioselective process, by employing platinum [42-44], rhodium [45] or gold [46-48] complexes. Following our previous work with chiral gold catalysts [46], we report a comprehensive study on gold-catalyzed enantioselective synthesis of bicyclo[4.1.0]heptenes, focusing on the scope and limitations of such systems.



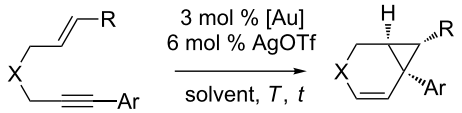
Scheme 1: First reports on the racemic and asymmetric synthesis of bicyclo[4.1.0]heptenes.

Results and Discussion

Optimization of the catalytic system

Based on our ongoing program on asymmetric gold catalysis [46,49-52], and on literature reports [53-55], we selected 4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP-(AuCl)$_2$ complex [56-58] as the best candidate for such a transformation. Initial experiments were performed using *N*-tosyl allyl substrate **1a** and oxygen-linked propargylic 1,6-enyne **2a** as model substrates (Table 1). The reaction of **1a** was evaluated in various solvents and proceeded smoothly leading to the desired alkene **3a** [59]. The reaction kinetics and stereoselectivity were found to be highly solvent-dependent, the enantiomeric excesses (ee) varying from 31% to 78% at room temperature (Table 1, entries 1–3). The reaction kinetic was very slow at room temperature in ether and toluene, but high ee's were obtained. Increasing the temperature to 40 °C in toluene or ether had a positive effect both on the conversion and on the ee's (Table 1, entries 4 and 5). The reaction was also conducted at 60 °C or 70 °C with good conversions and ee's (Table 1, entries 6–8), the best results being obtained in toluene. At 80 °C in toluene, a decrease in the stereoselectivity was observed as the ee dropped to 91% (Table 1, entry 9). The reactivity of oxygen-tethered enynes such as **2a** was different to that for **1a** as a complete conversion was observed at room temperature in toluene, dichloromethane, ether and tetrahydrofuran (Table 1, entries 10–13). A better ee

Table 1: Cycloisomerization reaction of nitrogen- and oxygen-linked 1,6-enynes **1a** and **2a**.



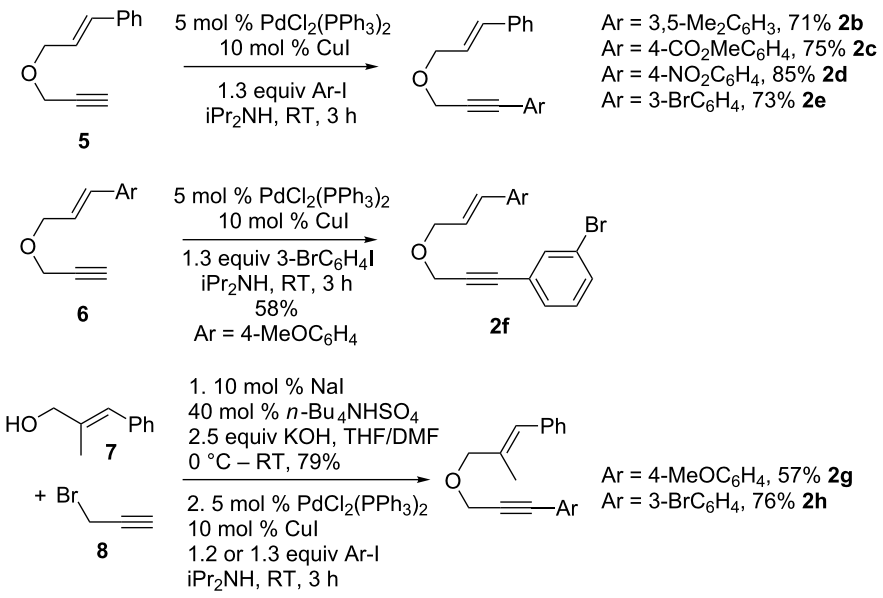
1a, **2a** → **3a**, **4a**

X = NTs, Ar = Ph, R = H **1a**
X = O, Ar = 4-MeOC$_6$H$_4$, R = Ph **2a**

[Au] = (*R*)-4-MeO-3,5-(*t*-Bu)$_2$MeOBIPHEP-(AuCl)$_2$

Entry	Substrate	Solvent	*T* [°C]	*t* [h]	Conv. (Yield) [%][a]	Product	ee [%][b]
1	**1a**	CH_2Cl_2	RT	36	78	**3a**	31 (−)
2	**1a**	Et_2O	RT	39	17	**3a**	75 (−)
3	**1a**	toluene	RT	39	11	**3a**	78 (−)
4	**1a**	Et_2O	40	41	28	**3a**	90 (−)
5	**1a**	toluene	40	96	100 (47)	**3a**	98 (−)
6	**1a**	toluene	60	96	100 (74)	**3a**	98 (−)
7	**1a**	THF	60	96	69	**3a**	74 (−)
8	**1a**	toluene	70	96	100 (83)	**3a**	96 (−)
9	**1a**	toluene	80	48	66	**3a**	91 (−)
10	**2a**	toluene	RT	30	100 (57)	**4a**	92 (−)
11	**2a**	CH_2Cl_2	RT	25	100 (26)	**4a**	70 (−)
12	**2a**	Et_2O	RT	25	100 (35)	**4a**	91 (−)
13	**2a**	THF	RT	25	100 (43)	**4a**	85 (−)
14	**2a**	toluene	0	120	100 (56)	**4a**	96 (−)

[a]Determined by ^{1}H NMR, [b]determined by HPLC.

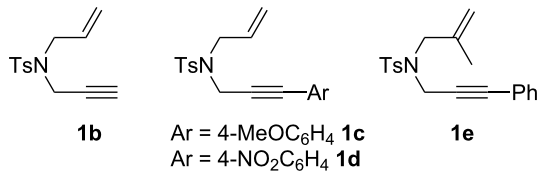


Scheme 2: Synthesis of oxygen-tethered 1,6-enynes.

was obtained in toluene compared to other solvents. Cyclopropyl alkene **4a** was isolated in 56% yield and 96% ee at 0 °C in toluene (Table 1, entry 14). Toluene was therefore chosen for further studies.

Synthesis of 1,6-enynes

We prepared various oxygen-tethered 1,6-enynes according to classic methodologies employing a Williamson alkylation reaction and/or a Sonogashira cross-coupling [60,61] (Scheme 2 and Scheme 3). The known enyne **5** [62,63] was engaged in Pd-catalyzed coupling in the presence of diversely functionalized aryl iodides (Scheme 2). The corresponding substituted alkynes **2b–e** [46] were isolated in 71–85% yield. An analogous 1,6-enyne **6** [64] was also reacted with 3-bromoiodobenzene under the same reaction conditions and led to the formation of substrate **2f** in 58% isolated yield. We also envisaged preparing two trisubstituted alkenes **2g** and **2h** by an alkylation/Sonogashira sequence starting from commercially available substrates **7** and **8**.



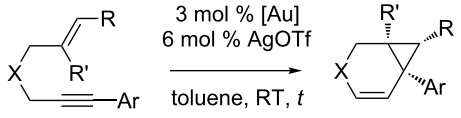
Scheme 3: Nitrogen-tethered 1,6-enynes.

We also selected some nitrogen-tethered 1,6-enynes **1b–e** from the literature [23,41-44] and synthesized them to evaluate the efficiency of the gold chiral catalytic system (Scheme 3).

Scope and limitations of the catalytic system

The prepared heteroatom-linked 1,6-enynes were then engaged in the cycloisomerization process in the presence of Au(I) cationic catalyst generated by mixing (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP-(AuCl)$_2$ complex and silver salts (Table 2). Anticipating the moderate reactivity of nitrogen-tethered enynes **1**, the reactions were conducted at 60 °C in toluene (Table 2, entries 1–5). The substitution of the aromatic ring on the alkyne moiety led to a substantial decrease of both isolated yields and ee's, as the presence of several by-products was detected, presumably due to degradation or polymerization [15]. A good ee was achieved in the case of enyne **1c**, by using AgNTf$_2$ [65] instead of AgOTf (Table 2, entry 2 compared to entry 1). The substitution of the allylic side chain seemed to slow down the degradation process, as the cyclic alkene **3e** was isolated in 61% yield (Table 2, entry 4). In the case of non-substituted enyne **1b** (Table 2, entry 5), the bicyclic alkenyl derivative **3b** was isolated in low yield and ee: The synthesis of **3b** was accompanied by the formation of known 1,3- and 1,4-dienes (5% and 10% isolated yield respectively) resulting from 5-*exo*- and 6-*endo* cycloisomerization reactions [20,66]. Thus, the gold catalytic system cannot compete with the results obtained for the cyclizations of nitrogen-tethered enynes in the presence of iridium, platinum or rhodium catalysts [41-45]. The cycloiso-

Table 2: Cycloisomerization reaction of nitrogen- and oxygen-linked 1,6-enynes.



1b–e, **2b–f** **3b–e**, **4b–f**

[Au] = (*R*)-4-MeO-3,5-(*t*-Bu)$_2$MeOBIPHEP-(AuCl)$_2$

X = NTs Ar = R = R' = H **1b**
Ar = 4-MeOC$_6$H$_4$, R = R' = H **1c**
Ar = 4-NO$_2$C$_6$H$_4$, R = R' = H **1d**
Ar = Ph, R = H, R' = Me **1e**

X = O Ar = 3,5-Me$_2$C$_6$H$_3$, R = Ph, R' = H **2b**
Ar = 4-CO$_2$MeC$_6$H$_4$, R = Ph, R' = H **2c**
Ar = 4-NO$_2$C$_6$H$_4$, R = Ph, R' = H **2d**
Ar = 3-BrC$_6$H$_4$, R = Ph, R' = H **2e**
Ar = 3-BrC$_6$H$_4$, R = 4-MeOC$_6$H$_4$, R' = H **2f**

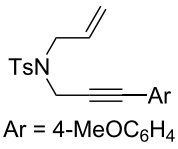
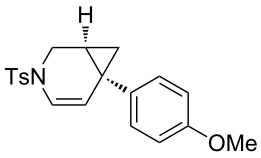
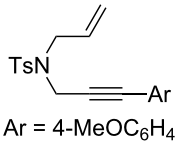
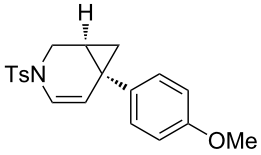
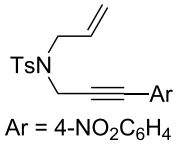
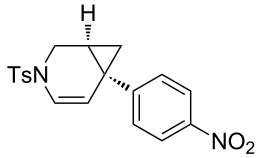
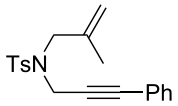
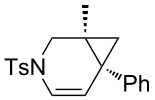
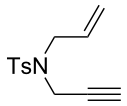
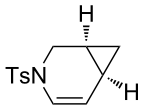
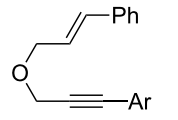
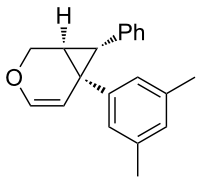
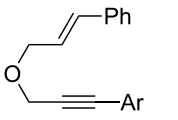
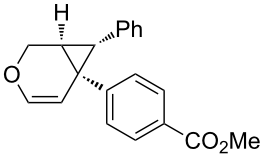
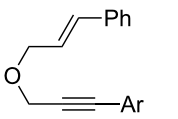
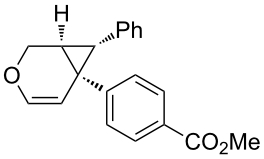
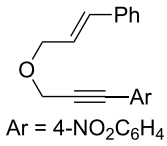
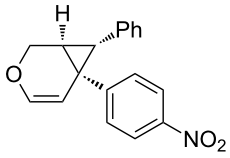
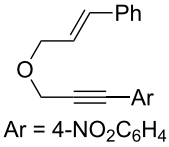
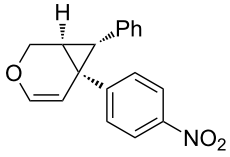
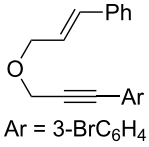
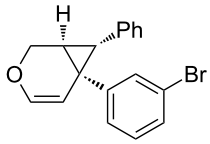
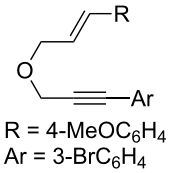
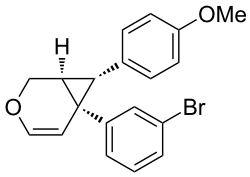
Entry	Enyne		*t* [h]	Yield [%][a]	Product		ee [%][b]
1[c]	 Ar = 4-MeOC$_6$H$_4$	**1c**	17	8		**3c**	77
2[c,d]	 Ar = 4-MeOC$_6$H$_4$	**1c**	17	8		**3c**	89
3[c]	 Ar = 4-NO$_2$C$_6$H$_4$	**1d**	24	7		**3d**	35
4[c]		**1e**	16	61		**3e**	13
5[c]		**1b**	16	23		**3b**	22
6	 Ar = 3,5-Me$_2$C$_6$H$_3$	**2b**	3.5	54		**4b**	93 (+)
7	 Ar = 4-CO$_2$MeC$_6$H$_4$	**2c**	15	25		**4c**	94 (−)
8[d]	 Ar = 4-CO$_2$MeC$_6$H$_4$	**2c**	15	64		**4c**	94 (−)

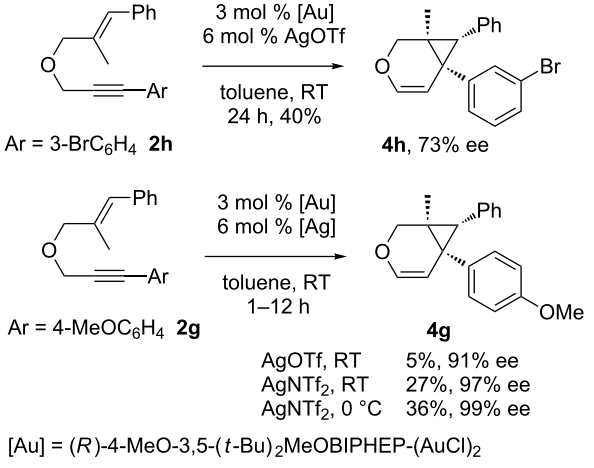
Table 2: Cycloisomerization reaction of nitrogen- and oxygen-linked 1,6-enynes. (continued)

9	 Ar = 4-$NO_2C_6H_4$	**2d**	15	32		**4d**	96 (−)
10[d]	 Ar = 4-$NO_2C_6H_4$	**2d**	15	63		**4d**	98 (−)
11	 Ar = 3-BrC_6H_4	**2e**	30	59		**4e**	95 (−)
12	 R = 4-$MeOC_6H_4$ Ar = 3-BrC_6H_4	**2f**	1	37		**4f**	95 (−)

[a]Isolated yield, [b]determined by HPLC, [c]60 °C, [d]$AgNTf_2$.

merization process was found to be highly stereoselective in the case of oxygen-tethered enynes (Table 2, entries 6–12). In all cases, the ee's were greater than 90% and in one case as high as 98%. The stability of the resulting bicyclic alkenes **4** was generally only moderate, which led to low isolated yields. In the case of 1,6-enynes **2c** and **2d**, the low yields (25% and 32% respectively) could be improved by switching from AgOTf salt to $AgNTf_2$, presumably due to the experimentally observed lower hygroscopicity of bistriflimide complex (Table 2, entry 7 compared to 8 and 9 compared to 10). The functionalized derivatives **4c** and **4d** were obtained in 64% and 63% yields respectively and in excellent ee's (Table 2, entries 8 and 10). The compatibility with another functional group on the aromatic ring such as bromine (Table 2, entry 11), and with a different allylic side chain (Table 2, entry 12) was also evaluated: The corresponding bicyclic adducts **4e** and **4f** were isolated in modest to good yield and 95% ee.

Considering the observed highly stereoselective reactions of oxygen-tethered 1,6-enynes, we decided to study the challenging asymmetric synthesis of pentasubstituted cyclopropyl derivatives [67-70] (Scheme 4). The bicyclic derivative **4h** was obtained in moderate yield and 73% ee. Conducting the reaction at 0 °C and using $AgNTf_2$ as a chloride scavenger led to the formation of the alkenyl functionalized derivative **4g** in 36% isolated yield and excellent 99% ee.



Scheme 4: Synthesis of pentasubstituted bicyclic cyclopropanes.

Conclusion

In conclusion, we have contributed to the development of an asymmetric gold-catalyzed cycloisomerization reaction allowing the formation of oxa- and aza-bicyclo[4.1.0]heptene derivatives. The combination of chiral Au(I) complex (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP-$(AuCl)_2$ associated to silver salts promotes the enantioselective rearrangement of oxygen and nitrogen-tethered 1,6-enynes in toluene at room temperature or 60 °C. The cycloisomerization reactions were found to

be highly substrate-dependent as low yield and ee's were generally obtained in the case of nitrogen-tethered enynes. The enantiomerically enriched functionalized oxabicyclo[4.1.0]heptenes were isolated in moderate yields but with excellent ee values ranging from 73% to 99%. This methodology was successfully applied to the synthesis of pentasubstituted cyclopropyl heterobicycles.

Experimental

All reactions were carried out under an argon atmosphere. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AV 300 instrument. All signals were expressed as ppm (δ) and internally referenced to residual proton solvent signals. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. Enantiomeric excesses were determined by high pressure liquid chromatography analyses (HPLC) on Waters instruments (Waters 486 detector, 717 autosampler equipped with Daicel Chiralcel OD-H, OJ and Chiralpak IA, AD, λ = 215 nm). Optical rotation measurements were conducted on a Perkin–Elmer 241 polarimeter at 589 nm. Enynes **5** [71], **2a** [72], **2b**–**e** [46], **1a** [73], **1b** [74], **1c**,**d** [75], **1e** [73], and **6** [64] were prepared according to published procedures. ^{1}H, ^{13}C NMR and mass spectrometry data for compounds **3a**,**b** [23], **3c**,**d** [75], **3e** [76] and **4a**–**e** [46] were described elsewhere.

(*E*)-1-Bromo-3-(3-(3-(4-methoxyphenyl)allyloxy)prop-1-ynyl)benzene (2f): CuI (46 mg, 0.1 equiv) and $PdCl_2(PPh_3)_2$ (86 mg, 0.05 equiv) were placed in a Schlenk tube under argon. Distilled diisopropylamine (3 mL) was added and the reaction mixture was stirred at RT for 5 min. 1-Bromo-3-iodobenzene (0.4 mL, 1.3 equiv) was added and the reaction mixture was stirred for 5 min. Enyne **6**, dissolved in 2 mL of distilled diisopropylamine was added and the reaction mixture stirred for 3 h at RT. After hydrolysis with sat. aq. NH_4Cl solution, the aqueous phase was extracted with EtOAc. The organic layer was successively washed with sat. aq. NH_4Cl solution and brine. The organic layer was then dried with $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate 90:10) to give **2f** as a colorless oil (509 mg, 58%). TLC (cyclohexane/ethyl acetate 70:30) R_f 0.77; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.17 (dd, *J* = 6.3, 1.2 Hz, 2H), 4.30 (s, 2H), 6.08 (dt, *J* = 15.9, 6.3 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 7.07 (t, *J* = 7.9 Hz, 1H), 7.16–7.33 (m, 3H), 7.36 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.5 (t, *J* = 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 57.9, 71.0, 85.1, 87.1, 114.4 (2C), 122.4, 123.2, 125.1, 128.1 (2C), 129.7, 130.1, 130.7, 132.0, 133.6, 134.9, 159.8.

(*E*)-1-Methoxy-4-(3-(2-methyl-3-phenylallyloxy)prop-1-ynyl)benzene (2g): Following the same procedure as for the synthesis of **2f**, in the presence of CuI (103 mg, 0.1 equiv) and $PdCl_2(PPh_3)_2$ (190 mg, 0.05 equiv), 1-methoxy-4-iodobenzene (1.52 g, 1.2 equiv) in distilled diisopropylamine (10 mL), (*E*)-(2-methyl-3-(prop-2-ynyloxy)prop-1-enyl)benzene [77] (1 g, 1 equiv) was transformed to **2g** (896 mg) in 57% yield. TLC (cyclohexane/ethyl acetate 90:10) R_f 0.71; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (d, *J* = 1.2 Hz, 3H), 4.07 (s, 3H), 4.44 (d, *J* = 0.9 Hz, 2H), 4.66 (s, 2H), 6.83 (s, 1H), 7.11 (m, 2H), 7.68–7.48 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 55.3, 57.8, 76.0, 83.8, 86.2, 113.9, 114.8, 126.5, 127.8, 128.1 (2C), 128.9 (2C), 133.3 (2C), 134.5, 137.4, 159.7.

(*E*)-1-Bromo-3-(3-(2-methyl-3-phenylallyloxy)prop-1-ynyl)benzene (2h): Following the same procedure as for the synthesis of **2f**, in the presence of CuI (62 mg, 0.1 equiv) and $PdCl_2(PPh_3)_2$ (115 mg, 0.05 equiv), 1-bromo-3-iodobenzene (0.53 mL, 1.3 equiv) in distilled diisopropylamine (6.8 mL), (*E*)-(2-methyl-3-(prop-2-ynyloxy)prop-1-enyl)benzene [77] (611 mg, 1 equiv) was transformed to **2h** (851 mg) in 76% yield. TLC (cyclohexane/ethyl acetate 90:10) R_f 0.63; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (d, *J* = 1.3 Hz, 3H), 4.31 (d, *J* = 0.8 Hz, 2H), 4.53 (s, 2H), 6.71 (d, *J* = 1.0 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.36–7.56 (m, 6H), 7.58 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.75 (t, *J* = 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 58.0 (2C), 85.1, 87.1, 122.5, 125.1, 127.0, 128.3, 128.5 (2C), 129.3 (2C), 130.1, 130.7, 132.0, 134.7, 134.9, 137.7.

General procedure for Au(I)-catalyzed cycloisomerization reactions: A mixture of L-$(AuCl)_2$ (L = (*R*)-4-MeO-3,5-(*t*-Bu)$_2$MeOBIPHEP) (3 mol %) and AgOTf (or $AgNTf_2$) (6 mol %) in distilled toluene (0.5 M) was stirred under an argon atmosphere at room temperature for 30 min. Enyne (1 equiv) was then added and the mixture stirred until completion of the reaction. The mixture was then filtered through a short pad of silica to eliminate the catalyst (EtOAc) and the solvents were concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (petroleum ether/ethyl acetate 98:2 to 80:20 v/v) if necessary.

6-(3-Bromophenyl)-7-(4-methoxyphenyl)-3-oxabicyclo[4.1.0]hept-4-ene (4f): TLC (cyclohexane/ethyl acetate 80:20) R_f 0.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (d, *J* = 5.4 Hz, 1H), 2.65 (d, *J* = 6.0 Hz, 1H), 3.61 (s, 3H), 3.96 (dd, *J* = 10.6, 1.9 Hz, 1H), 4.30 (d, *J* = 10.6 Hz, 1H), 5.21 (d, *J* = 6.0 Hz, 1H), 6.18 (d, *J* = 6.0 Hz, 1H), 6.52–6.65 (m, 4H), 6.86–6.92 (m, 2H), 7.12–7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 30.3, 37.3, 55.5, 61.6, 111.0, 113.7 (2C), 122.5, 128.7, 129.0 (2C), 129.4, 129.9, 130.1, 133.0, 141.2, 142.8, 158.2; HPLC (Chiralpack AD, hexane/propan-2-ol (97:3), flow rate 1.0 mL/min, λ = 215 nm): retention times 7 and 7.5 min, ee 95%; $[\alpha]_D^{23}$ −18.6 (*c* 1, $CHCl_3$).

6-(4-Methoxyphenyl)-1-methyl-7-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (4g): TLC (cyclohexane/ethyl acetate 90:10) R_f 0.66; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3H), 2.84 (s, 1H), 3.73 (d, J = 10.4 Hz, 1H), 3.80 (s, 3H), 4.15 (d, J = 10.4 Hz, 1H), 5.19 (d, J = 5.8, 1 Hz, 1H), 6.21 (d, J = 5.8 Hz,1H), 6.80–6.86 (m, 4H), 7.01–7.04 (m, 2H), 7.12–7.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 31.6, 35.2, 38.2, 55.2, 67.8, 113.7, 114.5, 125.4, 127.5 (2C), 130.0 (2C), 130.7, 132.1 (2C), 137.5, 140.0, 158.1; HPLC (Chiralcel OJ, hexane/propan-2-ol (99/1), flow rate 1.0 mL/min, λ = 215 nm): retention times 20.3 and 27.1 min, ee 99%; $[\alpha]_D^{23}$ +26.1 (*c* 1, $CHCl_3$).

6-(3-Bromophenyl)-1-methyl-7-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (4h): TLC (cyclohexane/ethyl acetate 90:10) R_f 0.71; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 2.80 (s, 1H), 3.64 (d, J = 10.5 Hz, 1H), 4.07 (d, J = 10.5 Hz, 1H), 5.09 (d, J = 5.8 Hz, 1H), 6.16 (d, J = 5.8 Hz, 1H), 6.75 (d, J = 2.1 Hz, 1H), 6.78 (d, J = 4.0 Hz, 1H), 6.92 (dt, J = 7.7, 1.4 Hz, 1H), 7.00–7.20 (m, 5H), 7.29 (dt, J = 7.8, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 33.2, 36.5, 39.7, 68.9, 114.6, 123.5, 127.2, 129.0 (2C), 131.1 (2C), 131.2, 131.3 (2C), 135.3, 138.2, 142.0, 142.5; HPLC (Chiralpak IA, hexane/propan-2-ol (99.9:0.1), flow rate 0.5 mL/min, λ = 215 nm): retention times 11.8 and 12.6 min, ee 73%; $[\alpha]_D^{23}$ +11.7 (*c* 1, $CHCl_3$).

Supporting Information

Supporting Information File 1

Spectral data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-116-S1.pdf]

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Recent developments in gold-catalyzed cycloaddition reactions

Fernando López*[1] and José L. Mascareñas*[2]

Review

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Address:
[1]Instituto de Química Orgánica General, CSIC, C/ Juan de la Cierva 3, 28006, Madrid, Spain, (+) 34 915622900, Fax: (+) 34 915644853 and [2]Departamento de Química Orgánica, Centro Singular de Investigación en Química Biológica y Materiales Moleculares, y Unidad Asociada al CSIC. Universidad de Santiago de Compostela, Avda. de las Ciencias, s/n, 15782, Santiago de Compostela, Spain, (+) 34 981563100 Fax: (+) 34 981595012

Email:
Fernando López* - fernando.lopez@iqog.csic.es;
José L. Mascareñas* - joseluis.mascarenas@usc.es

* Corresponding author

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Abstract

In the last years there have been extraordinary advances in the development of gold-catalyzed cycloaddition processes. In this review we will summarize some of the most remarkable examples, and present the mechanistic rational underlying the transformations.

Introduction

In modern organic synthesis, the criteria of efficiency, versatility, economy and ecology are of paramount importance [1]. Consequently, nowadays there is an increasing demand for the development of methods and strategies that allow the transformation of readily available precursors into target-relevant products in a rapid, economical and efficient manner. Cycloaddition reactions are among the synthetic tools that best fit these criteria, because by allowing the generation of at least two bonds and one cycle in a single operation, they produce a rapid increase in skeletal and also stereochemical complexity, and this is usually beneficial in terms of shortening the access to polycyclic products. Importantly, they generally involve the simple addition of two or more molecules, thereby being atom economical, and take place with high regio- and stereocontrol [2,3]. Unfortunately, the realm of classical cycloaddition reactions is relatively small and restricted to precursors presenting suitable electronic properties. In this regard, transition metal complexes, owing to their multiple coordination and activation properties, offer excellent opportunities for the discovery of new cycloaddition alternatives, and in many cases they can be used in a catalytic manner.

Although transition metal-catalyzed cycloadditions have been known since the mid-20th century, it was not until the 80s and 90s that they were recognized as versatile and powerful synthetic tools. So far, most examples of transition metal-catalyzed

cycloadditions have involved the use of rhodium, ruthenium, cobalt, nickel or palladium catalysts [4]. In recent years, however, platinum and particularly gold complexes have also emerged as excellent catalysts for the promotion of novel types of cycloaddition reactions, usually involving non-activated unsaturated systems (e.g., alkynes, allenes, alkenes or 1,3-dienes) [5-12].

Today it is well known that the excellent reactivity of these group-11 catalysts can in part be explained in terms of relativistic effects, particularly marked in the case of gold [13,14], that induce the contraction of 6s and the expansion of 5d orbitals. As a consequence this metal exhibits singular characteristics, such as a high carbophilicity, affinity for π-unsaturated systems (e.g., alkynes, alkenes or allenes), and a low propensity to participate in typical redox processes characteristic of other transition metal catalytic cycles (e.g., oxidative additions and reductive eliminations). Therefore, platinum(II) and particularly gold(I) or (III) complexes tend to activate alkynes, alkenes or allenes in a highly chemoselective manner; activation that opens interesting reaction pathways that usually involve carbocationic intermediates. Also very important is the possibility of modulating the properties of the metal through modification of its ancillary ligands (e.g., phosphines, *N*-heterocyclic carbenes, etc.), which considerably widens the potential and versatility of these catalysts, and in particular of those consisting of cationic gold(I) complexes (e.g., ligand–Au^+).

In this context, a number of research groups have in recent years embarked on the design and development of new cycloaddition reactions promoted by gold(I) and (III) catalysts, and hence the field has experienced a remarkable expansion. In the following section, we summarize some of the most recent contributions, organized according to the type of unsaturated system that is initially activated by the electrophilic gold complex [12].

Related Pt-catalyzed cycloadditions will only be mentioned when required in the context of a particular gold-catalyzed process, or to highlight the differences between these carbophilic catalysts. On the other hand, dipolar cycloaddition reactions in which the gold complex does not activate π-bonds, but rather behaves as a more conventional Lewis acid, are not discussed [15-17].

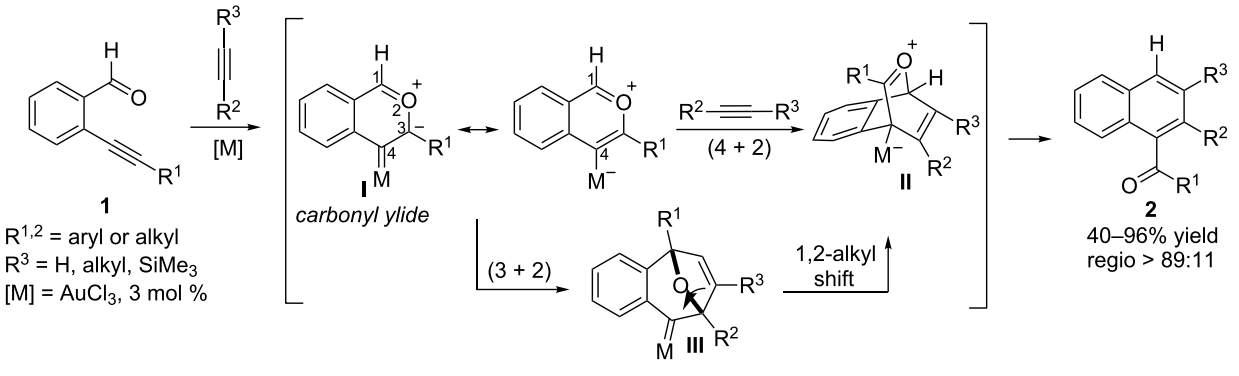
Review

Cycloadditions initiated by gold-activation of alkynes

Many examples of homogeneous catalysis employing gold complexes exploit the ability of these metal catalysts to bind chemoselectively to C–C triple bonds, promoting a subsequent attack of a nucleophile on these activated unsaturated systems. Although these metal carbophilic catalysts also coordinate to alkenes, dienes and allenes in a similar way [18-22], nucleophiles seem to have a kinetic preference for attacking activated alkynyl systems, which warrants high chemoselectivities.

Based on this reactivity pattern, several groups have demonstrated that certain substrates containing an alkyne and a carbonyl unit can be transformed, under Au(I/III) catalysts, into gold-containing zwitterionic intermediates that undergo different types of cycloaddition reactions with alkynes, alkenes or other unsaturated groups present in the reaction media. The cycloaddition usually generates a metal carbene that evolves through different pathways depending on the catalyst and on the reaction components. The reaction therefore can provide a variety of interesting polycyclic systems.

For example, Yamamoto reported in 2002 a $AuCl_3$-catalyzed formal (4 + 2) [23] benzannulation between *ortho*-alkynylbenzaldehydes of type **1** and alkynes (Scheme 1) [24,25]. The mechanism proposed by the authors involves an initial *5-endo* nucleophilic attack of the carbonyl moiety on the metal–alkyne



Scheme 1: $AuCl_3$-catalyzed benzannulations reported by Yamamoto.

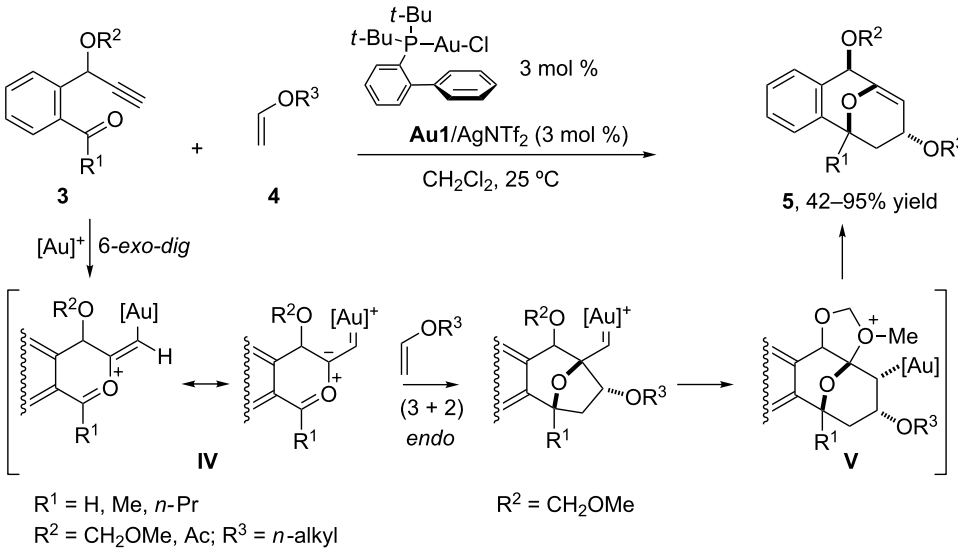
complex to generate a carbonyl ylide intermediate **I**, which undergoes a regioselective (4 + 2) cycloaddition with the external alkyne. A subsequent elimination process on the resulting intermediate **II** accounts for the formation of the naphthyl ketone products **2**, which were isolated in good yields. More recently, in 2004, Straub and coworkers reported a DFT study on these cycloadditions that led them to propose a modification of the aforementioned mechanistic pathway [26]. According to the theoretical data, the formal (4 + 2) cycloaddition would indeed comprise a two-step process consisting of a dipolar (3 + 2) cycloaddition of the carbonyl ylide **I** to afford a carbene species **III** [27,28], followed by a 1,2-alkyl migration to yield the previously suggested intermediate **II** (Scheme 1).

The synthetic utility of these cycloadditions has also been explored, and recently an intramolecular version was applied to the synthesis of the angucyclinone antibiotics, (+)-ochromycinone and (+)-rubiginone B_2 [29-32].

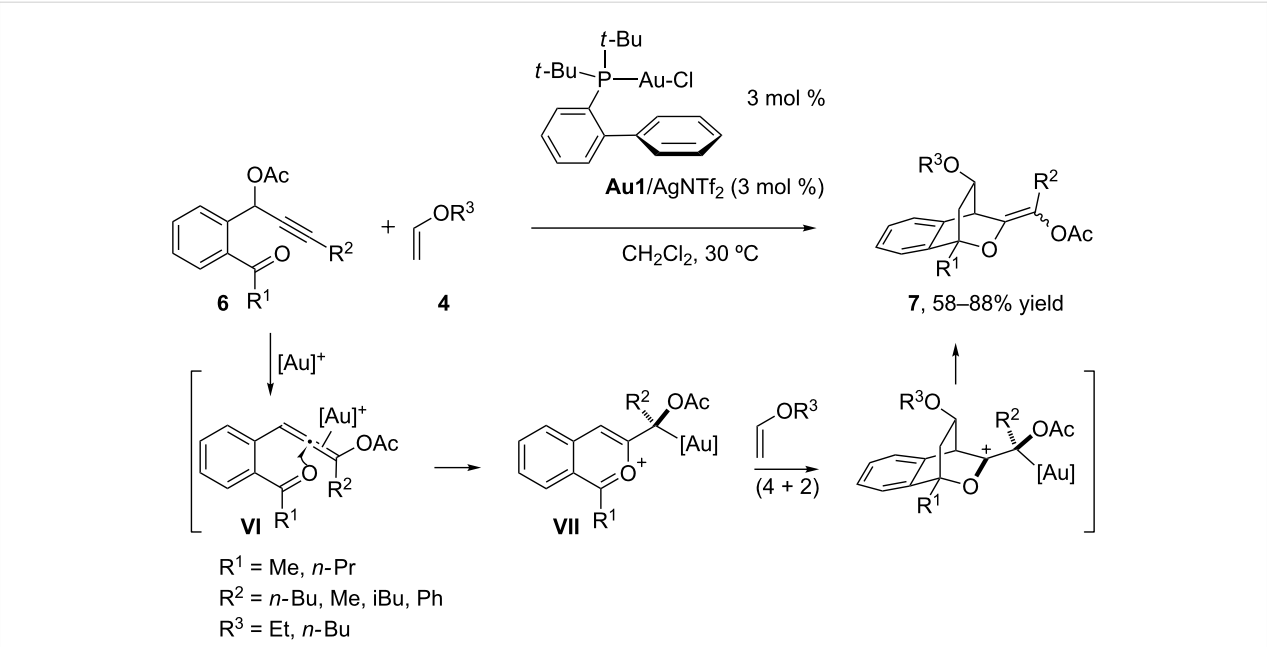
Closely related dipolar cycloadditions involving zwitterionic intermediates similar to **I** have also been developed with other transition metal catalysts such as tungsten, rhodium or platinum [32-35]. In particular, important developments were recently achieved with platinum catalysts [36,37], including the first enantioselective examples of these type of cycloadditions promoted by a chiral cationic platinum–diphosphine catalyst [38].

In contrast to these examples that proceed through an initial *endo-dig* cyclization and generate gold–carbonyl ylide species, the group of Liu recently demonstrated that it is also possible to produce alternative, reactive, zwitterionic intermediates of type **IV** through an *exo-dig* cyclization process when using 1-oxo-5-ynes such as **3** and a cationic gold complex prepared in situ from P(*t*-Bu)$_2$(*o*-biphenyl)AuCl (**Au1**) [39] and $AgNTf_2$ [40]. These dipolar intermediates undergo a cycloaddition with an external vinyl ether **4**, leading to interesting 9-oxabicyclo[3.3.1]nona-4,7-dienes **5** in good yields (Scheme 2). In view of the highly stereoselective outcome of these reactions and the requirement of an alkoxy or acyloxy group at the propargylic position of **3**, the authors proposed a reaction pathway based on an initial (3 + 2) dipolar cycloaddition between the carbonyl ylide **IV** and the alkene, followed by a ring expansion (1,2-alkyl migration) that is assisted by the oxy group and generates the oxonium intermediate **V** (Scheme 2). A final elimination process regenerates the catalyst and affords the oxacyclic product **5**. Importantly, the reaction also proceeds with non-aromatic 1-oxo-4-alkoxy-5-ynes [40].

Curiously, when the substrate features an internal alkyne, such as in alkynyl acetate **6**, the reaction evolves through alternative mechanistic pathways [41]. In particular, Liu showed that in these cases, the gold activation of the alkyne promotes a 1,3-acyloxy shift that leads to ketone allenic intermediates of type **VI** (Scheme 3) [42,43]. Then, an intramolecular attack of the carbonyl group on the activated allene generates a benzopyrilium intermediate (**VII**) which undergoes a concerted and highly stereoselective (4 + 2) cycloaddition with the vinyl ether to yield, after the elimination of the gold catalyst, highly substituted oxacyclic systems **7** in good yields and with notable diastereoselectivities. Importantly, this reaction tolerates a wide range of vinyl ethers, and different substituents at the ketone



Scheme 2: Synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes from 1-oxo-4-oxy-5-ynes [40].



Scheme 3: Stereocontrolled oxacyclization/(4 + 2)-cycloaddition cascade of ketone–allene substrates [43].

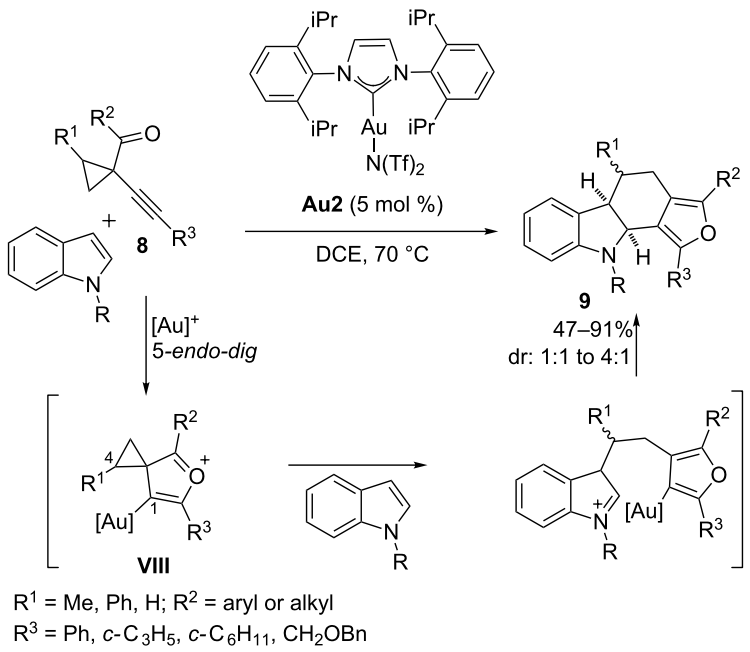
and alkyne units, as well as a variety of substituents at the aromatic ring of **6**.

During the last few years, the groups of J. Zhang and L. Zhang have independently described alternative procedures to transform substrates that incorporate carbonyl and alkyne units into polar intermediates that undergo subsequent intermolecular annulations with diverse partners.

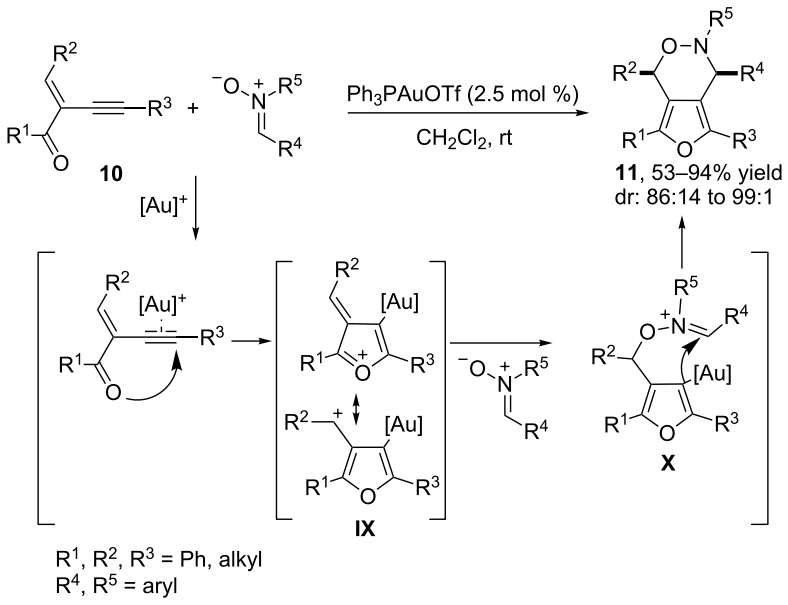
For example, in 2008, L. Zhang and coworkers demonstrated that a series of 1-(1-alkynyl)cyclopropyl ketones **8**, previously used by Schmalz for the synthesis of furans [44], can be used as precursors of reactive intermediates (**VIII**) that participate in (4 + 2) annulations with polarized alkenes such as indoles, carbonyls, imines or silyl enol ethers [45]. Thus, different types of 6-membered carbocycles and heterocycles were prepared in good yields and notable regioselectivities. An example of these annulations, using indoles as two carbon cycloaddition partners and $IPrAuNTf_2$ as catalyst [**Au2**, IPr = bis(2,6-diisopropylphenyl)], is shown in Scheme 4. The reaction is initiated by a *5-endo-dig* cyclization of the carbonyl oxygen onto the Au-activated C–C triple bond, giving rise to the oxocarbenium intermediate **VIII**. The authors proposed that these intermediates formally behave as an all-carbon 1,4-dipole that intermolecularly reacts with the indole providing the final polycyclic furan adducts **9** in a regioselective fashion (Scheme 4) [46].

In 2009, J. Zhang reported a gold(I)-catalyzed tandem cyclization/(3 + 3) cycloaddition of related 2-(1-alkynyl)-2-alken-1-ones **10** with nitrones [47]. The reactions provided a very practical entry to bicyclic oxazine derivatives **11**, which were obtained in good yields and excellent selectivities (Scheme 5). A plausible mechanism, proposed by the authors, consists of an initial activation of the alkyne group of **10** by the carbophilic gold catalyst ($Ph_3PAuCl/AgOTf$), followed by an intramolecular cyclization that generates the furanyl–gold complex **IX**. This intermediate is then trapped by the nucleophilic oxygen atom of the nitrone to afford **X**, which eventually evolves to the final cycloadduct by means of an intramolecular cyclization reaction, which generally proceeds with diastereoselectivities higher than 95:5 (Scheme 5). Interestingly, these cycloadditions can also be carried out in a highly enantioselective fashion using any of the bis(gold) complexes derived from (*R*)-C_1-tunephos [**L1**$(AuCl)_2$] or (*R*)-MeO-dtbm-biphep [**L2**$(AuCl)_2$], with the former being slightly more efficient in certain cases (Scheme 6) [48].

If instead of a nitrone, a nucleophilic α,β-unsaturated imine is used as the second cycloaddition component, furo[3,4-*c*]azepines such as **12** can be obtained [49]. An example of these cycloadditions is shown in Scheme 7. The mechanistic pathway proposed by the authors is also based on the interception of the furanyl–gold complex **IX** (see Scheme 5) by the nucleophile (the unsaturated imine), which is now followed by a 2,7-cyclization process and a ring cleavage to yield a furanyl intermediate featuring an iminium ion (**XI**). This species undergoes an intramolecular cyclization to yield the observed azepine product, and regenerates the gold catalyst.

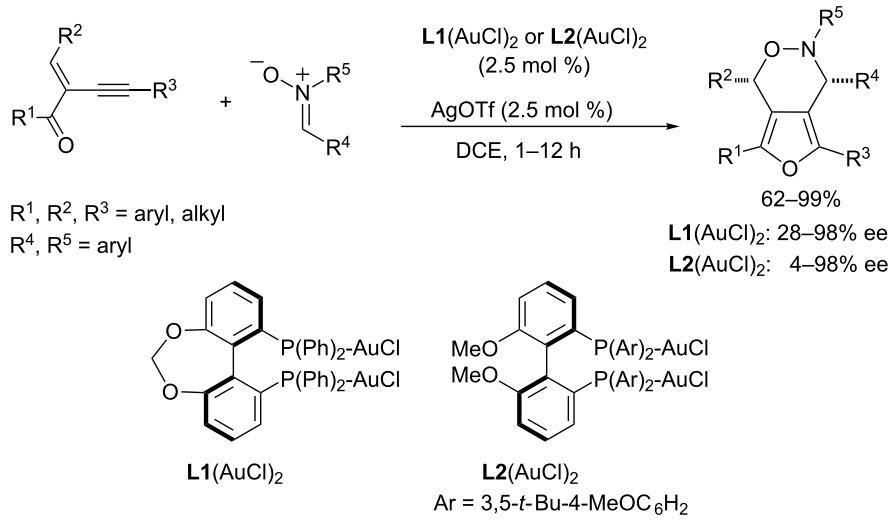


Scheme 4: Gold-catalyzed synthesis of polycyclic, fully substituted furans from 1-(1-alkynyl)cyclopropyl ketones [45].

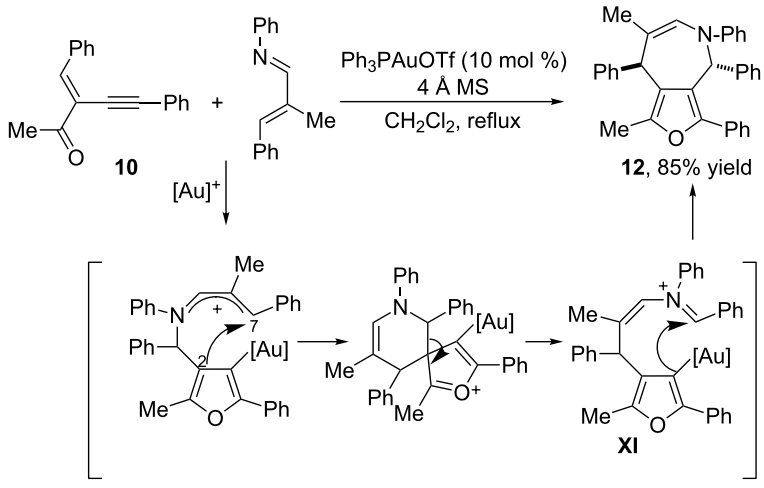


Scheme 5: Gold-catalyzed 1,3-dipolar cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with nitrones [47].

Very recently, the same group reported a related gold-triggered formal (4 + 3) cycloaddition between nitrones and 1-(1-alkynyl)oxiranyl ketones **13** [50]. The method provides heterobicyclic products of type **14** in a highly diastereoselective fashion. In these reactions, the gold complex **Au3**, derived from the bulky biaryl phosphine ligand RuPhos, provided the best reaction yields (Scheme 8). From a mechanistic point of view, the authors proposed an initial nucleophilic attack of the carbonyl oxygen on the gold(I)-activated alkyne to form a vinyl–gold intermediate **XII**, analogous to that previously shown in Scheme 5 (**IX**). Aromatization of this intermediate through C–C bond cleavage of the oxirane unit, followed by addition of the nitrone, delivers intermediate **XIII**, which evolves to the final cycloadduct by ring closure through a favored chair-



Scheme 6: Enantioselective 1,3-dipolar cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with nitrones [48].

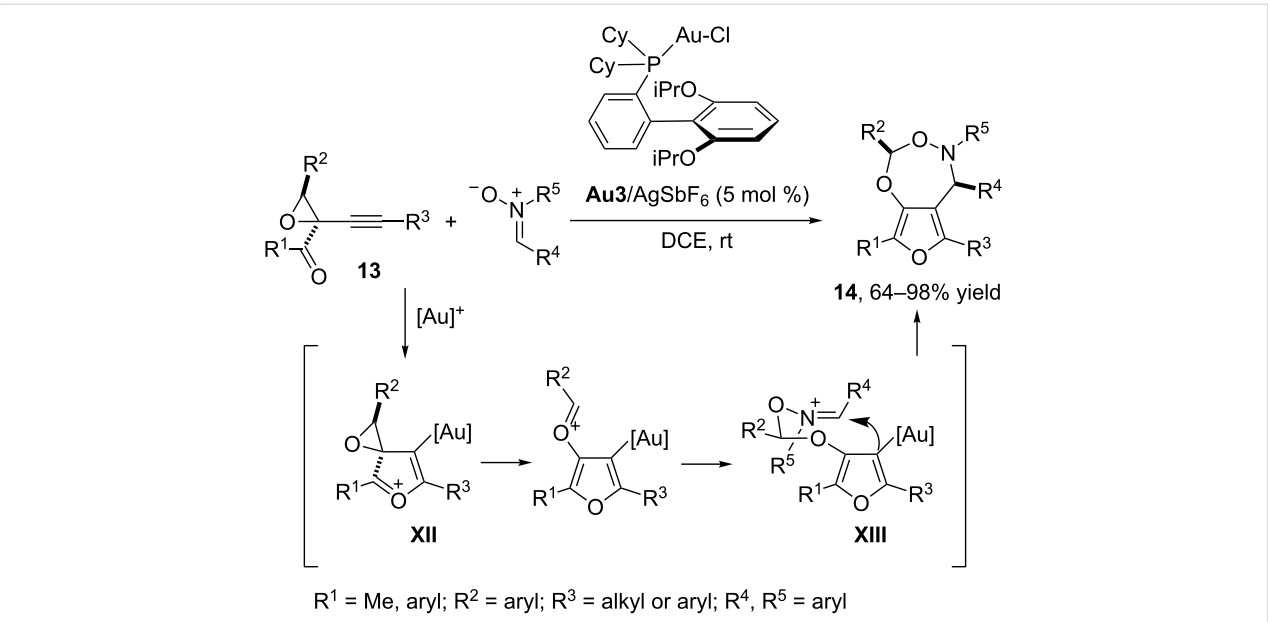


Scheme 7: Gold-catalyzed 1,3-dipolar cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with α,β-unsaturated imines [49].

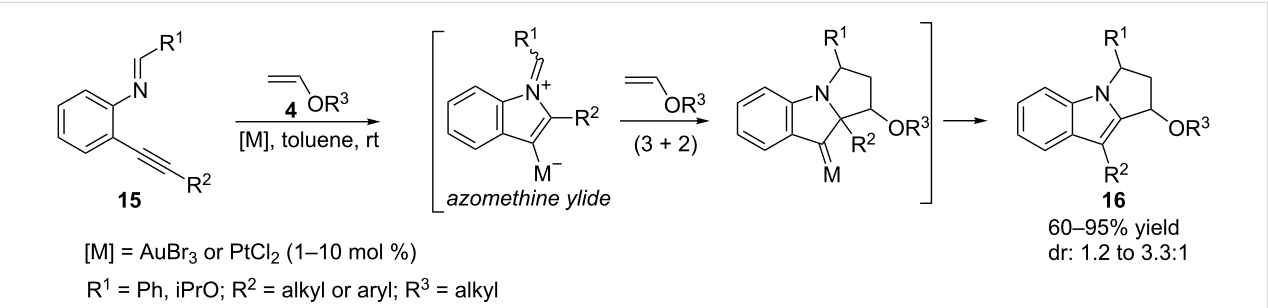
like conformation. An attack of the nitrone on intermediate **XII**, to directly generate species **XIII**, has also been proposed as an alternative pathway.

Common to all these reported cycloadditions is the initial nucleophilic addition of a carbonyl oxygen to the alkyne. As expected, an imine can also be used as a nucleophile, such as **15**, which leads to the generation of an azomethine ylide capable of participating in dipolar (3 + 2) cycloadditions to unsaturated systems such as electron-rich alkenes. Examples of these cycloadditions, originally reported under tungsten catalysis [51], have been recently reported by Iwasawa with Au(III) and Pt(II) catalysts [52], allowing the assembly of interesting tricyclic indole skeletons **16** in good yields (Scheme 9).

In 2008, Shin and coworkers reported an alternative procedure for the generation and subsequent cycloaddition of azomethine ylide intermediates under gold catalysis. Importantly, they demonstrated that the intramolecular attack of a nitrone oxygen to a tethered gold-activated alkyne leads, by means of an internal redox reaction, to an α-carbonyl carbenoid tethered to an imine group (Scheme 10). A subsequent attack of this imine to the carbenoid generates the reactive azomethine ylide intermediate **XIV**, which undergoes a (3 + 2) dipolar cycloaddition



Scheme 8: Gold-catalyzed (4 + 3) cycloadditions of 1-(1-alkynyl)oxiranyl ketones [50].

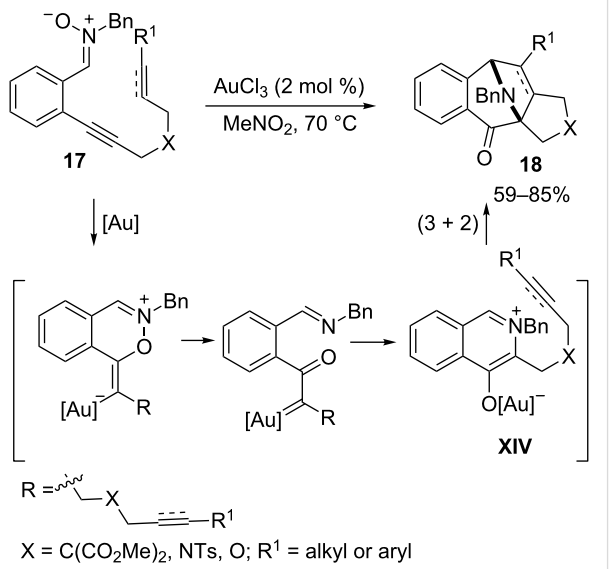


Scheme 9: (3 + 2) Cycloaddition of gold-containing azomethine ylides [52].

with an intramolecularly tethered alkene or alkyne. Thus, interesting azabicyclo[3.2.1]octane skeletons **18** could be obtained in a highly diastereoselective fashion, in good yields and in excellent atom-economy [53,54].

The above reactions involve an initial attack of a heteroatom on gold-activated alkynes. However, it is also possible to induce alternative cycloaddition reactions of alkynes that start by addition of a π-carbon nucleophile instead of a heteronucleophile. For instance it has been shown that it is possible to achieve gold-catalyzed formal intramolecular (4 + 2) cycloadditions between alkynes and non-activated dienes such as **19** (e.g., Scheme 11) [55]. This type of cycloaddition has been classically promoted by other metal complexes such as Rh [56], Ru [57], or Ni [58], among others, that are metals that usually promote reaction pathways via metallacyclic intermediates in which the metal atom undergoes redox changes. In the case of the gold-catalyzed process the mechanism does not involve a change in the oxidation level of gold. Indeed, it has been proposed that the alkyne activation promotes a cyclization that generates a key cyclopropyl carbene intermediate of type **XV**. This intermediate evolves to the final cycloadduct **20** through a rearrangement process in which the gold catalyst is regenerated.

When using a dienol silyl ether such as **21** (Scheme 12) as the diene component, the formation of the (4 + 2) products can be justified in terms of an alternative mechanism consisting of a 5-exo nucleophilic attack of the silyl enol ether moiety on the electrophilically activated alkyne, followed by addition of the generated alkenyl metallic species to the α,β-unsaturated silyl oxonium moiety, to give a bicyclic carbene intermediate **XVI** [59]. These species, which do not incorporate an α-hydrogen atom that could participate in a 1,2-hydrogen shift process, evolve through a 1,2-alkyl migration to give the ring-expanded products **22**, formally (4 + 2) cycloadducts. Interestingly, the stereoselectivity of these products is different from that of the



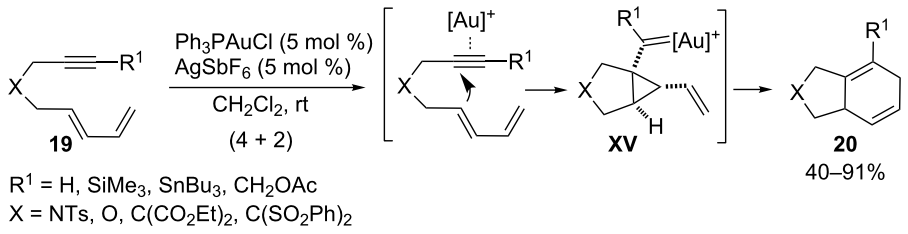
Scheme 10: Gold-catalyzed generation and reaction of azomethine ylides [53].

thermal Diels–Alder adducts that result when the substrates are heated under reflux in toluene.

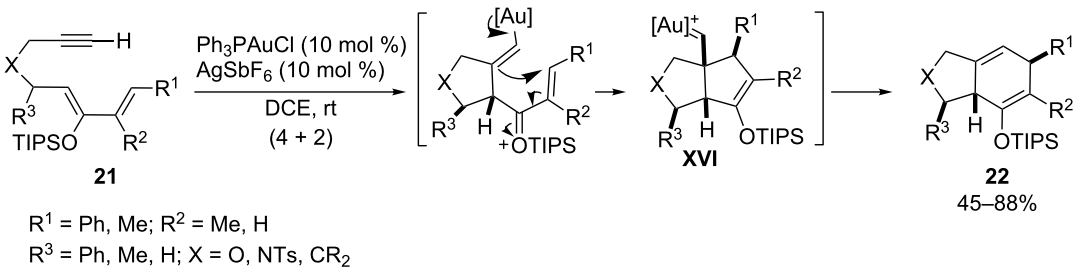
The use of 1-aryl-1,6-enynes such as **23** and cationic Au(I) catalysts also allows one to perform a complementary type of formal (4 + 2) cycloaddition reaction (Scheme 13). In these reactions, developed by Echavarren and coworkers, the intermediate carbene species of type **XVII** evolves through ring-opening of the cyclopropanic unit followed by a Friedel–Crafts-type cyclization, which completes the catalytic cycle and regenerates the gold catalyst [39,60].

Interestingly, small changes in the substitution of the alkene, or the use of other catalysts, such as $PtCl_2$ (under a CO atmosphere), affect the result of the annulation, such that it is now possible to induce (2 + 2) instead of (4 + 2) cycloadditions [61]. Very recently, Echavarren and coworkers reported an intermolecular variant of this type of (2 + 2) alkyne–alkene cycloaddition reaction (Scheme 14) [62,63].

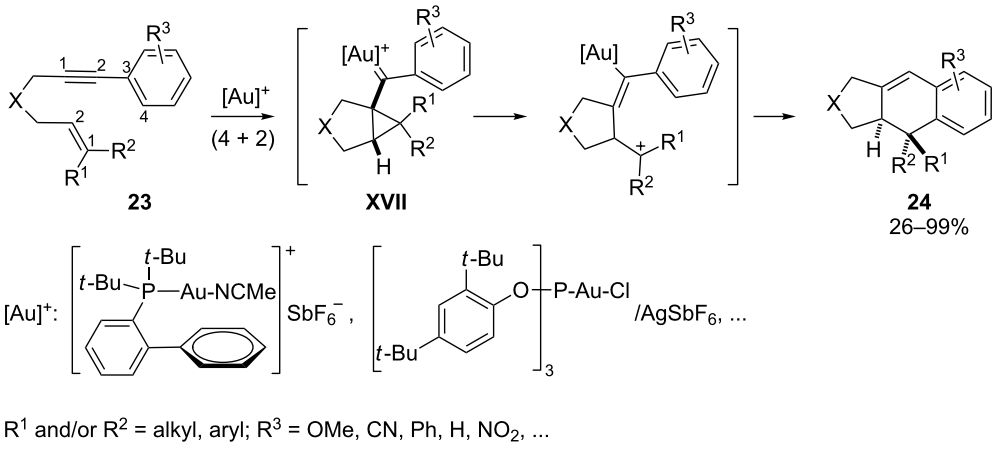
A less common annulation is the intramolecular (6 + 2) cycloaddition between non-activated alkynes and a cycloheptatriene. These cycloadditions were previously reported in the context of a stoichiometric chromium(0) activation of the triene unit [64]. The use of $AuCl_3$ or $PtCl_2$ rendered the reaction catalytic [65]. The mechanism entails a stepwise *exo*-cyclization of the cycloheptatriene onto the gold-activated alkyne, and ring closure of the resulting pentadienyl cation species (**XVIII**) to give the final tricyclic adducts in good yields. Although $PtCl_2$ is the most efficient catalyst for these intramolecular cycloadditions, the reaction of substrate **25** can also be performed with 5 mol % of $AuCl_3$ at room temperature, resulting in good yield (Scheme 15).



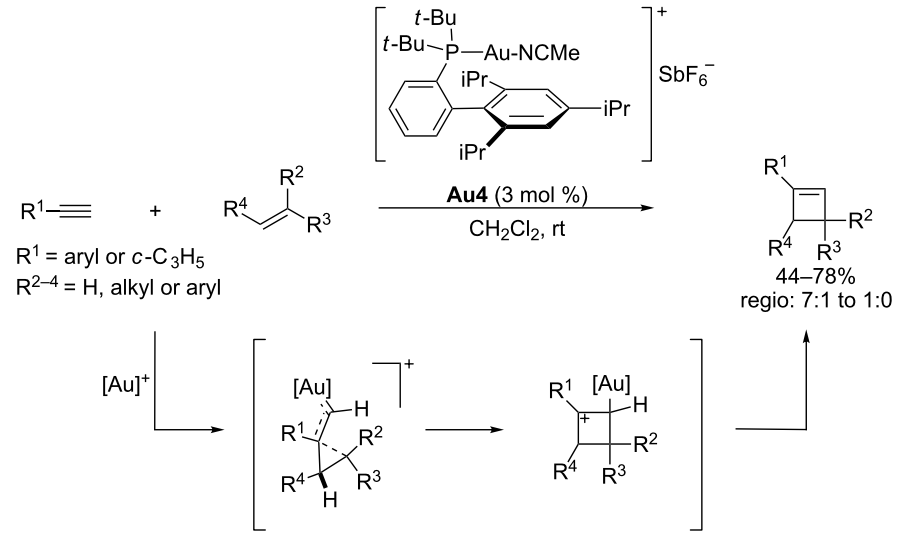
Scheme 11: Gold-catalyzed intramolecular (4 + 2) cycloadditions of unactivated alkynes and dienes [55].



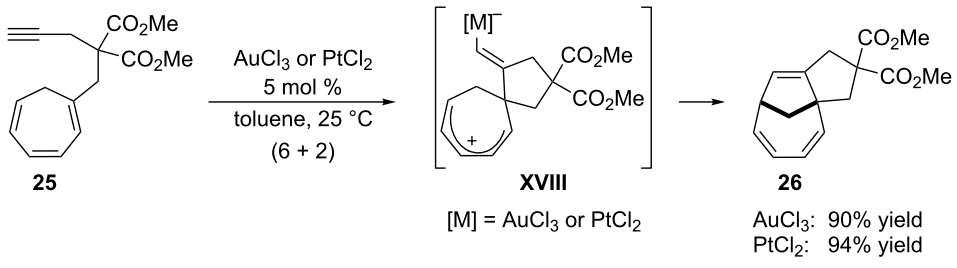
Scheme 12: Gold-catalyzed preparation of bicyclo[4.3.0]nonane derivatives from dienol silyl ethers [59].



Scheme 13: Gold(I)-catalyzed intramolecular (4 + 2) cycloadditions of arylalkynes or 1,3-enynes with alkenes [60].

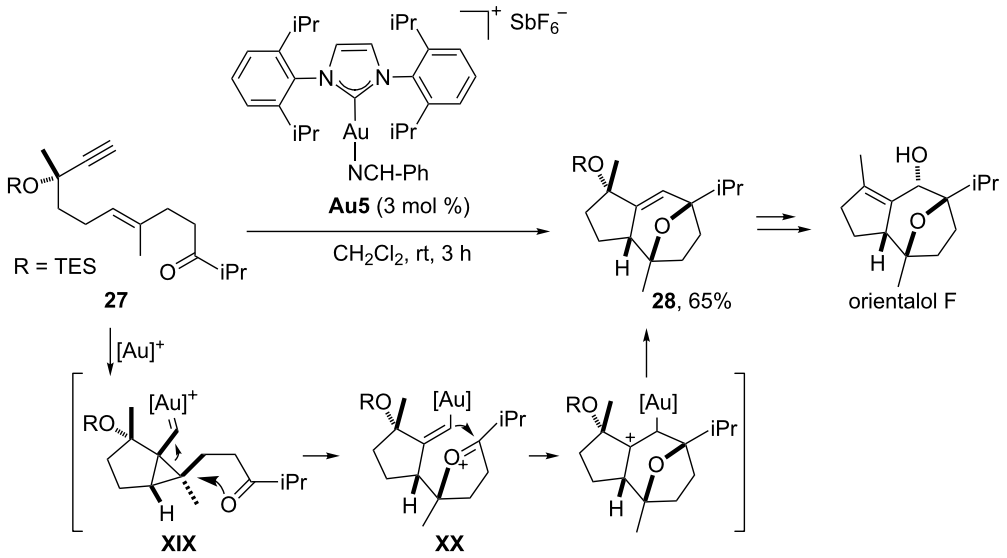


Scheme 14: Gold(I)-catalyzed intermolecular (2 + 2) cycloaddition of alkynes with alkenes [62].



Scheme 15: Metal-catalyzed cycloaddition of alkynes tethered to cycloheptatriene [65].

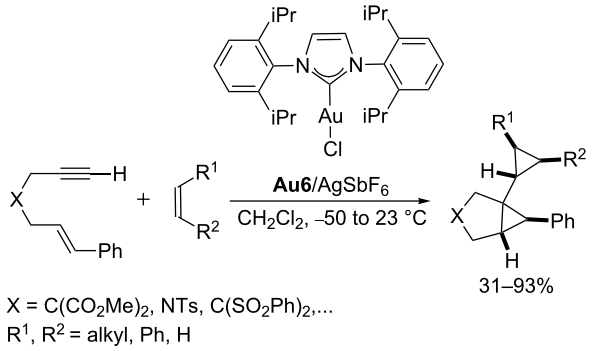
In addition to all of these cycloadditions involving the participation of an alkyne and a second component, several gold-catalyzed formal cycloadditions of three different reaction components have also been described. In particular, the group of Echavarren has recently developed a formal (2 + 2 + 2) gold-catalyzed synthesis of interesting oxa-bridged bicyclo[5.3.0]decanes from 1,6-enyne precursors equipped with an appropriately tethered carbonyl group (**27**, Scheme 16) [66].



Scheme 16: Gold-catalyzed cycloaddition of functionalized ketoenynes: Synthesis of (+)-orientalol F [68].

In these processes, the carbonyl acts as a nucleophile, attacking the gold–cyclopropyl carbene intermediate **XIX** to generate an oxonium cation species of type **XX**. Finally, a Prins-like cyclization renders the oxatricyclic product **28** and regenerates the gold(I) catalyst. Importantly, this strategy was successfully applied as a key step in the synthesis of orientalol F (Scheme 16) and englerins A and B [67-69].

Alternatively, the use of an alkene instead of a carbonyl nucleophile allows one to trap the carbene gold(I) intermediate in a (2 + 1) cycloaddition process that renders dicyclopropyl products. Both, intra- and intermolecular variants of these reactions have been reported in recent years (Scheme 17) [70,71].

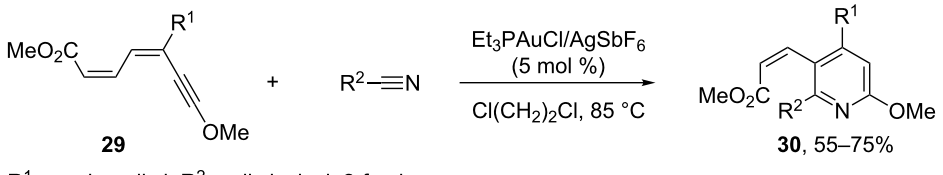


Scheme 17: Gold-catalyzed intermolecular cyclopropanation of enynes with alkenes [70].

Finally, the activation of alkynes with Au(I) has also been used recently to induce a hetero-dehydro Diels–Alder type of reaction. In particular, certain dienynes **29** with alkoxy groups at position 1 undergo a (4 + 2) cycloaddition with nitriles in the presence of cationic gold catalysts, such as $Et_3PAuCl/AgSbF_6$, to give tetrasubstituted pyridines **30** in good yields (Scheme 18) [72].

Cycloadditions initiated by gold-activation of propargyl esters

These cycloadditions are a special case of those based on the activation of alkynes and deserve a separate discussion due to their relevance, wide versatility, and mechanistic peculiarities.



Scheme 18: Gold-catalyzed intermolecular hetero-dehydro Diels–Alder cycloaddition [72].

Propargyl esters, usually acetates, are prone to undergo 1,2- or 1,3-acyloxy migrations in the presence of gold catalysts. The migration process begins with the nucleophilic intramolecular attack of the carboxyl unit on the metal-activated alkyne complex **XXI**. When a terminal alkyne is used (Figure 1, R = H), the 1,2-migration of the acetate moiety is preferred, affording an alkenyl–gold carbenoid species of type **XXIII**. In contrast, internal alkynes typically experience a 1,3-acyloxy migration rendering allenyl acetates of type **XXII** (Figure 1, R ≠ H), species which can be additionally activated by the metal catalyst to afford a wide range of gold-catalyzed transformations. Theoretical studies showed that all these species are in rapid equilibrium and the reactivity of the system depends not only on the substrate but also on the particular type of gold catalyst that is employed [73].

Several groups, in particular the group of Toste, have exploited the chemistry of these systems to develop new types of cycloaddition reactions [74-76]. For example, they showed that it is possible to trap the intermediate gold carbenoids of type **XXIII'**, resulting from 1,2-acyloxy migration on propargyl esters such as **31** (pivalates, acetates or benzoates), with external alkenes. Usually, the reactions are highly stereoselective, predominantly affording the *cis*-cyclopropanic adduct **32**. Moreover, the reaction tolerates a wide range of olefin substitutions (from mono- to tetra-substituted alkenes) and can be performed, in some cases, with excellent enantioselectivity using bis(gold) complexes derived from DTBM-Segphos (Scheme 19) [74-76].

Additionally, Toste and coworkers also described the reaction of propargylic benzoates with α,β-unsaturated imines to give azepine products **35** with excellent yields [77]. The formal (4 + 3) cycloaddition takes place in three basic stages: 1) Generation of the gold carbenoid by a 1,2-acyloxy migration, 2) attack of the imine on these electrophilic species to give an allyl–gold intermediate **XXIV**, and 3) final intramolecular cyclization to give the seven-membered heterocycle, a process

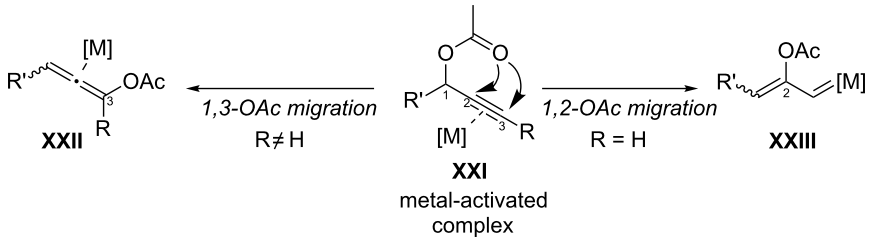
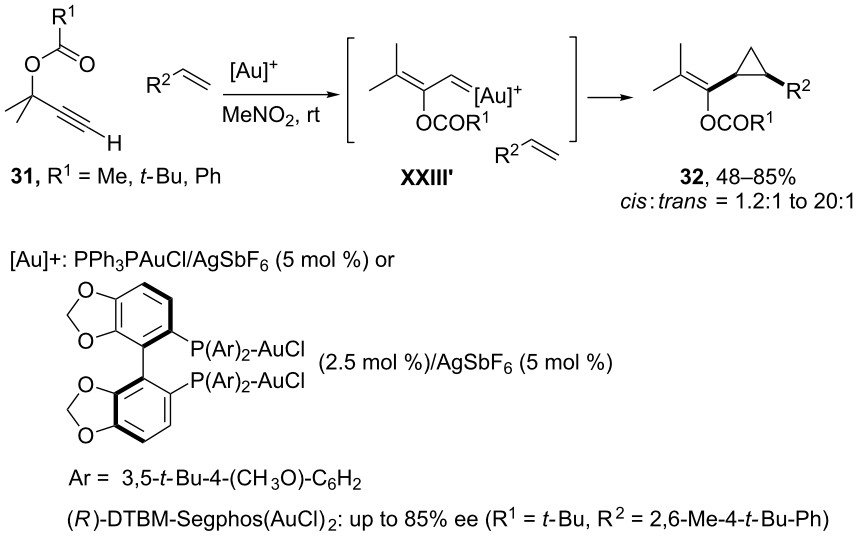
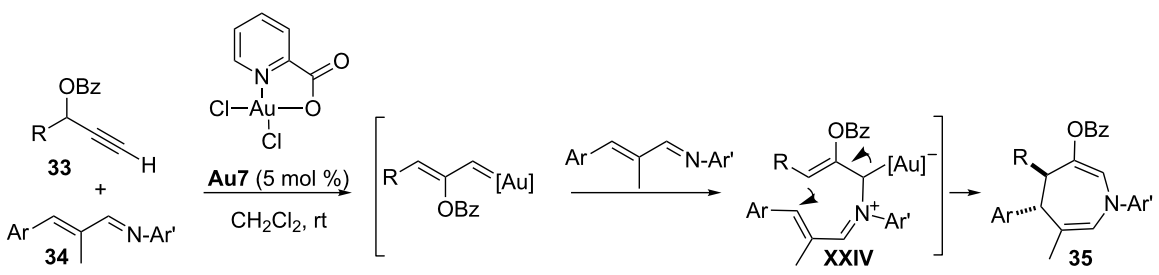


Figure 1: Gold-catalyzed 1,2- or 1,3-acyloxy migrations of propargyl esters.



Scheme 19: Gold(I)-catalyzed stereoselective olefin cyclopropanation [74].

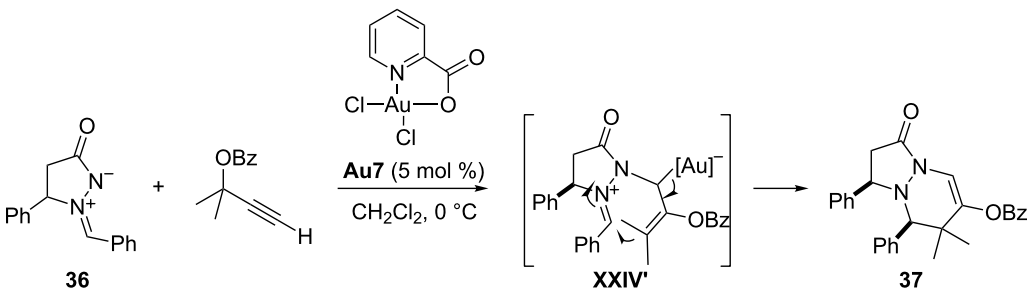


Scheme 20: Reaction of propargylic benzoates with α,β-unsaturated imines to give azepine cycloadducts [77].

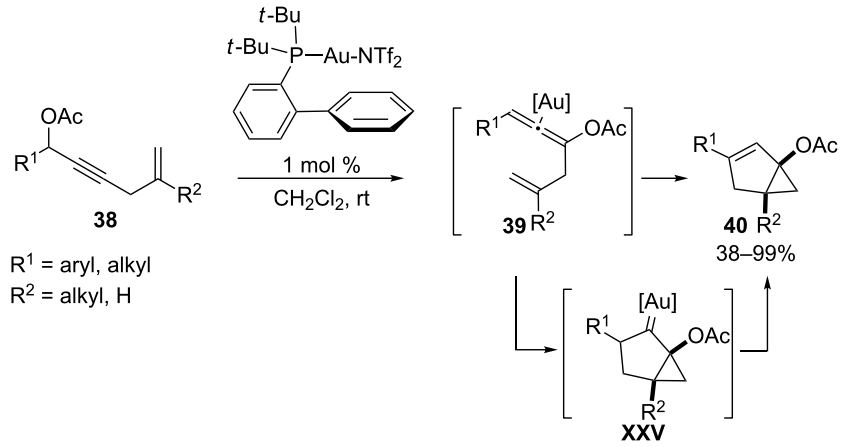
that occurs with high diastereoselectivity. Critical for the success of this reaction is the use of the picolinic acid-derived gold(III) catalyst **Au7** (Scheme 20).

This new gold-catalyzed transformation is somewhat related to those previously described by Doyle and by Barluenga that involved α,β-unsaturated imines and rhodium–vinyl carbenoids (Doyle) or Fischer carbenes (Barluenga). However, the stereochemical outcome of these three processes is different [78,79]. Therefore, the reactivity of gold species of type **XXIII** may be sometimes similar to that of other transition metal carbenoids or even to that of alkenyl Fischer carbenes. However, in many other cases, it is markedly different. For instance, while alkenyl Fischer carbenes act as two-carbon atom components in (3 + 2) cycloadditions with 1,3-dipoles [80], gold–carbenoids of type **XXIII**, generated from propargyl esters, can work as three-carbon synthons in cycloadditions with azomethine imines, also reported by Toste. An example is shown in Scheme 21 [81]. These (3 + 3) annulations take place through a stepwise mechanism related to that for the formation of azepines, consisting of a nucleophilic attack of the azomethine imines onto the intermediate alkenyl–gold carbenoid to afford an allyl–gold species **XXIV'**, which evolves to the final adduct through a stereoselective ring closure (Scheme 21). The scope of the method is rather broad, as it tolerates tertiary and secondary propargyl esters as well as the presence of several different substituents at the azomethine imine component. The picolinic acid-derived gold(III) catalyst **Au7** provided the best results.

On the other hand, allenyl acetates of type **XXII**, resulting from a 1,3-acyloxy migration of propargyl acetates can also participate in myriad gold-catalyzed cycloaddition reactions [82]. In 2006, Gagosz and co-workers reported a gold(I)-catalyzed isomerization of enynyl acetates such as **38** to afford bicyclo[3.1.0]hexenes **40** with excellent yields and stereoselectivities [83]. The authors demonstrated that these reactions are initiated by the 1,3-migration of the ester group to provide an allenyl ester intermediate **39**, which could be isolated and further transformed into the final products under the same catalytic conditions [84]. Thus, the authors proposed that the gold(I) catalyst is able to activate these allenic intermediates in situ, triggering a stepwise intramolecular (3 + 2) annulation reaction with the pendant alkene. This cycloaddition provides a cyclic gold carbene species **XXV**, which is eventually transformed into the final bicyclic adduct by a 1,2-hydrogen shift, with concomitant regeneration of the gold(I) catalyst (Scheme 22). Although the authors did not catalogue this method as a cycloaddition reaction, it can be considered as a pioneering example of a formal gold-catalyzed (3 + 2) intramolecular cycloaddition reaction, occurring in a stepwise fashion.



Scheme 21: Gold-catalyzed (3 + 3) annulation of azomethine imines with propargyl esters [81].

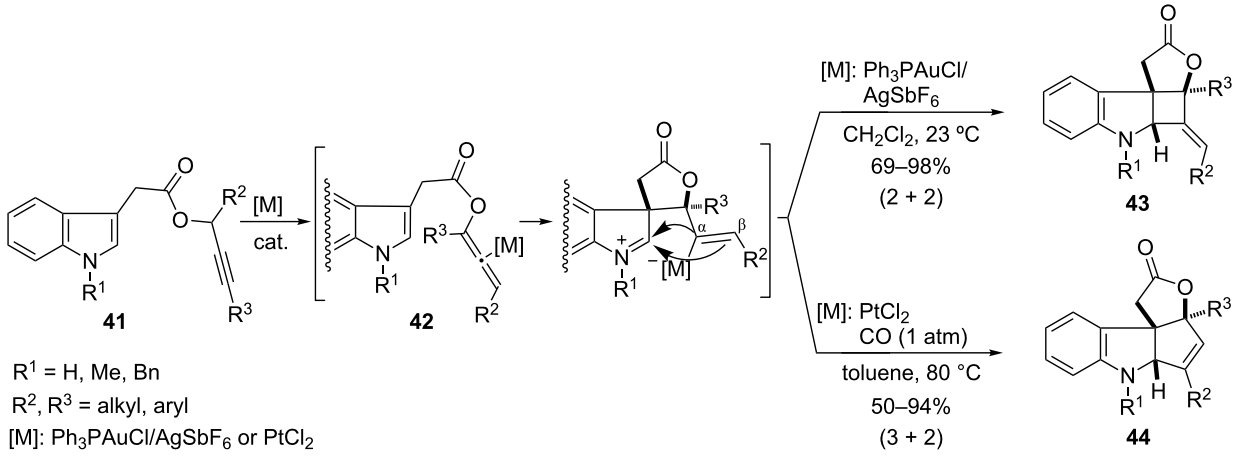


Scheme 22: Gold(I)-catalyzed isomerization of 5-en-2-yn-1-yl acetates [83].

The group of L. Zhang also developed several annulation reactions of allenyl esters generated in situ by a metal-catalyzed 1,3-migration of propargyl precursors [85,86]. In particular, they showed that propargyl indole-3-acetates **41** undergo gold(I)- or platinum(II)-catalyzed 1,3-migration to acyloxy allenic esters **42**; compounds which evolve in situ in the presence of the same metal catalyst to give adducts resulting from formal (3 + 2) and/or (2 + 2) annulation processes (Scheme 23). In the presence of $Ph_3PAuCl/AgSbF_6$, the (2 + 2) cycloaddition is favored furnishing **43** (upper arrow) [85]. However, when $PtCl_2$ (under an atmosphere of CO) is used, the major products are 2,3-indoline-fused cyclopentenes **44**, which arise from a formal (3 + 2) cycloaddition (lower arrow) [86]. Thus, the appropriate choice of a Pt or Au catalyst determines whether the allenyl intermediate **42** participates as a 2C- or as a 3C-atom component in the annulation. A precise explanation for this dichotomy has not been specifically addressed.

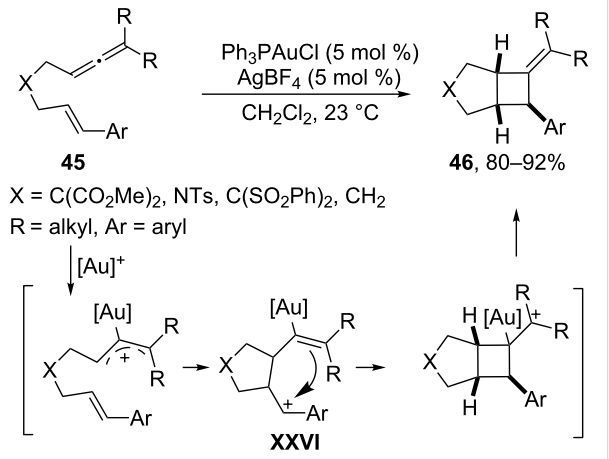
Cycloadditions initiated by gold-activation of allenes

Several gold catalysts can activate allenes in a very chemoselective way, triggering different types of cycloaddition processes. We have seen in the previous section some examples of cycloadditions involving allenes, in particular with acyloxy allenes, generated in situ by activation of propargyl esters with gold and/or platinum catalysts. It is therefore reasonable to assume that other allenes can also participate in these or related cycloaddition reactions. Indeed, the group of Toste described in 2007 a (2 + 2) intramolecular cycloaddition reaction between allenes and alkenes by gold catalysis [87]. The proposed mechanism is based on an activation of the allene to give a cationic metal species which undergoes a cyclization to give a stabilized carbocation **XXVI**, usually a benzylic cation (Scheme 24). A subsequent ring closure through the carbon adjacent to the gold atom provides the final cycloadduct **46**, featuring a four



Scheme 23: (3 + 2) and (2 + 2) cycloadditions of indole-3-acetates **41** [85,86].

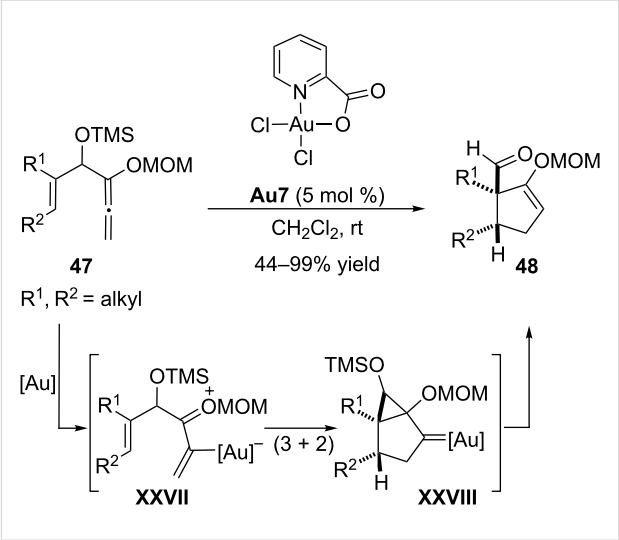
membered ring carbocycle. Importantly, these reactions could be rendered enantioselective with catalysts derived from DTBM-Segphos or, as recently demonstrated, with gold complexes derived from chiral phosphoramidites [88,89].



Scheme 24: Gold(I)-catalyzed (2 + 2) cycloaddition of allenenes [87].

Also in 2007, L. Zhang and co-workers reported another formal intramolecular cycloaddition between alkenes and allenes, in particular a (3 + 2) cycloaddition between allenyl MOM ethers and alkenes (MOM = methoxymethyl, Scheme 25) [90]. The activation of these allenes by the dichloro(pyridine-2-carboxylato)Au(III) complex **Au7** generates an oxocarbenium intermediate **XXVII**, which undergoes the (3 + 2) annulation with the alkene. The resulting bicyclo[3.1.0] species **XXVIII**, related to those previously proposed by Gagosz, evolves through a cyclopropane fragmentation and protodeauration to afford the products **48** in good yields and excellent stereoselectivities.

Based on these and other reports demonstrating the ability of gold(I) and platinum(II) catalysts to induce reactions of allenes through cationic intermediates [91-94], we investigated the possibility of using allenes as allyl cation surrogates, such that they could participate in concerted [4C(4π) + 3C(2π)] cycloadditions with conjugated dienes, a similar process to those previously reported between oxyallyl cations and dienes [95,96]. Initially, we found that $PtCl_2$ was an excellent catalyst for promoting these intramolecular [4C + 3C] cycloadditions between 1,3-dienes and allenes (Scheme 26) [97]. DFT calculations as well as experimental data agreed with a mechanistic pathway based on the metal activation of the allene to afford a metal–allyl cation intermediate of type **XXIX**, which subsequently undergoes a concerted (4 + 3) cycloaddition reaction with the diene. The resulting metal carbene species (**XXX**) eventually evolves through a 1,2-hydrogen shift, leading to seven-membered carbocycles **50** and regenerating the catalyst

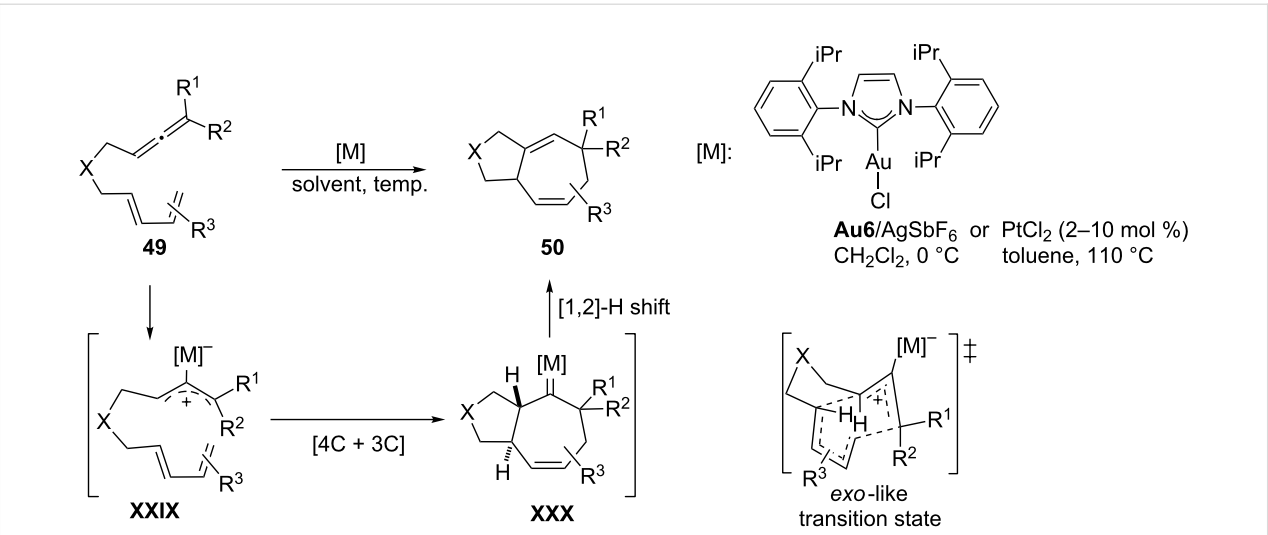


Scheme 25: Formal (3 + 2) cycloaddition of allenyl MOM ethers and alkenes [90].

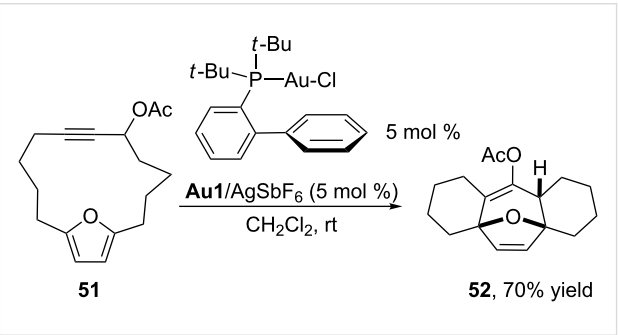
($PtCl_2$). In addition, DFT calculations suggested that gold catalysts could be even more active than $PtCl_2$. Accordingly, the use of a cationic Au(I) catalyst containing a σ-donating *N*-heterocyclic carbene ligand (**Au6**/$AgSbF_6$, Scheme 26) enabled these reactions at lower temperatures and increased the scope and synthetic utility of the process [98]. In general, the reactions are completely diastereoselective affording the products as a result of an *exo*-like approach of the allyl cation to the diene. The reaction tolerates a variety of substituents on the allene and the diene, providing a variety of bicyclo[5.3.0]decane systems in good yields.

Other gold(I) complexes, such as that including a highly donating biaryl di-*tert*-butylphosphine ligand **Au1**, also allow these cycloadditions, as recently reported by Gung and by Toste [99-101]. In particular, an interesting transannular cycloaddition was performed on the substrate **51** equipped with a furan (4C) and a propargyl acetate, which formally acts as an allene surrogate (Scheme 27).

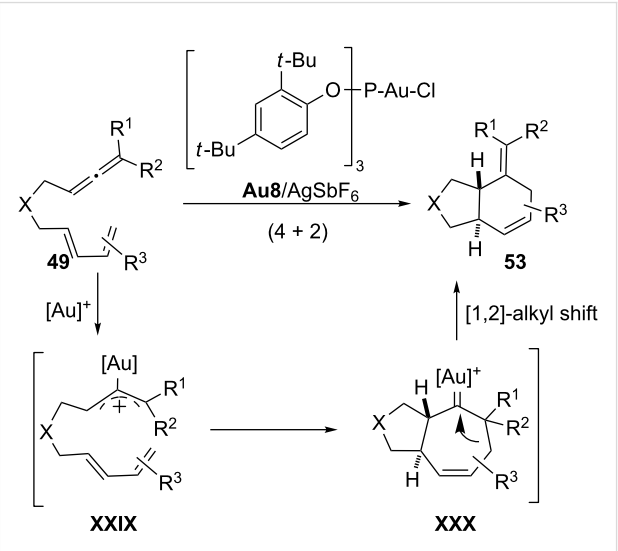
Curiously, the allenedienes **49**, when disubstituted at the distal position of the allene, give rise to formal (4 + 2) cycloaddition products **53** when treated with a gold(I) catalyst bearing a π-acceptor ligand, such as a triarylphosphite (**Au8**/$AgSbF_6$, Scheme 28) [98,99,102,103]. Several experimental results as well as theoretical calculations suggest that the observed (4 + 2) cycloadducts **53** are indeed the result of a ring contraction process (1,2-alkyl shift) in the initially formed cycloheptenyl–gold carbene intermediate **XXX** (Scheme 28). Thus, the ligand at gold determines the fate of this carbene and hence the formation of the (4 + 3) (**50**) or (4 + 2) (**53**) cycloadducts.



Scheme 26: (4 + 3) Cycloadditions of allenedienes [97,98].



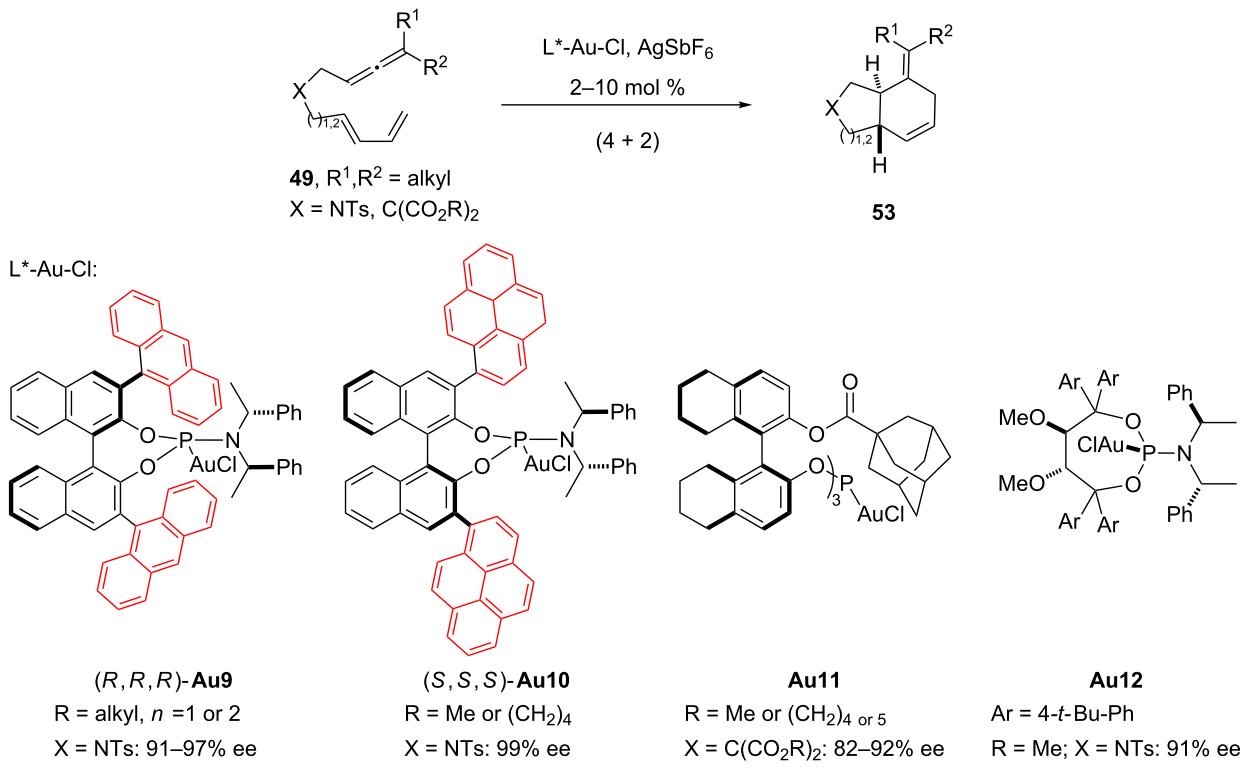
Scheme 27: Gold-catalyzed transannular (4 + 3) cycloaddition reactions [101].



Scheme 28: Gold(I)-catalyzed (4 + 2) cycloadditions of allenedienes [102].

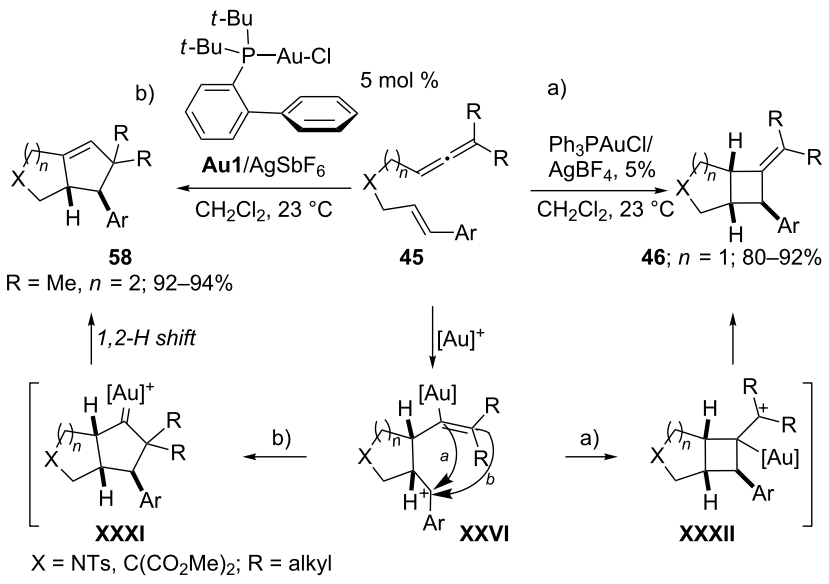
Based on the electronic similarity between phosphites and phosphoramidites, we also studied enantioselective variants of this cycloaddition using gold complexes derived from this highly versatile type of chiral ligand. We found that it was possible to obtain excellent enantioselectivities with gold complexes derived from bulky phosphoramidites with anthracenyl substituents at 3 and 3' positions of the binaphthol moiety (**Au9**, Scheme 29) [102]. Almost simultaneously, the group of Toste reported that related phosphoramidite–gold complexes, such as **Au10,** and the chiral gold catalyst **Au11** [104], derived from a C_3-symmetric phosphite ligand previously developed by Reetz and coworkers [105], are also capable of inducing excellent enantioselectivities in these (4 + 2) cycloaddition reactions of allenedienes. More recently, the group of Fürstner has also reported that Taddol-based phosphoramidite–gold complexes such as **Au12** (Scheme 29) are excellent catalysts for these (4 + 2) processes, as well as for the (2 + 2) cycloadditions of eneallenes such as those shown in Scheme 24 [88].

In addition to these allene–diene cycloadditions in which the type of gold catalyst determines whether the (4 + 2) or the (4 + 3) adduct is formed, Toste and Fürstner independently reported additional examples confirming that, depending on the ancillary ligands at gold, the allenes can behave either as 2C- or 3C-components in their intramolecular annulations to alkenes [99,106,107]. As previously shown in Scheme 24, the reaction of eneallene **45** with $Ph_3PAuCl/AgBF_4$ provides alkylidenecyclobutanes **46**, formally resulting from an internal (2 + 2) cycloaddition [87]. However, in 2009, Toste demonstrated that, when a gold catalyst such as **Au1**/$AgSbF_6$, with a more readily donating phosphine ligand is employed, the alternative (3 + 2) cycloaddition leading to bicyclo[4.3.0]nonanes **58** is favored



Scheme 29: Enantioselective gold(I)-catalyzed (4 + 2) cycloadditions of allenedienes [88,102,104].

(Scheme 30) [99]. The authors propose stepwise mechanisms proceeding through a common cationic intermediate **XXVI**, which can evolve into the cyclopentyl cycloadducts via the species **XXXI**. Alternatively, when the benzylic carbocation in **XXVI** is intercepted by the carbon atom bearing the gold atom, the (2 + 2) adduct **46** is formed. Nonetheless, the formation of adducts **46** by a ring contraction process in intermediate **XXXI** cannot be fully discarded.



Scheme 30: (3 + 2) versus (2 + 2) Cycloadditions of allenenes [87,99].

More recently, Fürstner and coworkers have further demonstrated this type of dichotomy depending on the electronic characteristics of the ligands at gold (Figure 2) [106]. In particular, they showed that the π-acceptor properties of NHC ligands such as **59** could be enhanced by introducing a second aromatic layer spanning the imidazopyridine-2-ylidene system, whereas the σ-donating abilities of both ligands remain basically equivalent.

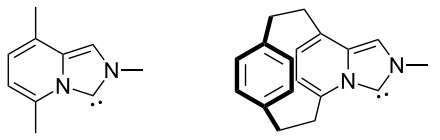
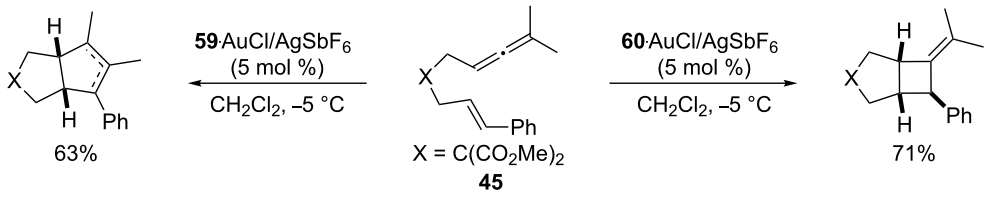


Figure 2: NHC ligands with different π-acceptor properties [106].

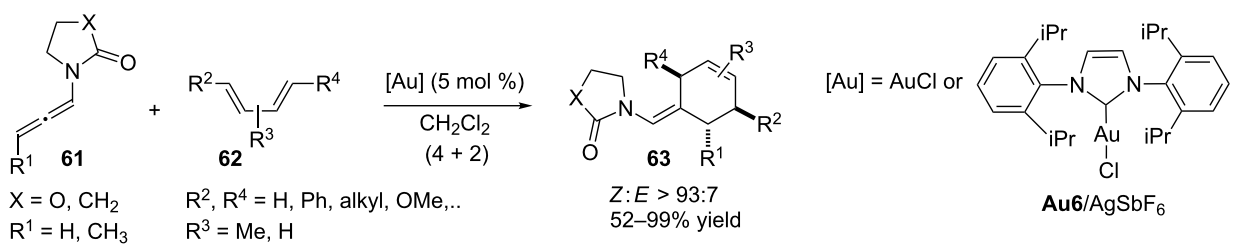
As a consequence, the new cyclophanic NHC ligand **60** and the related imidazopyridine-2-ylidene analog **59**, generate gold complexes that behave in a divergent manner. While complex **59**–AuCl, containing a poor π-acceptor ligand, is able to efficiently induce the (3 + 2) cycloaddition of eneallene **45** (R = Me, X = $C(CO_2Me)_2$, Ar = Ph, *n* = 1, Scheme 30), a related catalyst with the cyclophanic NHC ligand (**60**–AuCl) afforded the (2 + 2) cycloadduct with high selectivity and good yield (Scheme 31). From a mechanistic point of view, the authors suggested that both catalysts initially provide the common intermediate **XXVI** (Scheme 30). Then, a cationic catalyst derived from **59**–AuCl could favor the formation of the formal (3 + 2) cycloadduct via intermediate **XXXI**, that can also be interpreted as a gold-stabilized carbocationic species. On the contrary, a more electron-deficient catalyst such as **60**–AuCl/$AgSbF_6$ could favor the formation of intermediate **XXXII**, in which a cationic center is not directly bound to the gold complex, therefore leading to the (2 + 2) adduct (Scheme 30 and Scheme 31).

Importantly, the same NHC–Au complexes were also able to selectively induce either the (4 + 3) or the (4 + 2) cycloadditions of allenedienes **49** (R^1, R^2 = Me, R^3 = H, X = $C(CO_2Me)_2$). These examples clearly demonstrate the possibility of modulating the electronic properties of reactive intermediates generated upon activation of allenes with Au(I) complexes, and thereby influence the reaction outcome.

The development of intermolecular variants of gold-catalyzed cycloadditions with allenes remains much less studied, probably due to the inherent difficulties in controlling not only the chemo- but also the regioselectivity of the process. The first examples of an intermolecular cycloaddition with allenes and carbophilic catalysts were reported in 2009 by Iwasawa and consisted of an intermolecular (3 + 2) cycloaddition between allenes and enol silyl ethers, catalyzed by a platinum(II) catalyst [108]. Only in 2011, were the first examples with gold catalysts reported. In particular, an intermolecular (4 + 2) cycloaddition was described by our group between allenamides **61** and conjugated dienes **62** (Scheme 32); a process that provided a straight entry to a variety of differently substituted cyclohexenes **63**, and took place with excellent regio- and diastereoselectivity [109]. Almost simultaneously a (4 + 2) cycloaddition



Scheme 31: (3 + 2) versus (2 + 2) Cycloadditions of allenenes [106].



Scheme 32: Gold(I)-catalyzed intermolecular (4 + 2) cycloaddition of allenamides and acyclic dienes [109].

between allenyl ethers and dienes was also reported by Goeke using $Ph_3PAuCl/AgSbF_6$ as catalyst, although the scope was somewhat more limited. The mechanistic pathways of these reactions are under study (Scheme 32) [110].

Conclusion

In conclusion, in recent years there have been extraordinary advances in the development of gold-catalyzed cycloaddition reactions. The distinctive properties of these metal complexes compared to other, more conventional, transition metal catalysts (e.g., those based on Rh, Ir, Pd, Ru or Ni complexes) and, in particular, their high carbophilicity and ability to stabilize carbocationic intermediates, has allowed researchers to uncover new types of selective and very efficient cycloaddition reactions that would otherwise be unfeasible. Additionally, the scope and versatility of previously reported transition metal-catalyzed cycloaddition reactions (e.g., those based on tungsten or platinum catalysts) could be enhanced by using new gold catalysts. In the future, the current catalogue of cycloaddition reactions catalyzed by gold complexes, and in particular the number of enantioselective versions promoted by chiral gold complexes, is expected to grow.

Acknowledgements

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Efficient gold(I)/silver(I)-cocatalyzed cascade intermolecular N-Michael addition/intramolecular hydroalkylation of unactivated alkenes with α-ketones

Ya-Ping Xiao[1], Xin-Yuan Liu[2] and Chi-Ming Che[*1,2]

Full Research Paper

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Address:
[1]Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032 , P. R. China and [2]Department of Chemistry, State Key Laboratory of Synthetic Chemistry, and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

Email:
Ya-Ping Xiao - xiaoyaping82@hotmail.com; Xin-Yuan Liu - liuxy@hku.hk; Chi-Ming Che* - cmche@hku.hk

* Corresponding author

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Abstract

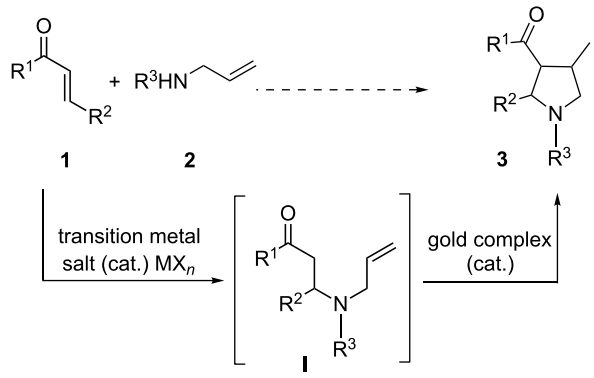
The gold(I)/silver(I)-cocatalyzed cascade intermolecular N-Michael addition/intramolecular hydroalkylation reaction offers a simple and efficient method for the synthesis of pyrrolidine derivatives in moderate to excellent product yields and with moderate to good diastereoselectivities. The reaction conditions and the substrate scope of this reaction are examined, and a possible mechanism involving $AgClO_4$ catalyzed intermolecular N-Michael addition and the subsequent gold(I)-catalyzed hydroalkylation is proposed.

Introduction

Gold complexes are presently receiving a surge of interest in the field of metal-catalyzed organic reactions. They have been shown to be versatile and efficient catalysts for the promotion of a large number of organic transformations, most of which are based on the propensity of gold ion to act as a soft and carbophilic Lewis acid to activate unsaturated C–C bonds towards nucleophilic attack [1-10] (for selected reviews on gold-catalyzed reactions see [1-9]). Based on this mode of acti-

vation, several methods for the gold-catalyzed inter- and intramolecular addition of oxygen- [11-15], nitrogen- [10,16-18] (for recent reviews on gold-catalyzed hydroamination see [16-18]), or carbon-nucleophiles [19-24] to unactivated alkenes [21-25] have been developed. On the other hand, in recent years, considerable efforts have been devoted to the development of dual-metal-catalyzed reactions as new strategies for the synthesis of organic compounds with intriguing diversity and selectivity [26-29] (for reviews on cooperative catalysis see [26,27] and for a general review on cocatalysis see [28]). This type of reaction could have the advantages of the combined characteristic features of two metals, often displaying unique reactivity, have a shortened synthetic route and generate less chemical waste. All of these features are of significant economic and environmental benefit. In this context, extensive studies have been conducted on the design and utilization of dual-metal catalyst systems in organic synthesis [26-40] (for recent examples of Au/Pd-cocatalysis see [30-33]; for Au/Mo-cocatalysis see [31,35]; for Au/Ag-cocatalysis see [36-38]; for Au/Yb-cocatalysis see [39] and for Au/Rh-cocatalysis see [40]). However, the use of homogeneous gold catalysts in cooperation with other metal catalysts has been reported only in a few cases [30-40]. In this work, we describe a highly efficient gold(I)/silver(I)-cocatalyzed cascade intermolecular N-Michael addition/intramolecular hydroalkylation process. A variety of pyrrolidine compounds were conveniently prepared in moderate to excellent yields and with moderate to good diastereoselectivities from the simple starting materials.

More recently, we have reported that gold(I) complexes can efficiently catalyze direct intramolecular hydroalkylation of unactivated alkenes with α-ketones, via the exo-trig cyclization, to build a variety of new five- and six-membered rings [24]. However, all of the substrates examined in this gold(I)-catalyzed reaction were prepared and isolated prior to use, and this is not desirable as the synthesis of these substrates could be tedious and time-consuming. The increasing demand for environmentally benign and economical synthetic processes calls for the development of cascade reactions for the efficient construction of cyclic compounds from simple starting materials [41]. We initially envisioned that the gold(I)-catalyzed cascade process could be established starting from the intermolecular N-Michael reaction of α,β-unsaturated ketone **1** and substituted allylamine **2** to furnish an α-ketone intermediate **I** [42-44] (for gold-catalyzed intramolecular N-Michael reaction see [42,43]), which further undergoes a subsequent gold(I)-catalyzed hydroalkylation to give pyrrolidine compounds **3** (Scheme 1); these compounds are versatile synthetic building blocks for organic synthesis and are important structural elements of many therapeutic drug molecules. Disappointingly, no conversion was observed when (*t*-Bu)$_2$(*o*-diphenyl)PAuOTf only was used as the catalyst. Since dual-metal-catalysis is of interest from the perspective of unique reactivity [26-40], we explored a new cascade reaction involving intermolecular N-Michael addition catalyzed by an appropriate transition metal salt and subsequent intramolecular hydroalkylation catalyzed by a gold complex (Scheme 1).

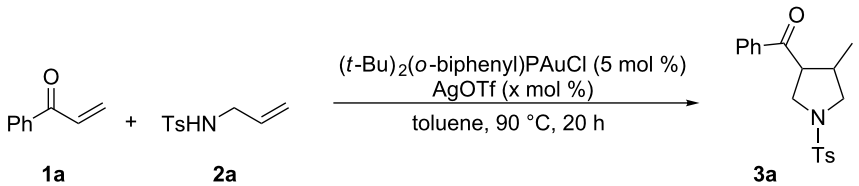


Scheme 1: Cascade intermolecular N-Michael addition/intramolecular hydroalkylation of unactivated alkenes with α-ketones catalyzed by a dual-metal catalytic system comprising a transition metal salt and a gold(I) complex.

Results and Discussion

The optimization of the reaction conditions was performed using the reaction of phenyl vinyl ketone (**1a**) with *N*-tosylallylamine (**2a**) in the presence of 5 mol % of (*t*-Bu)$_2$(*o*-diphenyl)PAuOTf. However, no desired product **3a** was observed (Table 1, entry 1). When using a combination of 5 mol % of (*t*-Bu)$_2$(*o*-diphenyl)PAuCl and AgOTf as catalyst, the corresponding product **3a** was obtained in 25% yield (Table 1, entry 2) (a small amount of silver salt may have remained in the reaction system when the mol ratio of silver salt to gold complex was 1:1, see [45]). Upon further increase of the AgOTf loading to 10 mol %, the corresponding product **3a** was formed in 58% yield with a diastereomeric ratio of 5.4:1 (Table 1, entry 3) [46]. Using a combination of 5 mol % of (*t*-Bu)$_2$(*o*-diphenyl)PAuCl and 15 mol % of AgOTf as a dual-metal catalyst system lead to the formation of pyrrolidine derivative **3a** as a 5.3:1 mixture of two diastereomers in 67% yield (Table 1, entry 4). The yield increased from 58% to 67% as the mol ratio of **2a** to **1a** was increased from 1.2/1 to 1.5/1 (Table 1, entries 4 and 5). However, the yield did not increase remarkably when the mol ratio of **2a** to **1a** was raised from 1.5/1 to 2.5/1 (Table 1, entries 4–7). As depicted in Table 1, varying the method of the addition of phenyl vinyl ketone (**1a**) to the reaction mixture did not have a noticeable effect on the yield of **3a** (Table 1, entries 8–11).

Table 1: The optimization of the reaction conditions.



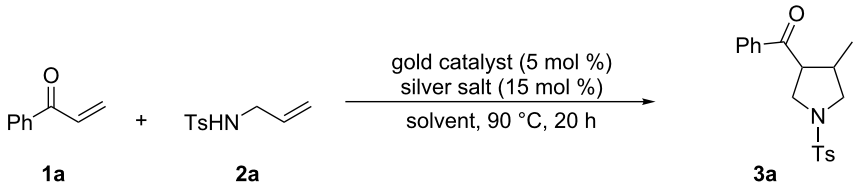
1a **2a** **3a**

entry[a]	x (mol %)	mol ratio (**2a**/**1a**)	*trans*/*cis*[b]	yield (%)[b]
1[c]	5	1.5/1	–	–[d]
2	5	1.5/1	1.4:1	25
3	10	1.5/1	5.4:1	58
4	15	1.5/1	5.3:1	67
5	15	1.2/1	5.7:1	58
6	15	2.0/1	5.9:1	66
7	15	2.5/1	5.5:1	64
8	15	1/1.5	5.5:1	64
9[e]	15	1/1.5	5.2:1	60
10[f]	15	1/1.5	5.5:1	65
11[g]	15	1/1.5	5.5:1	64

[a]Reactions were carried out in toluene (0.5 mL) at 0.25 mmol scale based on **1a** or **2a**, **1a** was added in one portion. [b]Yield and selectivity were determined by ^{1}H NMR spectroscopy (internal standard: trimethyl(phenyl)silane). [c]5 mol % of (*t*-Bu)$_2$(*o*-diphenyl)PAuOTf was used as catalyst. [d]no desired product **3a** was detected. [e]**1a** (dissolved in 0.3 mL of toluene) was added dropwise over 6 h. [f]**1a** was added in two portions every 3 h. [g]**1a** was added in three portions every 2 h.

To identify further the optimal reaction conditions for the gold(I)/silver(I)-cocatalyzed cascade reaction, a number of dual-metal catalyst systems, composed of 15 mol % of silver salt with 5 mol % of gold(I) complex in different organic solvents, were tested in the reaction of phenyl vinyl ketone (**1a**) with 1.5 equiv of *N*-tosylallylamine (**2a**) (Table 2). $AgClO_4$ was found to be the best silver salt for this reaction (Table 2, entries 1–5). A panel of Au(I) complexes with different ancillary ligands was also screened for activity and diastereo-induction in this cascade reaction (Table 2, entries 5–9). Among the complexes examined, (*t*-Bu)$_2$(*o*-biphenyl)PAuCl gave the best result (Table 2, entry 5). Further screening of solvents revealed that toluene gave the best result, while the other solvents, dioxane, nitromethane, 1,2-dichloroethane, tetrahydrofuran, benzene, and acetonitrile, gave low product yields and low diastereoselectivity (Table 2, entries 5 and 10–15). After optimization of the reaction conditions, the protocol with the combination of 5 mol % of (*t*-Bu)$_2$(*o*-biphenyl)PAuCl and 15 mol % of $AgClO_4$ as a dual-metal catalyst system at 90 °C in toluene for 20 h gave the product **3a** in 76% yield.

Table 2: Screening catalysts and solvents.



1a **2a** **3a**

entry[a]	gold catalyst/silver salt	solvent	*trans*/*cis*[b]	yield (%)[b]
1	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgOTf	toluene	5.3:1	67
2	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/$AgSbF_6$	toluene	2.2:1	35
3	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/$AgPF_6$	toluene	2.6:1	62
4	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl /$AgBF_4$	toluene	–	<5

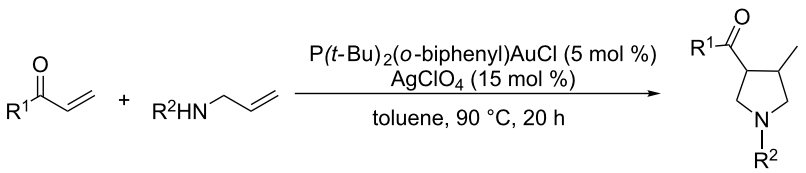
Table 2: Screening catalysts and solvents. (continued)

5	**(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$**	**toluene**	**4.1:1**	**76**
6	Ph$_3$PAuCl/AgClO$_4$	toluene	–	<5
7	Cy$_3$PAuCl/AgClO$_4$	toluene	–	<5
8	IPrAuCl/AgClO$_4$[c]	toluene	4.4:1	63
9	L^{1}AuCl/AgClO$_4$[d]	toluene	3.1:1	50
10	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$	dioxane	4.0:1	63
11	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$	CH_3NO_2	2.8:1	47
12[e]	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$	DCE	1.8:1	34
13[e]	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$	THF	1.8:1	76
14[e]	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$	benzene	3.2:1	60
15[e]	(*t*-Bu)$_2$(*o*-biphenyl)PAuCl/AgClO$_4$	CH_3CN	–	<5

[a]Reactions were carried out in toluene (0.5 mL) at 0.25 mmol scale, **1a** (0.25 mmol) and **2a** (0.375 mmol) were added in one portion. [b]Yield and selectivity were determined by ^{1}H NMR spectroscopy (internal standard: trimethyl(phenyl)silane). [c]IPr= *N*,*N*'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [d]L^1 = (Cy)$_2$(2',4',6'-triisopropyl-*o*-biphenyl)P. [e]Reactions were carried out under reflux.

With the optimal reaction conditions, we next explored the substrate scope with the protocol for the Au(I)/Ag(I)-cocatalytic system (Table 3). For example, treatment of substrate **1b**, which has an electron-donating *para*-methoxy group on the phenyl ring, with **2a** under the optimized reaction conditions gave the expected product **3b** in 92% yield, albeit with no diastereoselectivity (Table 3, entry 2). In addition to substrate **1b**, α,β-unsaturated ketone **1c**, with electron-withdrawing substituent on the phenyl ring, underwent this cascade reaction to afford the corresponding product **3c** in 58% yield with a diastereomeric ratio of 1.7:1 (Table 3, entry 3). Reaction of alkyl α,β-unsaturated ketone **1d** in the presence of 5 mol % of (*t*-Bu)$_2$(*o*-

Table 3: Cascade synthesis of pyrrolidine catalyzed by a dual-metal catalytic system comprising of gold(I) and silver(I) catalysts.



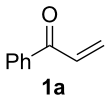
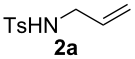
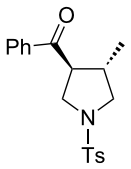
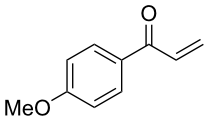
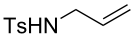
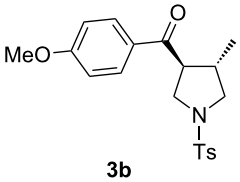
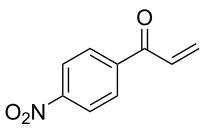
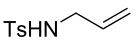
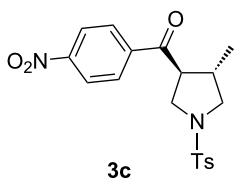
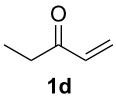
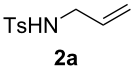
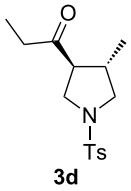
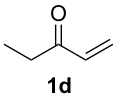
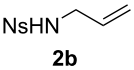
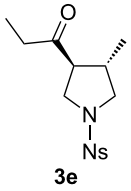
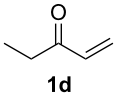
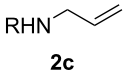
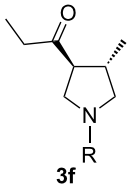
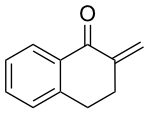
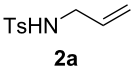
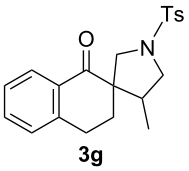
entry[a]	α,β-unsaturated ketone	substituted allylamine	major product	dr[b]	yield (%)[b]
1	 **1a**	 **2a**	 **3a**	4.1:1	76
2	 **1b**	 **2a**	 **3b**	1.0:1	92
3	 **1c**	 **2a**	 **3c**	1.7:1	58

Table 3: Cascade synthesis of pyrrolidine catalyzed by a dual-metal catalytic system comprising of gold(I) and silver(I) catalysts. (continued)

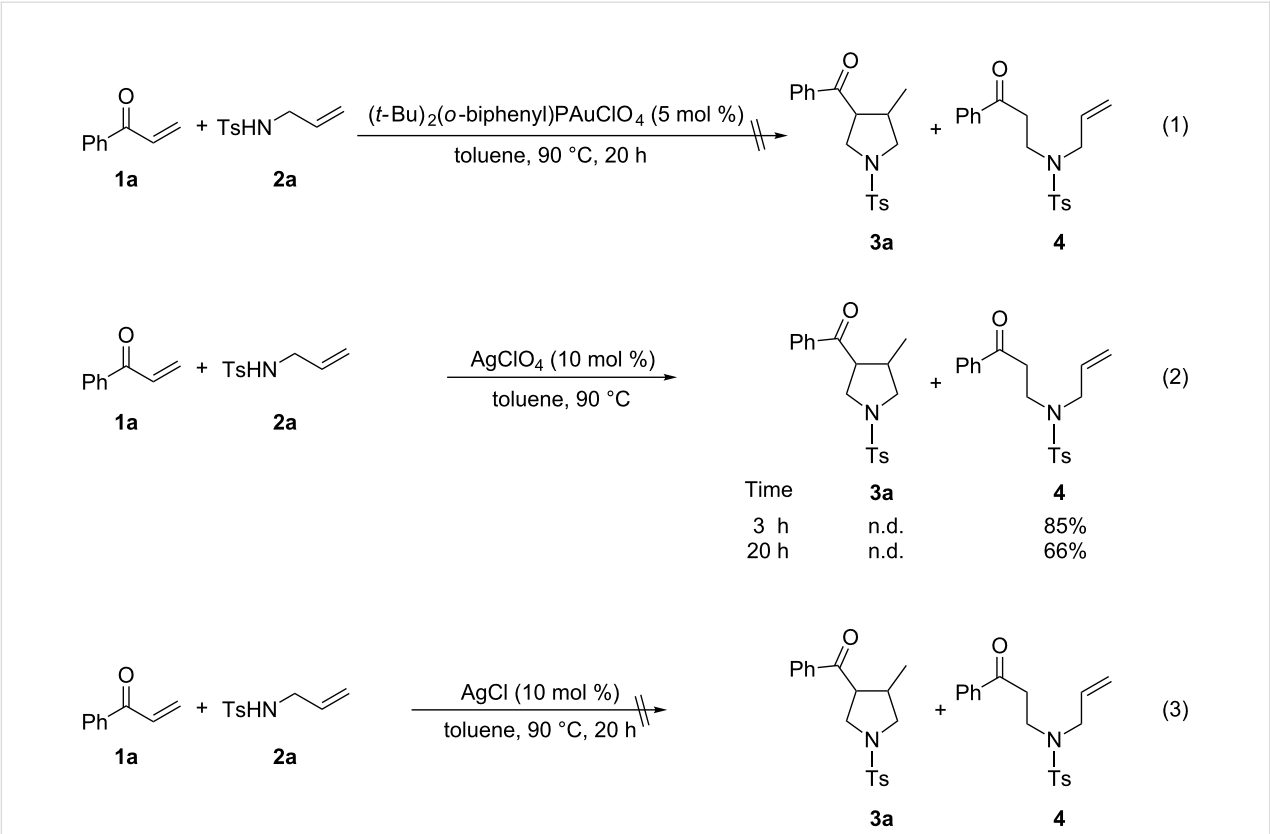
4	 **1d**	 **2a**	 **3d**	5.5:1	92
5	 **1d**	 **2b**	 **3e**	5.3:1	76
6[c]	 **1d**	 **2c**	 **3f**	5.2:1	91
7	 **1e**	 **2a**	 **3g**	1.8:1	52

[a]Reactions were carried out in toluene (0.5 mL) at 0.25 mmol scale. The α,β-unsaturated ketone (0.25 mmol) and the substituted allyl amine (0.375 mmol) were added in one portion. [b]Yield and selectivity were determined by ^{1}H NMR spectroscopy (internal standard: trimethyl(phenyl)silane). [c]R = 2,4,6-triisopropylbenzenesulfonyl.

biphenyl)PAuCl and 15 mol % of $AgClO_4$ also gave the desired product **3d** in 92% yield with a diastereomeric ratio of 5.5:1 (Table 3, entry 4). Other substituted allylamines were also examined. A series of substituted allylamines with 4-nitrobenzenesulfonyl group and 2,4,6-triisopropylbenzenesulfonyl group were similarly treated with alkyl α,β-unsaturated ketone **1d**, and the corresponding products **3e** and **3f** were obtained in moderate to excellent yields with similar diastereomeric ratios of around 5.2:1 (Table 3, entries 4–6). Notably, the gold(I)/silver(I)-cocatalyzed cascade reaction was also successfully applied to furnish spirocyclic pyrrolidine derivative **3g** in 52% yield starting from the readily available precursor 2-methylene-3,4-dihydronaphthalen-1(2*H*)-one (**1e**) and *N*-tosylallylamine (**2a**) (Table 3, entry 7).

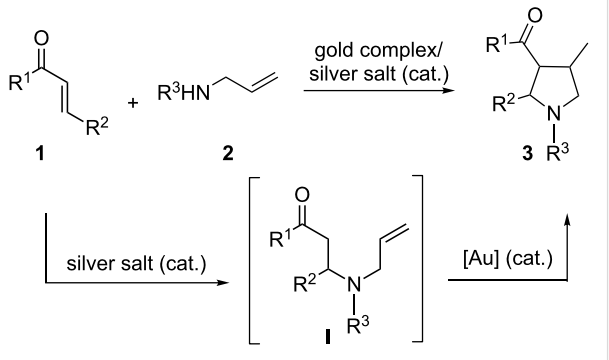
To gain insight into the mechanism of the gold(I)/silver(I)-cocatalyzed cascade reaction, we first examined the reaction of phenyl vinyl ketone (**1a**) with 1.5 equiv of *N*-tosylallylamine (**2a**) in the presence of 5 mol % of (*t*-Bu)$_2$(*o*-biphenyl)PAuClO$_4$ at 90 °C in toluene for 20 h, however, no desired product **3a** or α-ketone intermediate **4** was observed by ^{1}H NMR analysis of the reaction mixture (Scheme 2, reaction 1). This finding revealed that the gold(I) complex is ineffective in the catalysis of the intermolecular N-Michael reaction. Upon subsequent treatment of phenyl vinyl ketone (**1a**) with *N*-tosylallylamine (**2a**) in the presence of 10 mol % of $AgClO_4$ at 90 °C for 3 h, the α-ketone intermediate **4** was formed in 85% yield, however, no product **3a** was observed. Even after a longer reaction time (20 h) under the same reaction conditions, **3a** was also not detected, and α-ketone intermediate **4** was isolated in lower yield (66%) (Scheme 2, reaction 2), which may be due to the *retro*-N-Michael reaction [47]. On the other hand, product **3a** and α-ketone intermediate **4** were not observed in the presence of 10 mol % of AgCl under the same reaction conditions (Scheme 2, reaction 3), revealing that the newly formed AgCl from the reaction of (*t*-Bu)$_2$(*o*-biphenyl)PAuCl and $AgClO_4$ did not affect the reaction. All the results demonstrated the dual roles of the silver salt that serves firstly to abstract the coordinated Cl^- ligand, to give a reactive gold catalyst, and secondly to act as an efficient catalyst for the intermolecular N-Michael addition.

On the basis of these observations and our previous work on gold(I)-catalyzed intramolecular hydroalkylation of unactivated



Scheme 2: Some control experiments.

alkenes with α-ketones [24], a reaction mechanism for the formation of pyrrolidine **3** from the reaction of α,β-unsaturated ketone **1** with substituted allylamine **2** is proposed (Scheme 3), which involves silver-catalyzed intermolecular N-Michael addition of substituted allylamine **2** to α,β-unsaturated ketone **1** to generate the α-ketone intermediate **I** and subsequent gold(I)-catalyzed intramolecular hydroalkylation of the α-ketone intermediate **I** to form the cyclic compound **3** (Scheme 3).



Scheme 3: The reaction pathway.

Conclusion

In summary, we have developed a simple and efficient gold(I)/silver(I)-cocatalyzed cascade intermolecular N-Michael addition/intramolecular hydroalkylation reaction. The present protocol with a dual-metal catalytic system provides a highly efficient method for the synthesis of a variety of pyrrolidine compounds in moderate to excellent product yields and with moderate to good diastereoselectivities from α,β-unsaturated ketones and substituted allylamines. Further studies to expand the substrate scope are currently in progress.

Supporting Information

Supporting Information File 1

Experimental section and spectra of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-126-S1.pdf]

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Gold(I)-catalyzed synthesis of γ-vinylbutyrolactones by intramolecular oxaallylic alkylation with alcohols

Michel Chiarucci, Mirko Locritani, Gianpiero Cera and Marco Bandini*

Letter

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Address:
Dipartimento di Chimica "G. Ciamician", Alma Mater Studiorum – Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

Email:
Marco Bandini* - marco.bandini@unibo.it

* Corresponding author

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Abstract

Gold(I)-*N*-heterocyclic carbene (NHC) complexes proved to be a reliable catalytic system for the direct synthesis of functionalized γ-vinylbutyrolactones by intramolecular oxaallylic alkylation with primary alcohols. Good isolated chemical yields were obtained for a range of malonyl and acetate derivatives. The good performance in reagent-grade solvents and the functional group/moisture tolerance make this catalytic process a promising route for the synthesis of architecturally complex polycyclic structures.

Introduction

Allylic alcohols are highly desirable, readily available, cheap, and environmental sustainable reaction partners for allylic alkylation reactions in the presence of C- as well as X-based (X: heteroatom) nucleophiles [1,2]. Despite their undoubted synthetic/economic advantages (i.e., water is the only stoichiometric byproduct produced), the intrinsic lower reactivity of allylic alcohols compared to allyl halides/acetates/carbonates generally necessitates harsher reaction conditions and/or the need for activating agents (i.e., Brønsted or Lewis acids) [3,4].

Recently, late-transition metal (LTM) catalysis (i.e., Hg, Pd, Pt, Au, and Ru) has received growing attention in organic synthesis and enables unprecedented manipulations of unfunctionalized hydrocarbons under mild reaction conditions [5-9]. In this context, electrophilic LTM activation of carbon–carbon unsaturations, adjacent to alcoholic moieties (i.e., allylic, benzylic, and propargylic alcohols, usually referred to as π-activated alcohols), deserves a particular mention [10-13].

As a part of our ongoing interest in the gold-catalyzed allylic functionalization of C- and heteroatom-based nucleophiles with alcohols [14-17], we previously observed the formation of synthetically useful vinylbutyrolactones [18-22] as minor products in the Friedel–Crafts-type allylic alkylation of arenes [23]. The wide impact of functionalized γ-lactones on the synthesis of naturally occurring compounds [24-26] prompted us to optimize a direct synthesis of vinylbutyrolactones by direct gold activation of allylic alcohols [27-31] with esters [32-37].

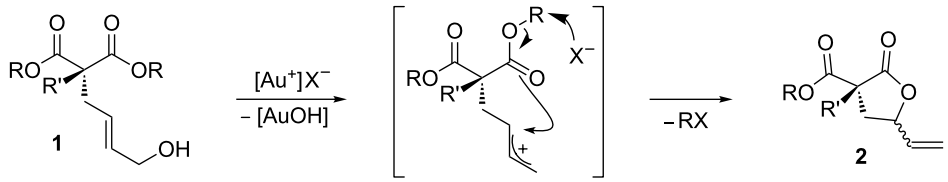


Figure 1: Working hypothesis for the present gold-catalyzed oxaallylic alkylation reaction.

In this direction, we targeted malonyl alcohols **1** as a readily available class of model acyclic precursors to create chemical diversity through an oxaallylic ring-closing reaction (Figure 1).

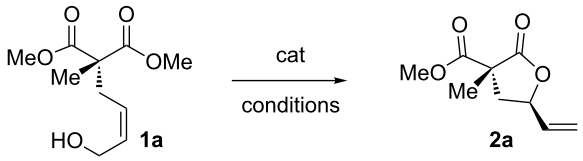
It should be noted that the synthesis of such a class of heterocyclic compounds has been the subject of several investigations. Among them, a multi-step synthetic pathway with final TBAF-promoted cyclization was proposed by Lepore [38] and, almost simultaneously, Poli and Prestat described a Pd-catalyzed Tsuji–Trost-type allylic alkylation procedure to obtain valuable precursors (i.e., lactams and lactones) of podophyllotoxin analogs [39,40]. However, to the best of our knowledge, no examples of metal-catalyzed lactonization through direct activation of allylic alcohols have been described so far.

Results and Discussion

At the outset of our investigation, we focused our attention on the non-enolizable allyl alcohol (*Z*)-**1a**, as a model candidate for the intramolecular oxaallyl alkylation. Our choice was dictated by the well-known reluctance of disubstituted malonyl derivatives to provide vinylbutyrolactones. This aspect was convincingly highlighted in a recent report by Chen and coworkers that described an analogous catalytic approach based on allyl acetate derivatives [41].

At this stage, an extended survey of reaction parameters (metal source, solvent, and temperature) was conducted in order to ascertain the optimal catalytic conditions (Table 1).

Table 1: Optimization of the reaction conditions for the lactonization of **1a**.[a]



Entry	Cat (%)	Solvent	Yield (%)[b]	(*trans*:*cis*)[c]
1	[P(*t*-Bu)$_2$*o*-biphenyl](AuCH$_3$CN)SbF$_6$ (5)	DCE	42	nd
2	[P(Cy)$_2$*o*-biphenyl-2,4,6(iPr)$_3$]AuNTf$_2$ (5)	DCE	82	1.5:1
3	PPh$_3$AuNTf$_2$ (5)	DCE	52	1.1:1
4	[(PPh$_3$Au)$_3$O]BF$_4$ (2)	DCE	Trace	nd
5	AuCl$_3$ (5)	DCE	<20	nd
6	[biphepAu$_2$Cl$_2$/AgOTf] (2.5)	DCE	56	1.3:1
7	[dppf(AuNTf$_2$)$_2$] (2.5)	DCE	98	1.2:1
8[d]	[dppf(AuNTf$_2$)$_2$] (0.5)	DCE	96	1.4:1
9[d,e]	IMesAuOTf (5)	DCE	94	2.1:1
10[f]	IMesAuOTf (5)	DCE	Trace	nd
11	IMesAuOTf (5)	Toluene	31	1.9:1
12	IMesAuOTf (5)	CH$_3$CN	Trace	nd
13	IMesAuOTf (5)	THF	79	1.9:1
14	AgOTf (5)	DCE	35	nd
15	TsOH (10)	DCE	64	1.3:1
16[d,e,g]	IMesAuOTf (5)	DCE	Trace	nd

[a]All the reactions were carried out under nitrogen atmosphere at 80 °C for 16 h, unless otherwise stated. [b]Isolated yield after flash chromatography. [c]Determined by GC on the reaction crude. The relative configuration was determined by NOE experiments on the single diastereoisomers separated by flash chromatography. [d]Under no moisture restriction, with reagent-grade solvent. [e]Reaction time: 4 h. [f]At room temperature. IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. [g]In the presence of K_2CO_3 (1 equiv). nd: not determined.

Initial attempts to perform the lactonization reaction of **1a** were carried out by means of a silver-free cationic complex [P(*t*-Bu)$_2$*o*-biphenyl](AuCH$_3$CN)SbF$_6$ (5 mol %). The desired butyrolactone **2a** was obtained selectively under reflux in DCE for 16 h (entry 1), although only in low yield. With the less bulky triphenylphosphine ligand, the corresponding cationic gold(I) complex (i.e., PPh$_3$AuNTf$_2$) led to an increase in the isolated yield up to 52%, although the diastereoselection remained elusive (≈ 1:1, entry 3). After demonstrating that the Au(III) catalysis promoted the cyclization in lower extent compared to the Au(I) counterpart (entry 5 versus entries 1–3), we also observed that dinuclear [dppf(AuNTf$_2$)$_2$] provided **2a** with almost complete conversion (entry 7). The possibility to reduce the loading of the catalyst (0.5 mol %) further, without the need for moisture restriction, was successfully verified by the isolation of **2a** in 96% isolated yield (entry 8). Interestingly, the diastereoselection of the protocol was slightly improved (up to 2.1:1) and the reaction time shortened to 4 h, by employing the carbene-based gold complex IMesAuCl/AgOTf (5 mol %, entry 9) [42,43]. Therefore, by addressing NHCAuOTf as the optimal catalytic system, the impact of the reaction media on the chemical output of the process was investigated (entries 10–13). Here, although **2a** was also isolated in good yield in reagent-grade THF (yield = 79%, dr = 1.9:1, entry 13), DCE was employed as the solvent of choice.

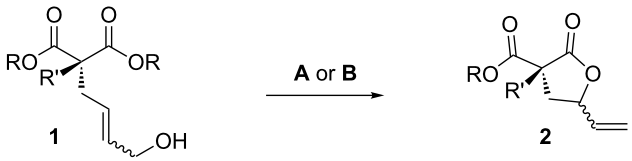
In order to confirm that the catalysis was indeed due to the presence of gold, a control experiment with AgOTf (5 mol %) was performed on compound **1a**. Under comparable reaction conditions (80 °C, 16 h), lactone **2a** was isolated in poor yield (35%). Finally, the hypothetical cocatalysis by Brønsted acids (BA) was verified by means of experimental controls with TsOH (entry 15), and also in the presence of an acid scavenger (entry 16). Here, the desired cyclic compound **2a** was obtained in lower yield (64%) with concomitant substantial decomposition of the starting allylic alcohol. Such evidence confirms the allylic S$_N$1 mechanism for the present methodology [44].

The high chemoselectivity guaranteed by the gold catalysts is worthy of note, as it channels the reaction toward the allylic alkylation mechanism without any contamination deriving from transesterification reactions. This evidence is reasonably rationalized in terms of the high π-acidity and poor oxophilicity of the Au(I) species [37].

With the optimal catalytic systems in hand (IMesAuOTf or [dppf(AuNTf$_2$)$_2$], DCE, 80 °C), we verified the generality of the method by subjecting a range of malonyl alcohols **1b**–**j** to the gold-catalyzed lactonization (Table 2).

The impact of the carbon–carbon double bond configuration on both chemical and stereochemical outputs of the process was

Table 2: Proving the scope of the gold-catalyzed intramolecular allylation of **1**.[a]



1 **2**

(*E*)-**1a**: R = Me, R' = Me
(*Z*)-**1b**: R = Et, R' = H
(*Z*)-**1c**: R = *t*-Bu, R' = H
(*Z*)-**1d**: R = Bn, R' = H
(*Z*)-**1e**: R = Me, R' = H
(*Z*)-**1f**: R = Me, R' = allyl
(*Z*)-**1g**: R = Me, R' = Bn
(*Z*)-**1h**: R = Me, R' = Br
(*Z*)-**1i**: R = Et, R' = –(CH$_2$)$_2$CH(OCH$_2$)$_2$
(*Z*)-**1j**: R = Me, R' = –CH$_2$CH=CHCH$_2$OH

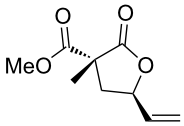
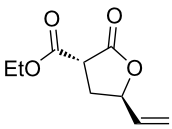
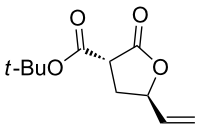
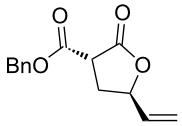
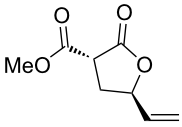
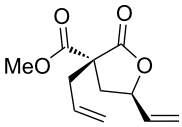
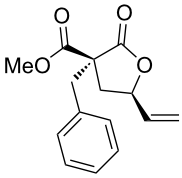
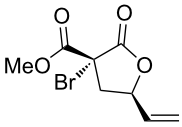
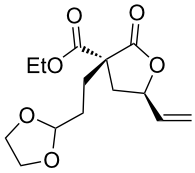
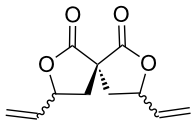
Entry	**1**	Catalytic system	Product	Yield (%)[b]	*trans*:*cis*[c]
1	(*E*)-**1a**	**A**	 **2a**	72	1.3:1
2	(*Z*)-**1b**	**A**	 **2b**	95	1:1

Table 2: Proving the scope of the gold-catalyzed intramolecular allylation of **1**.[a] (continued)

3	(*Z*)-**1c**	**A**	 **2c**	66	1.1:1
4	(*Z*)-**1d**	**A**	 **2d**	67	1.4:1
5	(*Z*)-**1e**	**A**	 **2e**	85	1:1
6	(*Z*)-**1f**	**A**, **B**	 **2f**	94, 35	1.5:1, 1.5:1
7	(*Z*)-**1g**	**A**[d], **B**[e]	 **2g**	63, 12	1:1.4, 1:1.4
8	(*Z*)-**1h**	**A**	 **2h**	54	3.2:1
9	(*Z*)-**1i**	**A**	 **2i**	45	1.4:1
10	(*Z*)-**1j**	**A**[f]	 **2j**	93	1.1:1

[a]All the reactions were carried out in reagent-grade solvents under air (80 °C, 0.3 M). Catalytic systems: **A** = IMesAuCl/AgOTf (5 mol %), DCE, 80 °C, 7–9 h. **B** = [dppf(AuNTf$_2$)$_2$] (2.5 mol %), THF, 80 °C, 16 h. [b]Isolated yield after flash chromatography. [c]Determined by GC on the reaction crude. [d]Dihydronaphthalene derived from undesired Friedel–Crafts alkylation (yield = 14%). [e]A considerable amount of Friedel–Crafts dihydronaphthalene (yield = 67%) was isolated [23]. [f]10 mol % of catalyst was used.

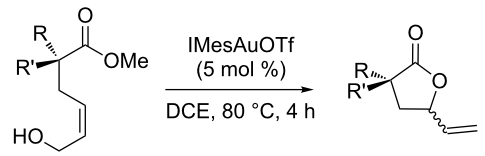
initially investigated. Here, by subjecting (*E*)-**1a** to the reaction conditions **A** (i.e., IMesAuCl/AgOTf, DCE, 80 °C) the corresponding lactone **2a** was isolated in comparable yield (72%, entry 1) and similar diastereomeric ratio. Here, although the impact of the C─C double bond configuration on the stereochemical outcome of S_N2'-type gold-catalyzed intramolecular

O- [45] and *N*-alkylations [37,46] with allylic alcohols was demonstrated, we consider it likely that an allylic S_N1 mechanism is involved in the present methodology, due to the similar optical outcomes obtained in the presence of BA metal-free catalysts (entry 15, Table 1).

Then, enolizable substrates carrying different malonyl residues (**1b**–**e**) were taken into account. In all cases the cyclization occurred smoothly leading to the disappearance of the acyclic precursors within 7–9 h reaction time (entries 2–5). Interestingly, in this case no appreciable differences in reaction rate were observed between substrates carrying labile and nonlabile ester alkyl groups.

In some specific cases, both catalytic systems were tested and a direct comparison of performances can be made. Clear evidence was gained for the higher activity of the catalytic system **A** in the expected oxaallylic alkylation process. As an example, when multiple reactive channels were available (i.e., lactonization and Friedel–Crafts-type alkylation, **1g**) dppf-based species (catalytic system **B**) led to a complex mixture of crude reaction products (entry 7), while carbene–gold complex provided mainly the butyrolactone **2g**. Moreover, the methodology proved to be tolerant toward several functional groups/atoms at the methylene carbon atom of the malonyl derivative. In particular, 3,5-*trans*-3-bromo-γ-vinylbutyrolactone **2h** was isolated with 54% yield and in 76:24 diastereoisomeric ratio (entry 8). A protected carbonyl moiety was also tested leading to the corresponding lactone **2i** in moderate yield (45%, entry 9). Finally, the methodology proved to be adaptable allowing a double lactonization event with **1j**, hence providing spiro-lactone **2j** in 93% yield.

Apart from the generality on malonyl substrates, we decided to explore the applicability of the present methodology to less reactive monoester analogs [47]. In this context, readily available alcohols **3a**,**b** were subjected to cyclization in the presence of the gold catalytic system **A**. In both cases lactones **4a**,**b** were isolated in good to excellent yields (93 and 75%, respectively, Scheme 1).



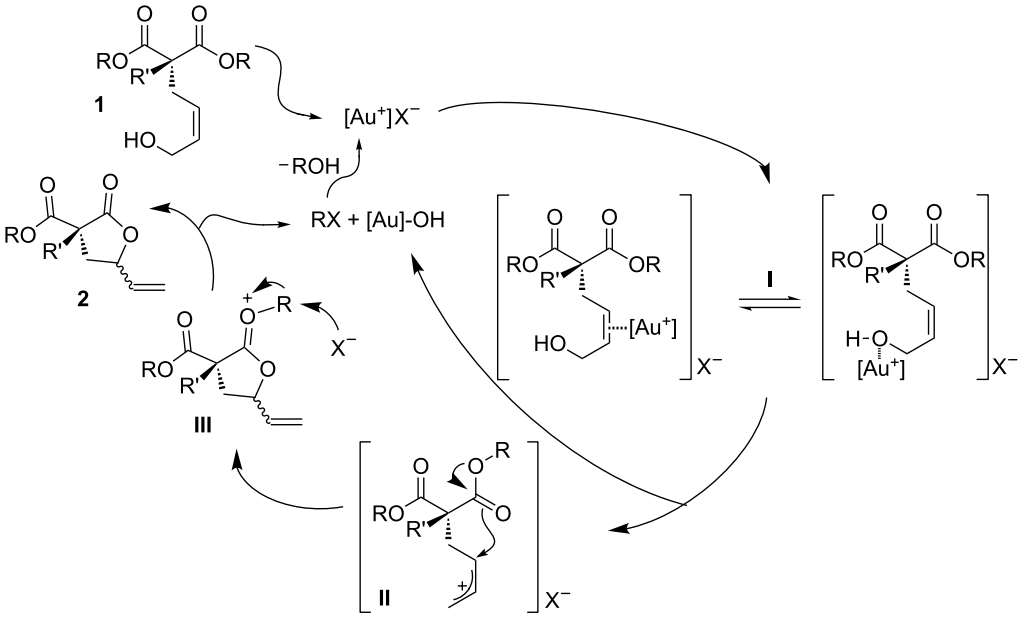
(+/-)-**3a**: R = Ph, R' = H
3b: R = R' = Ph
(+/-)-**3c**: R = COMe, R' = H

4a: yield = 93%, dr = 1.1:1
4b: yield = 75%
4c: decomposition

Scheme 1: Gold-catalyzed synthesis of γ-lactones **4** from the corresponding monoesters **3**.

Finally, the 1,3-ketoester **3c** was also subjected to the optimized conditions, but a complex reaction mixture was observed with concomitant decomposition of the starting material.

The mechanistic proposal for the formation of γ-vinylbutyrolactones **2** is depicted in Scheme 2. As previously mentioned,



Scheme 2: Mechanistic sketch of the gold-promoted oxaallylic alkylation reaction.

the formation of an allylic cationic species (**II**) is assumed, upon coordination of the gold catalyst to the allylic alcohol (**I**). In Scheme 2, the possible coordination modes for [Au^+] to the allylic alcohol are reported. As a matter of fact, although we have previously demonstrated the C=C···Au interaction in the presence of allylic alcohols [16], a concomitant [Au]···OH contact cannot be ruled out [48,49]. Subsequently, the direct nucleophilic attack by the carboxylate unit would lead to an oxonium intermediate **III** [50,51] that, after dealkylation, resulted in the final lactone **2**. Control experiments have been performed to indentify the presence of a Brønsted acid cocatalysis in the ring-closing procedure (see [52] and entry 15 in Table 1). Regeneration of the active cationic gold species or assistance in the formation of the reactive allylic carbocation intermediate **II** are key steps in which the Brønsted cocatalysis could be exerted [52]. Finally, the mandatory role of enol tautomer (or gold–enolate intermediates) [53-55] in the nucleophilic attack was excluded; non-enolizable compounds being suitable candidates for the cyclization reaction.

Conclusions

In conclusion, we have documented an unprecedented example of gold-catalyzed lactonization with primary allylic alcohols. Cationic NHCAu carbene gold complexes allowed the preparation of a range of functionalized malonyl esters by direct activation of the allylic alcohol by gold. The methodology appears highly chemoselective toward the allylic lactonization, with the possibility to extend the protocol also to acetate derivatives.

Supporting Information

Supporting Information File 1

Experimental details and characterization of the synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-139-S1.pdf]

Acknowledgment

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Combination of gold catalysis and Selectfluor for the synthesis of fluorinated nitrogen heterocycles

Antoine Simonneau, Pierre Garcia, Jean-Philippe Goddard, Virginie Mouriès-Mansuy, Max Malacria* and Louis Fensterbank*

Full Research Paper

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Address:
UPMC Univ Paris 06, Sorbonne Universités, Institut Parisien de Chimie Moléculaire (UMR CNRS 7201), 4 place Jussieu, C. 229, 75005 Paris, France

Email:
Max Malacria* - max.malacria@upmc.fr; Louis Fensterbank* - louis.fensterbank@upmc.fr

* Corresponding author

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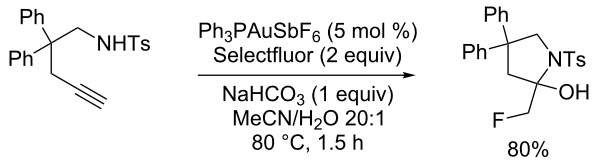
Abstract

We herein report the synthesis of 3-fluoro-2-methylene-pyrrolidine (**3a**) and -piperidine (**3b**) from 1,5- and 1,6-aminoalkynes, respectively, using a combination of a gold-catalyzed hydroamination reaction followed by electrophilic trapping of an intermediate cyclic enamine by Selectfluor. Careful attention was paid to the elucidation of the mechanism and Selectfluor was suggested to play the double role of promoting the oxidation of gold(I) to a gold(III) active species and also the electrophilic fluorination of the enamine intermediates.

Introduction

The useful properties of fluorinated compounds in medicinal chemistry have motivated an intense effort towards the synthesis of new molecules bearing fluorine substituents [1,2]. Therefore, the development of a rapid access to C–F bonds is of great importance. Quite recently, in their study on the synthesis α-fluoro ketones, Nevado et al. observed the formation of fluorinated pyrrolidinol obtained by a gold-catalyzed cyclization of a 1,5-aminoalkyne in the presence of Selectfluor (Scheme 1) [3]. These authors proposed that the formation of the C(sp^3)–F bond could be explained either by direct fluorination of the enamine resulting from the gold-promoted alkyne hydroamination or by oxidation of the intermediate vinyl gold(I) complex by Selectfluor into a gold(III) fluoride species followed by a reductive elimination.

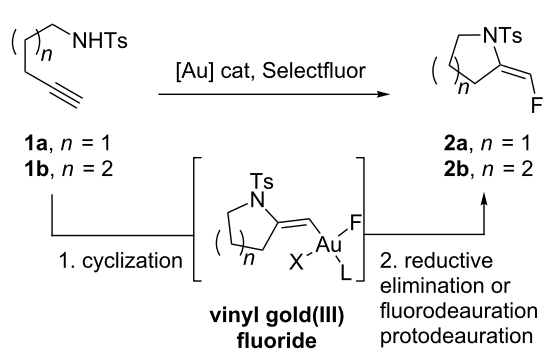
Moreover, the formation of C(sp^2)–F bonds, either by hydrofluorination of alkynes catalyzed by N-heterocyclic carbene gold(I) complexes [4], or by fluorodeauration of transient vinyl gold species [5,6], has been previously reported in the literature.



Scheme 1: Amino-hydroxyfluorination of alkynes reported by Nevado et al. [2].

On the basis of our recent results on the gold-catalyzed cyclization of enynes [7-10] and allenylhydrazones [11], as well as the studies from Nevado [3], Hammond and Xu [12], Liu and Xu [13], and Liu [14], we were attracted by the possibility to access fluorinated nitrogen heterocycles **2a** and **2b** by performing subsequently an intramolecular nucleophilic attack of nitrogen onto the gold-activated triple bond on compounds **1a**,**b** in a 5- and 6-exo-dig manner, respectively, and reductive elimination occurring at a vinyl gold(III) fluoride species or bimolecular fluorodeauration (Scheme 2). We also anticipated from this study to gain more insight into the reactivity of gold catalysts/Selectfluor combinations [15-17].

Indeed, pyrrolidine and piperidine skeletons are very attractive ring systems because of their occurrence in numerous biologically active substances, and the design of methodologies allowing the easy introduction of a fluorine atom onto these skeletons could be attractive for medicinal chemists. Recently



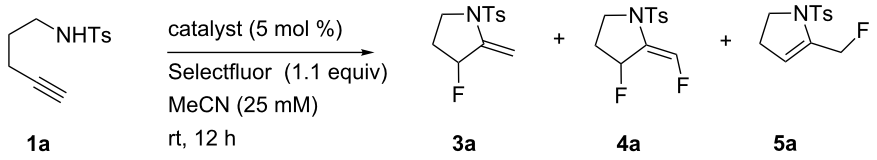
Scheme 2: Proposed access to fluoromethylene pyrrolidines and piperidines.

also, the literature has featured valuable access routes to pyrrolidine promoted by catalytic systems [18-26].

Results and Discussion

Studies on the scope and limitation of the cyclization–fluorination sequence were carried out with Selectfluor as a source of electrophilic fluorine. Readily available 4-methyl-*N*-(pent-4-ynyl)benzenesulfonamide (**1a**) was used as a model substrate, and all the reactions were performed in anhydrous acetonitrile as the solvent. Various gold catalysts were screened. The results of the optimization of the cyclization reaction conditions are summarized in Table 1.

Table 1: Gold catalyst influence on the cyclization of **1a**.[a]



1a **3a** **4a** **5a**

Entry	Catalyst	**3a** (yield %)	**4a** (yield %)	**5a** (yield %)
1[b]	Ph_3PAuCl	75	17	0
2[c]	AuCl	46	0	7
3[b]	$AuCl_3$	14	2	2
4	IPrAuCl	65	13	0
5[d]	(biphenyl)(*t*-Bu)$_2$PAuCl	0	0	0
6	$(PhO)_3PAuCl$	35	7	0
7	(2,4-di-*t*-BuPhO)$_3$PAuCl	35	5	0
8	(*t*-Bu)$_3$PAuCl	35	6	0
9	dppm(AuCl)$_2$	43	0	14
10	$Ph_3PAuNTf_2$	35	0	11
11	$[Ph_3PAu]SbF_6$	-	-	-

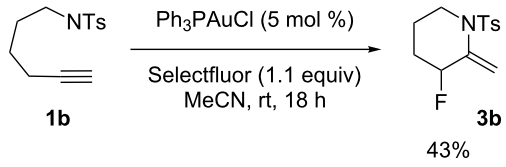
[a]Products **3a**, **4a** and **5a** were characterized by ^{1}H, ^{13}C and ^{19}F NMR. Compound **4a** was obtained as a single (*E*)-isomer and the configuration of the double bond was confirmed by NOE measurements. [b]When the reaction was performed without Selectfluor, the starting material was recovered unchanged. [c]Reaction time: 5 h.[d]An inextricable mixture was obtained.

The reaction of **1a** in the presence of commercially available Ph_3PAuCl (5 mol %) and Selectfluor (1.1 equiv) in acetonitrile at rt afforded an inseparable mixture of pyrrolidines **3a** in 75% yield and **4a** in 17% yield (Table 1, entry 1). Difluoro derivative **4a** was isolated as a single diastereomer, and its relative stereochemistry was determined by F–F NOE measurement. The expected fluoromethylene tosylpyrrolidine **2a** was not detected. When a AuCl complex was used, product **3a** was obtained in 46% yield with a new monofluorinated 2-pyrroline **5a** in 7% yield (Table 1, entry 2). In the presence of $AuCl_3$, a lower yield of **3a** was observed (14%) with trace amounts of **4a** and **5a** (2% yield each, Table 1, entry 3). The use of the *N*,*N*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) gold(I) chloride as catalyst led to the formation of **3a** in 65% yield, together with 13% yield of **4a**. Under these conditions, the formation of **5a** was not detected (Table 1, entry 4). Gold(I) phosphite catalysts gave **3a** and **4a** in low yields (Table 1, entries 6 and 7). A similar result was observed with tri(*tert*-butyl)phosphine gold(I) chloride (Table 1, entry 8). The dinuclear complex, $dppm(AuCl)_2$, led to **3a** and **5a** in a manner comparable to AuCl (Table 1, entry 9). When we used cationic gold(I) catalyst, $Ph_3PAuNTf_2$, **3a** was obtained in 35% yield with 11% of **5a** (Table 1, entry 10). Finally in the presence of $[Ph_3PAu]SbF_6$ a complex mixture of compounds was obtained (Table 1, entry 11). To the best of our knowledge, these fluorinated pyrrolidines **3a**, **4a** and 2-pyrroline **5a** are unknown and could be interesting building blocks for organic synthesis.

Following the previous catalyst screening, we stuck with the use of PPh_3AuCl as the catalyst and next investigated the effect of the concentration of **1a** and the stoichiometry of Selectfluor (Table 2).

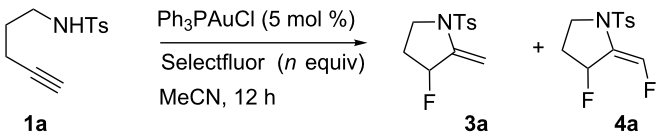
Reaction of a 75 mM solution of **1a** with Ph_3PAuCl (5 mol %) and Selectfluor (1.5 equiv) in acetonitrile under reflux (Table 2, entry 1) afforded an inseparable mixture of **3a** and **4a** both in 25% yield. When the reaction was performed at room temperature, **3a** could be isolated in 47% yield with 17% of **4a** (Table 2, entry 2). Using lower amounts of Selectfluor raised the yield of **3a** to 54% and **4a** to 13% (Table 2, entry 3). In the presence of two equivalents of potassium carbonate the cyclization reaction did not occur (Table 2, entry 4). Lowering the temperature to 5 °C led to a dramatic decrease of the yield of **3a** and **4a** (Table 2, entry 5). Interestingly, the yield of **3a** increased up to 75% when a lower substrate concentration was used (25 mM, Table 2, entry 6). Going to an even more dilute medium resulted in the sole formation of **3a** (Table 2, entry 7). It is noteworthy that in the absence of either the gold catalyst or Selectfluor, the starting material was recovered.

The homologue of **1a**, compound **1b**, was treated with Ph_3PAuCl (5 mol %) and Selectfluor (1.1 equiv) in acetonitrile at rt. As expected, the 6-exo-dig cyclization occurred and only led to one compound, **3b**, which was isolated in 43% yield (Scheme 3).



Scheme 3: Cyclization of **1b** under standard conditions.

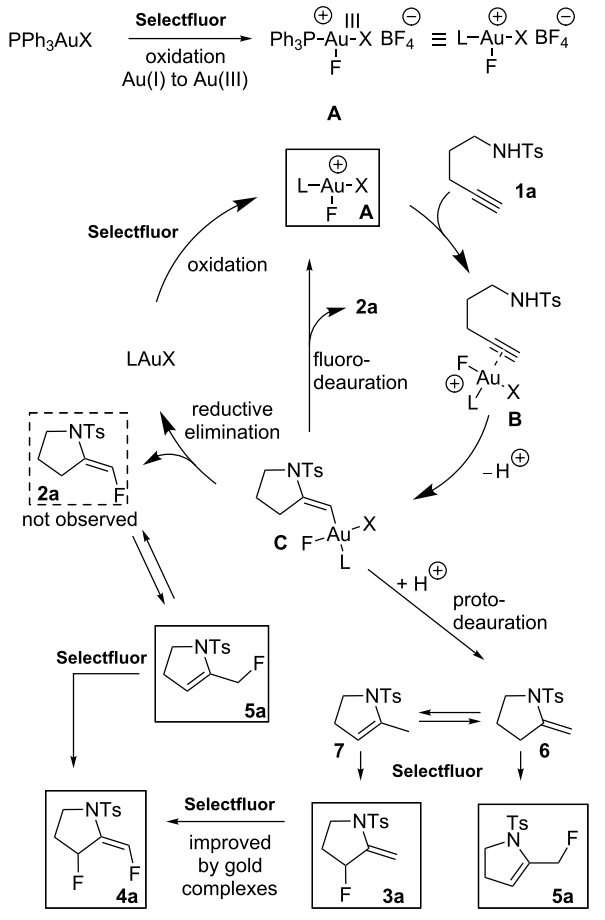
Table 2: Effects of reaction conditions on the Au(I)-catalyzed cyclization of **1a** in the presence of Selectfluor.



Entry	*n* (equiv)	Substrate concentration (mM)	Temperature	**3a** (yield %)	**4a** (yield %)
1[a]	1.5	75	reflux	25	25
2	1.5	75	rt	47	17
3	1.1	75	rt	54	13
4[b]	1.1	75	rt	0	0
5	1.1	75	5 °C	17	2
6	1.1	25	rt	75	17
7	1.1	15	rt	73	0

[a]Reaction time: 1 h. [b]2 equiv of K_2CO_3 were added.

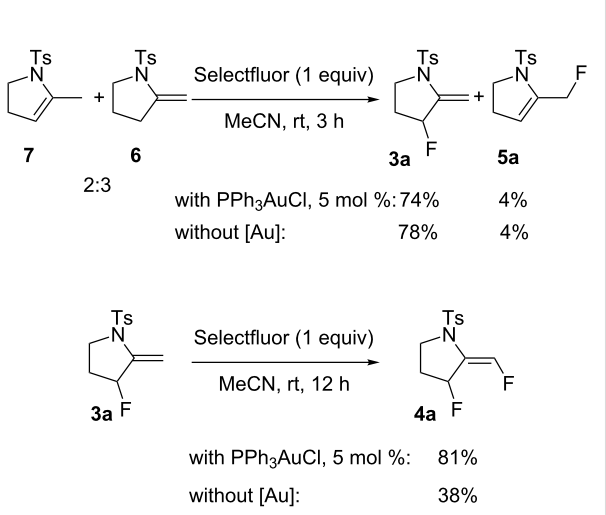
Our mechanistic proposal for the formation of fluorinated pyrrolidines is outlined in Scheme 4. Oxidation of the Au(I) complex by Selectfluor should give the active cationic Au(III) species **A**. Formation of **A** is consistent with ^{19}F NMR experiments analogous to those previously described in the literature [12,27]. Thus, upon addition of Selectfluor to PPh_3AuCl, a new peak at −181.6 ppm in CD_3CN was observed that is characteristic of Au(III) species **A** [28]. Coordination of **1a** to **A** would lead to complex **B** in which the coordinated triple bond is activated towards a nucleophilic attack by the NH moiety. The resulting σ-vinyl Au(III) intermediate **C** could undergo a reductive elimination of its σ-vinyl and F ligands to give **2a**, or a protodeauration leading to pyrrolidine **6**, which would also rapidly isomerize into **7**. Both **6** and **7** under the given reaction conditions would evolve to **3a** and **5a**.



Scheme 4: Proposed mechanism.

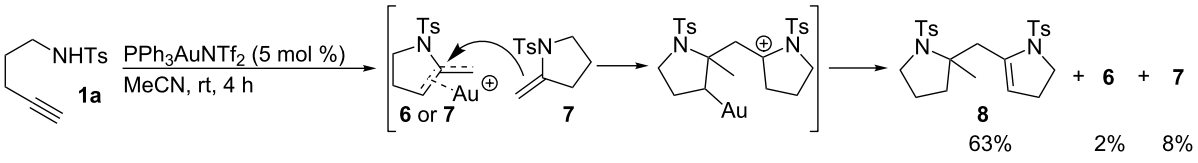
The following experiments were performed to probe the mechanism proposed in Scheme 4. The reaction of a mixture of **6** and **7**, in a 2:3 ratio, with PPh_3AuCl (5 mol %) and Selectfluor (1 equiv) in acetonitrile at rt during 3 h, led to a mixture of **3a** and **5a** with yields of 74% and 4%, respectively. In the absence of a gold catalyst, a similar result was obtained (Scheme 5) confirming that Selectfluor itself can react with **6** and **7** to give **3a** and **5a**, which is consistent with Shreeve's study on the fluorination of enamines [29].

However, the formation of **5a** may also be ascribed to the reductive elimination of **C**, which leads to **2a**, and then further isomerization of the double bond of **2a** (Scheme 4). As far as the formation of **4a** is concerned, we found that treatment of **3a** with one equivalent of Selectfluor in the presence of Ph_3PAuCl (5 mol %), led to **4a** in 81% yield. Nevertheless, in the absence of Au(I) catalyst, **4a** was also formed but with a lower yield of 38% (Scheme 5). These results suggest that the formation of **4a** may not exclusively result from the Selectfluor-mediated fluorination of **3a**. These findings are consistent with Gouverneur's study [5], which showed a competition between fluorodeauration and protodeauration. In our case, protodeauration appears to be the major, if not the exclusive, pathway.



Scheme 5: Mechanistic probes.

In a final experiment, **1a** was treated with PPh_3AuNTf_2, without Selectfluor, and dimer **8** was formed in 63% yield along with **6** and **7** in low yields of 2% and 8%, respectively. The formation of **8** could be explained as outlined in Scheme 6. The cationic Au(I) catalyst would promote the cyclization of **1a** to the mixture of enamines **6** and **7** as previously observed with cationic Au(III) species (Scheme 4). Activation of the electron rich double bond of **6** or **7** by the cationic Au(I) complex could finally trigger the dimerization and so the formation of **8**.



Scheme 6: Cationic Au(I)-catalyzed reaction of **1a** without Selectfluor.

Conclusion

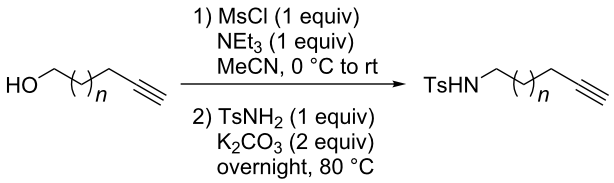
In conclusion, we have reported a gold-catalyzed synthesis of fluorinated pyrrolidines from 1,ω-aminoalkynes using Selectfluor as the source of fluorine. This method allows a rapid, efficient and mild conversion of readily available aminoalkynes into valuable nitrogen heterocycles substituted by a fluorine atom in position 3 of the ring. This could certainly be applied to the synthesis of biologically relevant substrates. Current efforts are being made in this direction and a more exemplified study will be reported in due course.

Experimental

General methods

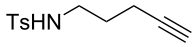
Acetonitrile was distilled over calcium hydride. Other reagents were commercially available and used without further purification. Thin layer chromatography (TLC) was performed on Merck 60 F_{254} silica gel. Acros aluminium oxide, basic, Brockmann I, 50–200 µm, 60A was used for column chromatography. NMR spectra (^{1}H, ^{13}C, DEPT, COSY, HMQC, HMBC, NOE) were recorded at room temperature at 300 or 400 MHz on a Bruker AVANCE spectrometer. Chemical shifts are given in ppm, referenced to the residual proton resonance of the solvents (δ = 7.26 for $CHCl_3$) or to the residual carbon resonance of the solvent (δ = 77.16 for $CDCl_3$). Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t and q refer to multiplet, singlet, doublet, triplet and quartet; br means that the signal is broad. When possible, ^{1}H and ^{13}C signals were assigned on the basis of DEPT and 2D NMR (COSY, HMBC) experiments. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a Bruker MicroTOF mass spectrometer. Infrared spectra (IR) were recorded on a Bruker Tensor 27 spectrometer and melting points were measured on a Wagner & Munz HEIZBANK Kofler bench.

General procedure for the synthesis of precursors

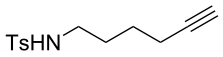


To a cold solution (0 °C) of the starting alcohol in MeCN, MsCl and Et_3N were successively added, and the mixture was warmed to rt. After 1 h, K_2CO_3 and $TsNH_2$ were added and the mixture was warmed at 80 °C overnight. Once back to rt, the mixture was directly purified by flash chromatography being eluted first with petroleum ether and then with petroleum ether/ethyl acetate 9:1.

Spectral data of cyclization precursors

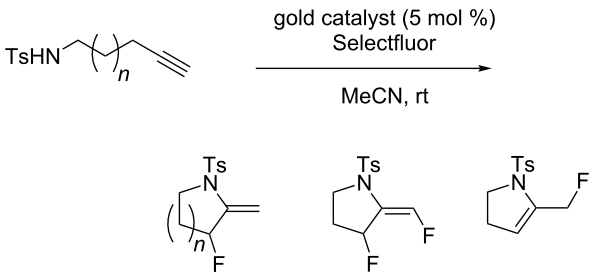


1a. In agreement with the literature data [30,31].



1b. In agreement with the literature data [31,32].

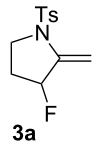
General procedure for the cyclization reaction



Into an oven-dried Schlenk apparatus, the Selectfluor (0.33 mmol, 117 mg, 1.1 equiv) and the gold catalyst (16 µmol, 0.05 equiv) were loaded under a flow of argon. These solids were dried under vacuum at 70–80 °C for 2 h. The aminoalkyne (0.30 mmol, 1 equiv) was then added, followed by anhydrous MeCN (12 mL), under a flow of argon. The mixture was stirred at rt until complete consumption of the starting material was observed by TLC. The reaction was then filtered on a short plug of basic alumina. After removal of the solvents under reduced

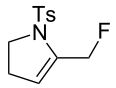
pressure, the crude product was purified by flash column chromatography on alumina with pentane/ethyl acetate 85:15 as eluent.

Spectral data of cyclic products



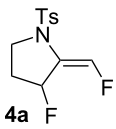
3a

3a. White solid, mp 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.38 (d, J = 5.2 Hz, 1H), 5.09 (ddd, $J_{H\text{-}F}$ = 54.6, $J_{H\text{-}H}$ = 4.2, 1.9 Hz, 1H), 4.76 (d, J = 6.0 Hz, 1H), 3.88–3.82 (m, 1H), 3.63 (td, J = 9.8, 6.5 Hz, 1H), 2.42 (s, 3H), 2.14–1.87 (m, 2H); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −168.4 (m, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C), 143.2 (d, $J_{C\text{-}F}$ = 15.4 Hz, C), 134.2 (C), 129.7 (2CH), 127.6 (2CH), 97.2 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH_2), 93.7 (d, $J_{C\text{-}F}$ = 178.5 Hz, CH), 48.6 (CH_2), 29.5 (d, $J_{C\text{-}F}$ = 22.3 Hz, CH_2), 21.7 (CH_3); IR (neat) 2358, 1652, 1338, 1251, 1156, 1085, 1000, 866, 814, 651 cm^{-1}; HRMS (m/z): $[M + Na]^+$ calcd for $C_{12}H_{14}FNO_2S$, 278.0621; found, 278.0632.



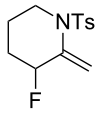
5a

5a. Isolated as a minor product in mixture with **3a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 5.39–5.37 (m, 1H), 5.22 (d, $J_{H\text{-}F}$ = 46.8 Hz, 2H), 3.78 (t, J = 8.9 Hz, 2H), 2.43 (s, 3H), 2.33–2.22 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −213.6 to −213.9 (m, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C), 139.5 (d, $J_{C\text{-}F}$ = 20.7 Hz, C), 134.1 (C), 130.1 (2CH), 127.8 (2CH), 115.4 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 78.5 (d, $J_{C\text{-}F}$ = 167.4 Hz, CH_2), 50.4 (CH_2), 27.7 (CH_2), 21.7 (CH_3).



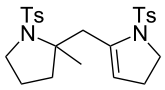
4a

4a. White solid, mp 68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.39 (dd, $J_{H\text{-}F}$ = 80.7, $J_{H\text{-}H}$ = 6.1 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 5.63 (dt, $J_{H\text{-}F}$ = 53.8 Hz, $J_{H\text{-}H}$ = 3.2 Hz, 1H), 3.83 (t, J = 9.2 Hz, 1H), 3.48 (ddd, J = 11.1, 10.1, 6.2 Hz, 1H), 2.43 (s, 3H), 2.09 (ddd, J = 17.5, 14.4, 6.1 Hz, 1H), 1.97–1.76 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −149.5 (dd, $J_{H\text{-}F}$ = 80.7, $J_{F\text{-}F}$ = 8.9 Hz, 1F), −171.6 to −173.7 (m, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 142.0 (dd, $J_{C\text{-}F}$ = 250.4, 10.1 Hz, CH), 133.3 (C), 129.9 (2CH), 128.2 (C), 127.8 (2CH), 88.1 (dd, $J_{C\text{-}F}$ = 178.7, 3.5 Hz, CHF), 48.7 (CH_2), 30.4 (d, $J_{C\text{-}F}$ = 23.1 Hz, CH_2), 21.8 (CH_3); IR (neat) 2359, 1597, 1353, 1163, 1133, 1090, 1060, 1011, 964, 814, 664 cm^{-1}; HRMS (m/z): $[M + Na]^+$ calcd for $C_{12}H_{13}F_2NO_2S$, 296.0527; found, 296.0535.



3b

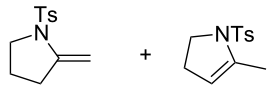
3b. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.35 (s, 1H), 5.16 (s, 1H), 4.70 (dt, $J_{H\text{-}F}$ = 49.6 Hz, $J_{H\text{-}H}$ = 5.3 Hz, 1H), 3.68–3.54 (m, 2H), 2.42 (s, 3H), 1.97–1.81 (m, 2H), 1.73 (m, 1H), 1.61–1.48 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −173.4 (m, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (C), 140.5 (d, $J_{C\text{-}F}$ = 19.0 Hz, C), 137.3 (C), 129.7 (2CH), 127.7 (2CH), 110.7 (d, $J_{C\text{-}F}$ = 7.7 Hz, CH_2), 88.4 (d, $J_{C\text{-}F}$ = 178.6 Hz, CHF), 46.9 (CH_2), 30.7 (d, $J_{C\text{-}F}$ = 21.7 Hz, CH_2), 21.7 (CH_3), 20.9 (d, $J_{C\text{-}F}$ = 5.4 Hz, CH_2); IR (neat) 1647, 1598, 1451, 1340, 1157, 1098, 1057, 950, 908, 814, 690, 653 cm^{-1}; HRMS (m/z): $[M + Na]^+$ calcd for $C_{13}H_{16}FNO_2S$, 292.0778; found, 292.0776.



8

8. White solid, mp 66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 5.2 Hz, 2H), 7.28 (d, J = 6.3 Hz, 2H), 5.41 (br s, 1H), 3.89–3.69 (m, 2H), 3.54–3.46 (m, 1H), 3.30–3.23 (m, 3H), 2.66–2.52 (m, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 2.01–1.87 (m, 3H), 1.78–1.58 (m, 2H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9 (C), 142.8 (C), 140.9 (C), 138.8 (C), 134.1 (C), 129.7 (2CH), 129.5 (2CH), 127.8 (2CH), 127.3 (2CH), 119.5 (CH), 68.20 (C), 51.3 (CH_2), 49.9 (CH_2), 39.6 (CH_2), 39.2 (CH_2), 27.7 (CH_2), 26.6 (CH_3), 22.7 (CH_2), 21.7 (CH_3), 21.6 (CH_3); IR (neat) 1452, 1332, 1154, 1089, 1000, 811, 655 cm^{-1}; HRMS (m/z): $[M + Na]^+$ calcd for $C_{24}H_{30}N_2O_4S_2$, 497.1539; found, 497.1517.

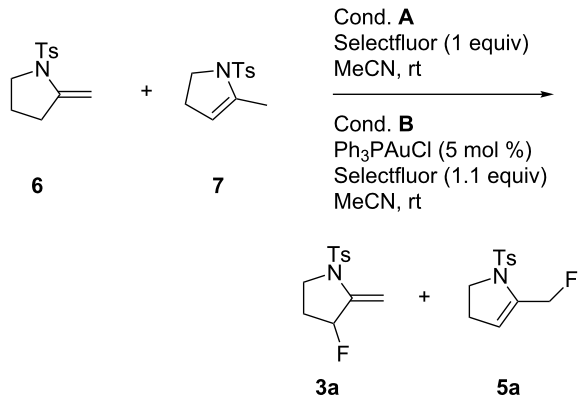
Synthesis of cyclic enamines



6 **7**

Cyclic enamines were synthesized in 59% yield (endo/exo 2:3) according to a literature procedure [32]. Spectral data matched those reported.

General procedure for the fluorination reactions of the enamines



6 **7** **3a** **5a**

Conditions **A**: In an oven-dried Schlenk apparatus the Selectfluor (0.17 mmol, 1 equiv) was loaded under a flow of argon. This was then dried under vacuum at 70–80 °C for 2 h. The mixture of cyclic enamines (0.17 mmol, 40 mg, 1 equiv) was then added, followed by anhydrous MeCN (7 mL), under a flow of argon. The mixture was stirred at rt until complete consumption of the starting material was observed by TLC. The reaction mixture was then filtered on a short plug of basic alumina. After removal of the solvents under reduced pressure, the crude product was purified by flash column chromatography on alumina with pentane/ethyl acetate 85:15 as eluent.

Conditions **B**: In an oven-dried Schlenk apparatus, the Selectfluor (0.33 mmol, 117 mg, 1.1 equiv) and triphenylphosphine gold chloride (16 μmol, 7.4 mg, 0.05 equiv) were loaded under a flow of argon. These solids were dried under vacuum at 70–80 °C for 2 h. A mixture of cyclic enamines (0.3 mmol, 72 mg, 1 equiv) was then added, followed by anhydrous MeCN (12 mL), under a flow of argon. The mixture was stirred at rt until complete consumption of the starting material was observed by TLC. The reaction was then filtered on a short plug of basic alumina. After removal of the solvents under reduced pressure, the crude product was purified by flash column chromatography on alumina with pentane/ethyl acetate 85:15 as eluent.

Supporting Information

Supporting Information File 1

^{1}H, ^{13}C, ^{19}F NMR spectra of products **3a**, **4a**, **5a**, **3b** and **8**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-162-S1.pdf]

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Synthesis of fluoranthenes by hydroarylation of alkynes catalyzed by gold(I) or gallium trichloride

Sergio Pascual[1], Christophe Bour[1], Paula de Mendoza[1] and Antonio M. Echavarren[*1,2]

Full Research Paper

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Address:
[1]Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain and [2]Additional affiliation: Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/ Marcel·li Domingo s/n, 43007 Tarragona, Spain

Email:
Antonio M. Echavarren[*] - aechavarren@iciq.es

* Corresponding author

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Abstract

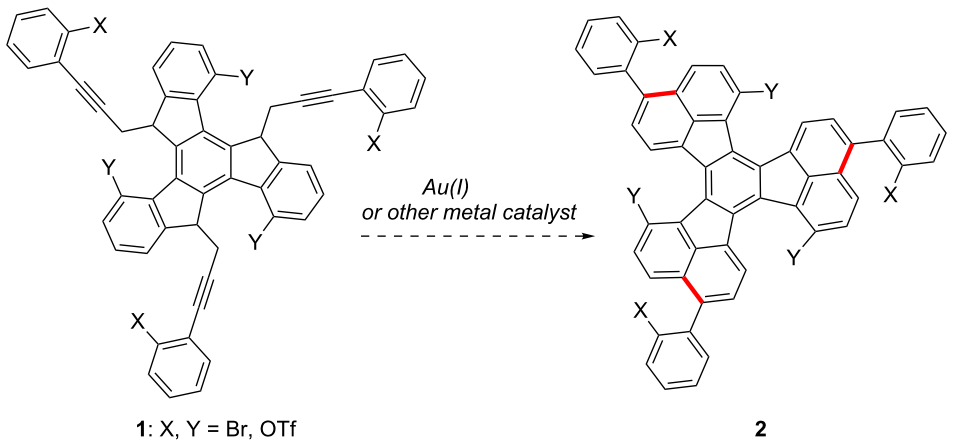
Electrophilic gold(I) catalyst **6** competes with $GaCl_3$ as the catalyst of choice in the synthesis of fluoranthenes by intramolecular hydroarylation of alkynes. The potential of this catalyst for the preparation of polyarenes is illustrated by a synthesis of two functionalized decacyclenes in a one-pot transformation in which three C–C bonds are formed with high efficiency.

Introduction

Electrophilic activation of alkynes in functionalized substrates by gold catalysts allows for the synthesis of complex molecules under mild conditions [1-8]. Alkynes can react in gold-catalyzed Friedel–Crafts-type reactions with arenes to give products resulting from the intermolecular hydroarylation of the alkynes (or alkenylation of the arenes) [9-21]. In addition to gold, the intramolecular version of this reaction was also carried out with Ru(II) [22], Pt(II) [12,22,23], Pt(IV) [24], Ga(III) [25,26], and Hg(II) [27,28] as catalysts.

Electron-rich indoles also react with alkynes in the presence of gold catalysts to form 6–8-membered rings [29-31]. A similar reaction can also be carried out with $GaCl_3$ [32] and Pt(II) [33] as catalysts. In contrast, alkynyl furans react with gold to give phenols by using Au(III), Au(I) [1,2,34-37], or Pt(II) as the catalyst [38,39].

In our efforts towards the synthesis of large polyarenes [40-43], which are related to the fullerenes [44], we used the palladium-catalyzed arylation reaction as the main tool [45-48]. We decided to try the triple hydroarylation of substrates of type **1** to give 3,9,15-triaryldiacenaphtho[1,2-*j*:1',2'-*l*]fluoranthenes **2** with X and Y substitutes at strategic positions, which could be activated by palladium in subsequent intramolecular arylations



Scheme 1: Proposed metal catalyzed annulation for the synthesis of triaryldiacenaphtho[1,2-*j*:1',2'-*l*]fluoranthenes **2**.

(Scheme 1). Substituted fluoranthenes are of interest since some derivatives have been shown to be useful in light-emitting devices [49-52]. Fluoranthene derivatives have already been synthesized by palladium-catalyzed arylation reactions [53,54]. Strategically halogenated decacyclenes with a substitution pattern similar to that of **2** have been used for the synthesis of circumtrindene by flash vacuum pyrolysis [55]. Here we report the results on the synthesis of large polyarenes **2** and more simple 3-arylfluoranthenes by using gold(I)- or gallium(III)-catalyzed hydroarylation reactions.

Results and Discussion

First, we examined the cyclization of **3** to give **4** or **4'** [22,24,26] (Table 1) with cationic gold(I) catalysts **5** [56] and **6** [57] (Figure 1), which have been demonstrated to be amongst the best catalysts in many gold(I)-catalyzed cyclizations [6,58]. No reaction was observed with complex **5** after heating for 5 min at 70 °C in CH_2Cl_2 under microwave irradiation (Table 1, entry 1), whereas the more electrophilic **6**, bearing a less donating phosphite ligand, led almost quantitatively to **4'** (Table 1, entry 2). Under these conditions, $AuCl_3$ was not effective as a catalyst (Table 1, entry 3). As previously reported [25,26], $GaCl_3$ is an excellent catalyst for the cyclization of **3** to give **4'** (Table 1, entry 4). In all cases the reaction proceeds exclusively though the 6-*exo*-*dig* pathway.

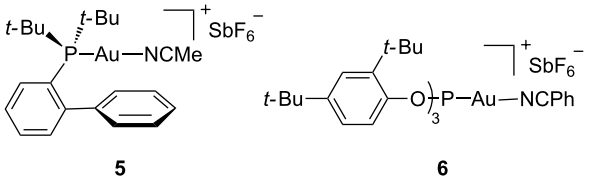
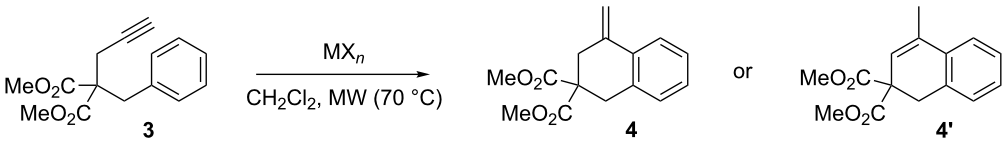


Figure 1: Cationic gold complexes **5** and **6**.

The cyclization of 9-(3-phenylprop-2-ynyl)-9*H*-fluorene (**7a**) to form 3-phenylfluoranthene (**8a**) [59] was also examined by using catalysts **5**, **6**, and $GaCl_3$ (Table 2). Since the initial

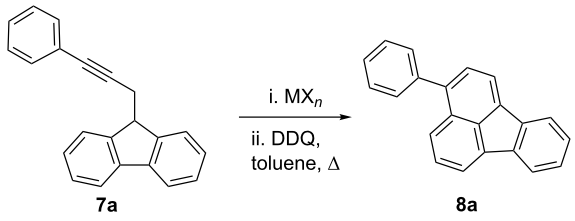
Table 1: Hydroarylation of **3** to give dihydronaphthalene **4'**.[a]



entry	MX_n	**4'** (yield, %)
1	**5**	—[b]
2	**6**	99
3	$AuCl_3$	—[c]
4	$GaCl_3$	99

[a]2 mol % catalyst, microwave irradiation, 5 min. [b]100% **3** was recovered. [c]87% **3** was recovered.

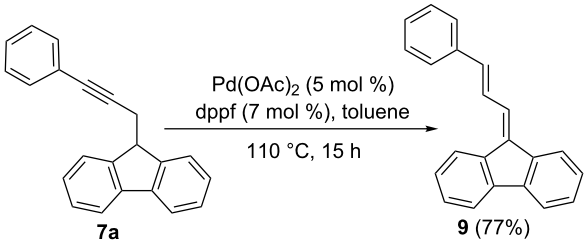
Table 2: Hydroarylation of 9-(3-phenylprop-2-ynyl)-9*H*-fluorene (**7a**) to give 3-phenylfluoranthene (**8a**).[a]



entry	MX_n (mol %)	solvent	*T* (°C)	*t* (h)	yield (%)
1	**5** (2)	CH_2Cl_2	70[b]	0.7	—[c]
2	**5** (5)	toluene	110	1	—[d]
3	**6** (5)	CH_2Cl_2	r.t.	17	64
4	**6** (2)	CH_2Cl_2	r.t.	16	70
5	**6** (1)	CH_2Cl_2	r.t.	16	70
6	$PtCl_2$ (5)	toluene	110	17	—[c]
7	$AuCl_3$ (5)	toluene	110	17	—[c]
8	$InCl_3$ (5)	toluene	110	17	—[d]
9	$GaCl_3$ (2)	CH_2Cl_2	r.t.	26	16[e]
10	$GaCl_3$ (2)	toluene	70[b]	0.2	57
11	$FeCl_3{\cdot}6H_2O$ (10)	DCE[f]	r.t.	40	36[e]
12	$FeCl_3{\cdot}6H_2O$ (5)	DCE[f]	70[b]	0.2	34[e]

[a]Crude reaction mixtures were aromatized by heating in toluene with DDQ (3 equiv) for 12 h. [b]Microwave irradiation. [c]No reaction. [d]Product decomposition. [e]Yield determined by ^{1}H NMR. [f]DCE = 1,2-dichloroethane.

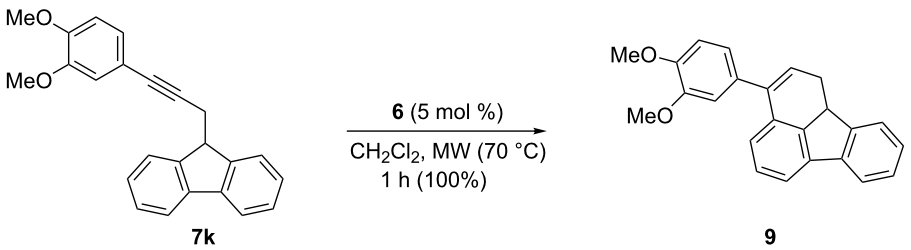
gold(I)-catalyzed reaction provided a mixture of 3-phenyl-1,10b-dihydrofluoranthene, 3-phenyl-1,2,3,10b-tetrahydrofluoranthene, and **8a**, the crude mixtures were treated with excess DDQ in toluene under reflux to provide pure **8a**. No reaction or decomposition was observed when the reaction was carried out with gold(I) complex **5** (Table 2, entries 1 and 2). In contrast, the more electrophilic gold(I) complex **6** with phosphite as the ligand led to **8a** in 64–70% yield by stirring at room temperature in CH_2Cl_2 (Table 2, entries 3–5). Satisfactory results were obtained by simply using 1 mol % of **6** (Table 2, entry 5). No reaction was observed with $PtCl_2$ or $AuCl_3$ even after heating in toluene under reflux (Table 2, entries 3–5). Whereas $InCl_3$ led to decomposition of **7a** under these conditions (Table 2, entry 6), $GaCl_3$ led to **8a**, although satisfactory results were only obtained in toluene at 70 °C (Table 1, entry 10). Interestingly, $FeCl_3$ was also catalytically active, although fluoranthene **8a** was only obtained in moderate yields (Table 2, entries 11 and 12). The reaction of **3a** with $Pd(OAc)_2$ as catalyst proceeded differently to give known (*E*)-9-(3-phenylallylidene)-9*H*-fluorene (**9**) [60], presumably via the formation of the corresponding allene as an intermediate (Scheme 2).



Scheme 2: $Pd(OAc)_2$-catalyzed isomerization of **7a** to form (*E*)-9-(3-phenylallylidene)-9*H*-fluorene (**9**).

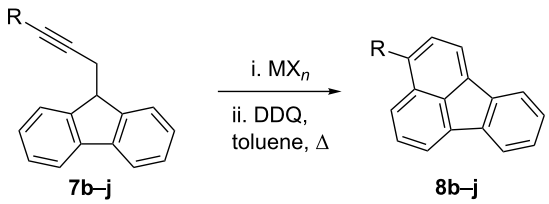
Substrates **7b**–**j**, prepared by alkylation of fluorenyl lithium with the corresponding propargyl bromide or by Sonogashira couplings of 9-(prop-2-ynyl)-9*H*-fluorene [61], were cyclized by using gold(I) complex **6** or $GaCl_3$ as the catalyst (Table 3). Although both catalysts could be used for the synthesis of 3-arylfluoranthenes **8b**–**h**, better yields were obtained with $GaCl_3$ in toluene at 100 °C. However, in the case of 9-(3-bromoprop-2-yn-1-yl)-9*H*-fluorene (**7i**), gold(I) complex **6** gave more satisfactory results (Table 3, compare entries 10 and 11). The reaction proceeded satisfactorily with aryl-substituted substrates bearing either electron-donating (*p*-Me, *o*-OMe) or electron-withdrawing (*p*-Cl, *p*-Br, *p*-CN, *p*-NO_2) groups. However, no reaction was observed for *n*-butyl derivative **7j** with **6** or with $GaCl_3$ (Table 3, entries 12 and 13).

Cyclization of substrate **7k**, having an electron-rich aryl group at the alkyne, with catalyst **6** gave 1,10*b*-dihydrofluoranthene **9** cleanly in quantitative yield (Scheme 3).



Scheme 3: Gold(I)-catalyzed hydroarylation of **7k** to give 1,10b-dihydrofluoranthene **9**.

Table 3: Hydroarylation of **7b–j** to give 3-substituted fluoranthenes **8b–i**.[a]



7b–j **8b–j**

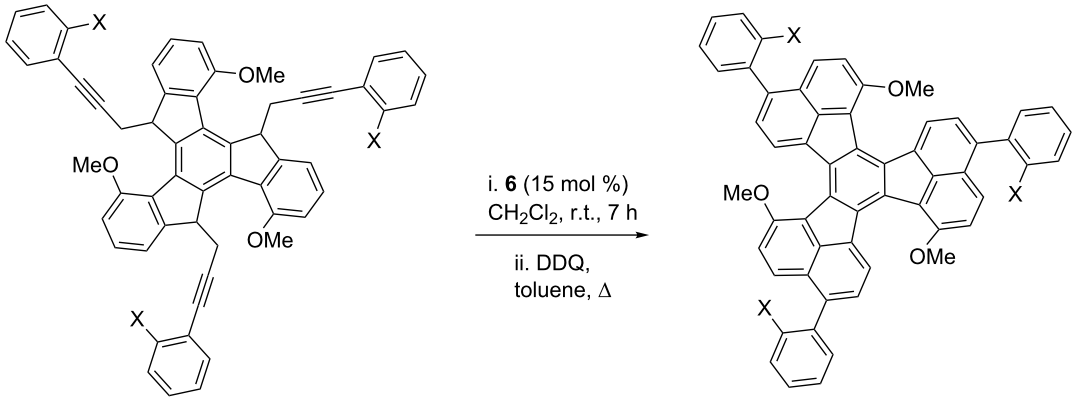
entry	fluorene	R	MX_n (mol %)	solvent	*T* (ºC)	*t* (h)	yield (%)
1	**7b**	*p*-Tol	$GaCl_3$ (5)	toluene	100[b]	0.2	45
2	**7b**	*p*-Tol	**6** (5)	CH_2Cl_2	r.t.	17	28
3	**7c**	*p*-ClC_6H_4	$GaCl_3$ (5)	toluene	100[b]	0.2	71
4	**7d**	*p*-NCC_6H_4	$GaCl_3$ (2)	toluene	100[b]	0.2	88
5	**7e**	*p*-$O_2NC_6H_4$	$GaCl_3$ (2)	toluene	70[b]	0.2	92
6	**7f**	*o*-$MeOC_6H_4$	**6** (5)	CH_2Cl_2	r.t.	17	17
7	**7f**	*o*-$MeOC_6H_4$	$GaCl_3$ (5)	toluene	100[b]	0.2	57
8	**7g**	*o*-BrC_6H_4	$GaCl_3$ (5)	toluene	100[b]	0.2	44
9	**7h**	C_6F_5	$GaCl_3$ (5)	toluene	100[b]	2	74
10	**7i**	Br	**6** (5)	CH_2Cl_2	r.t.	20	44
11	**7i**	Br	$GaCl_3$ (5)	toluene	100[b]	0.2	21
12	**7j**	*n*-Bu	**6** (5)	CH_2Cl_2	r.t.	7	—[c]
13	**7j**	*n*-Bu	$GaCl_3$ (2)	toluene	70[b]	0.2	—[c]

[a]Crude reaction mixtures were aromatized by heating in toluene with DDQ (3 equiv) for 12 h. [b]Microwave irradiation. [c]No reaction.

Derivatives **1a** and **1b** were readily prepared by the triple alkylation of the lithium anion of 4,9,14-trimethoxytruxene (Scheme 4) [41,62]. The cyclization reaction was carried out efficiently with gold(I) catalyst **6** (15 mol %) at room temperature in CH_2Cl_2 to give triaryl substituted diacenaphtho[1,2-*j*:1',2'-l]fluoranthenes (decacyclenes) **2a** and **2b** in very good overall yields after aromatization of the crude products with DDQ. Remarkably, this triple hydroarylation occurs efficiently with an average yield per C–C bond formation that is greater than 90%.

Conclusion

Highly electrophilic gold(I) catalyst **6** with a bulky phosphite ligand competes with $GaCl_3$ as the catalyst of choice for the hydroarylation of alkynes. The synthetic potential of this catalyst is illustrated by the synthesis of functionalized triarylated



1a: X = H
1b: X = Br

2a: X = H (72%)
2b: X = Br (77%)

Scheme 4: Gold(I)-catalyzed triple hydroarylation of **1a**,**b** to give **2a**,**b**.

decacyclenes in which three C–C bonds are formed with high efficiency in a one-pot transformation. The reaction is totally compatible with aryl bromides, which do not undergo subsequent arylation reaction due to the inertness of gold(I) catalysts towards oxidative addition reactions under homogeneous conditions [63,64].

Supporting Information

Supporting Information features experimental details and characterization data for new compounds.

Supporting Information File 1

Experimental details
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-178-S1.pdf]

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