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Beilstein Journal of Organic Chemistry

Carbometallation chemistry

Ilan Marek

Editorial

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Following the pioneering Ziegler addition of nucleophiles to nonactivated unsaturated carbon–carbon bonds, the controlled carbometallation reaction has emerged. Since then, reactions that result in the addition of a carbon–metal bond of an organometallic across a carbon–carbon unsaturated system, leading to a new organometallic in which the newly formed carbon–metal bond can be used for further synthetic transformations, are called carbometallation reactions. In the past few decades, the intra- as well as intermolecular additions of various organometallic species to a large variety of alkynes, alkenes and allenes have been successfully reported. Although the carbometallation reaction on alkynes is generally a well-controlled and predictable transformation, leading to large variety of substituted stereocontrolled alkenyl metals, the addition of organometallic species to acyclic nonactivated alkenes still represents a formidable and yet unresolved synthetic challenge. Particularly stimulating would be the regio-, stereo- and enantioselective addition of organometallic species on α,β-disubstituted double bonds, leading to a configurationally stable sp^3 organometallic that would subsequently react with electrophiles. This landmark transformation would formally result in the 1,2-bisalkylation of nonactivated alkenes! In this Thematic Series, you will find excellent contributions tackling various problems of carbometallation reactions, indicating a lively and rapidly moving field, and I have no doubt that more elegant transformations of C–C unsaturated bonds will continue to appear, including the enantioselective carbometallation reaction of substituted nonactivated alkenes. I would like to warmly thank all the contributors of this Thematic Series that have beautifully highlighted the state of the art of the field.

I have tremendously enjoyed reading this Thematic Series and I am convinced that you will all share in this pleasure!

Ilan Marek

Haifa, January 2013

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Beilstein Journal of Organic Chemistry

Stereoselective synthesis of tetrasubstituted alkenes via a sequential carbocupration and a new sulfur–lithium exchange

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Letter

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Abstract

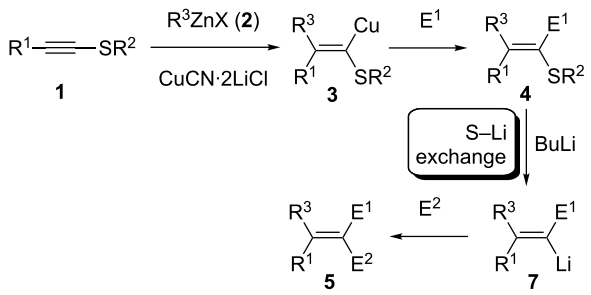
We have designed a new sequential carbocupration and sulfur–lithium exchange that leads stereo- and regioselectively to trisubstituted alkenyllithiums. Subsequent trapping with various electrophiles yields tetrasubstituted olefins with good control of the double-bond geometry (*E*/*Z* ratio up to 99:1). The novel sulfur–lithium exchange could be extended to the stereoselective preparation of *Z*-styryl lithium derivatives with almost complete retention of the double-bond geometry.

Introduction

The stereoselective synthesis of tetrasubstituted alkenes is an important synthetic goal, which may be achieved by carbometalation methods [1-9]. The Normant carbocupration of terminal acetylenes allows the stereoselective preparation of trisubstituted alkenes with excellent *E*/*Z* ratio [10-12]. However, in order to obtain tetrasubstituted alkenes, a carbometalation of an internal alkene is required. This reaction is usually difficult due to steric hindrance and proceeds only if electron-withdrawing groups are attached to the alkyne unit to facilitate the carbometalation step. Recently, we studied the chemistry of alkenyl sulfides and their use for carbometalation extensively [13].

Therefore, we envisioned using an alkynyl thioether such as **1** as an activated alkyne. After a carbocupration of the alkynyl thioether **1** with the organozinc reagent **2** in the presence of CuCN·2LiCl [14], the alkenylcopper species **3** should be obtained. Stereoselective quenching with an electrophile (E^1) should afford the tetrasubstituted alkenyl thioether **4**. Extensive experimentation showed that thioethers **4** do not undergo Ni- or Pd-catalyzed cross couplings leading to products of type **5** (R = Me, Ph) [15,16]. Thus, we designed a new sulfur–lithium exchange (Scheme 1).

Sulfur–lithium exchanges proceed only readily with sulfoxides [17-19] and these reactions are often complicated by radical side reactions [20,21]. This new, direct sulfur–lithium exchange on an alkenyl thioether of type **4** involves the use of a bromobiphenyl R-group, which by treatment with BuLi at low



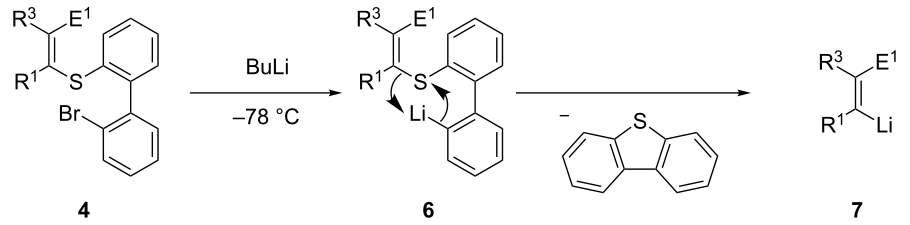
Scheme 1: Synthesis of tetrasubstituted olefins by a successive carbocupration and S–Li exchange.

temperatures, undergoes first a fast bromine–lithium exchange leading to an intermediate biphenyllithium derivative of type **6**, followed by an intramolecular ring-closing sulfur–lithium exchange [22] leading to the desired alkenyllithium **7** (Scheme 2).

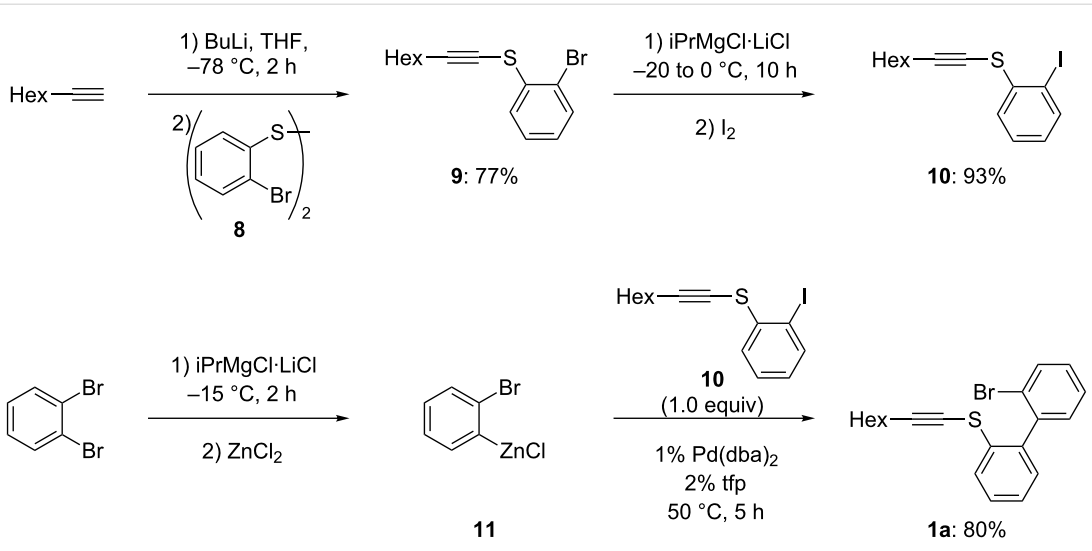
Subsequent quenching with a different electrophile E^2 should afford the tetrasubstituted alkene of type **5**; (Scheme 1). Herein, we demonstrate the feasibility of this methodology and thus prepare tetrasubstituted alkenes with *E*/*Z* stereoselectivities up to 99:1. Furthermore, we show that this sulfur–lithium exchange can be extended to the stereoselective preparation of *Z*-styryl derivatives.

Results and Discussion

First, we wish to report the synthesis of the alkynyl biphenyl thioether **1a** required for the carbometalation step. Thus, octyne was deprotonated with butyllithium (1.1 equiv, THF, −78 °C, 2 h) followed by the addition of the diaryl disulfide [23] (**8**: 1.1 equiv, −78 °C to 25 °C, 3 h) providing the bromothioether **9** in 77% yield. Direct Pd-catalyzed Negishi cross-coupling [24-28] of **9** with an arylzinc derivative failed. However, the bromide **9** could be readily converted to the corresponding iodide **10** by a bromine–magnesium exchange using iPrMgCl·LiCl [29-35] followed by iodolysis leading to the iodide **10** in 93% yield. Treatment of 1,2-dibromobenzene with iPrMgCl·LiCl at −15 °C for 2 h followed by a transmetalation with $ZnCl_2$ gives the required zinc reagent **11**, which undergoes a Negishi cross-coupling with the iodide **10** at 50 °C (5 h) leading to the alkynyl thioether **1a** in 80% yield (Scheme 3).



Scheme 2: Proposed mechanism of the sulfur–lithium exchange starting with the alkenyl thioether **4**.



Scheme 3: Synthesis of the precursor **1a**.

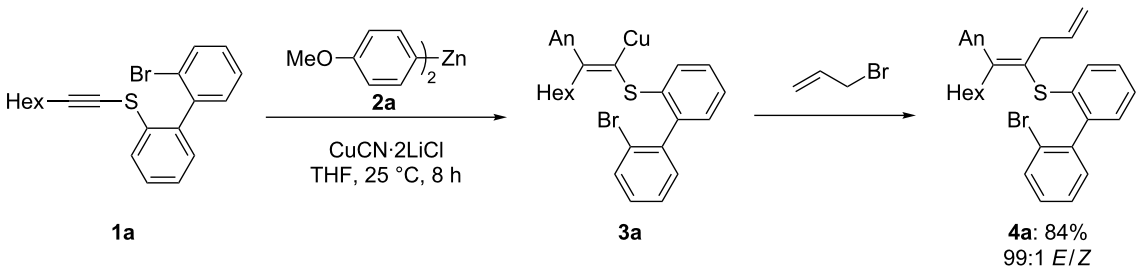
The harsh cross-coupling conditions may be due booth to the presence of the ortho-bromo substitution in the zinc reagent **11**, which considerably reduces the nucleophilicity of this arylzinc reagent by inductive effects, and also to the sulfur atom of the electrophile, which poisons the Pd catalyst. With the thioether **1a** in hand, we have performed the Normant carbocupration with di-*para*-anisylzinc (An_2Zn: **2a**) according to a procedure previously developed by us [36]. Thus, the reaction of **1a** (1.0 equiv) with An_2Zn (1.5 equiv, THF) in the presence of CuCN·2LiCl (1.5 equiv) at 25 °C for 8 h produces the intermediate copper reagent **3a**, which, after allylation with allyl bromide, provides the thioether **4a** in 84% yield and an *E*/*Z* ratio of 99:1 (Scheme 4). The reaction of **3a** with other typical electrophiles is possible, but proceeds in moderate yields due to the low reactivity of copper reagent **3a**.

The bromothioether **4a** was then treated with *s*-BuLi (1.3 equiv, −78 °C, 10 min), leading to the formation of the intermediate aryllithium **6a**, which undergoes the desired intramolecular sulfur–lithium exchange affording the alkenyllithium reagent **7a** (Scheme 5).

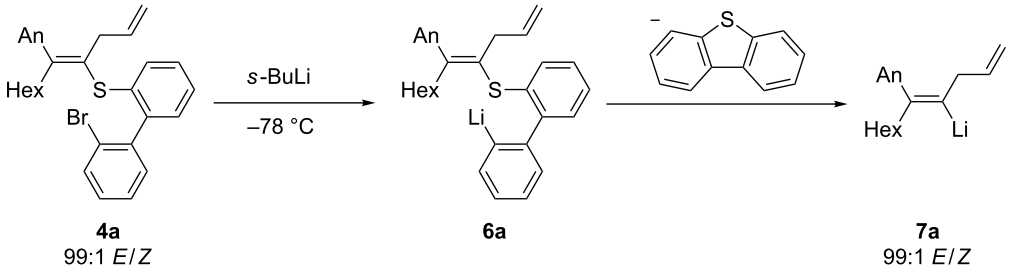
This alkenyllithium was quenched with typical electrophiles with a high retention of the double-bond geometry. Thus, the treatment of **7a** with EtI (2 equiv, −78 °C, 15 min) provides the tetrasubstituted alkene **5a** in 75% yield and an *E*/*Z* ratio of 1:99. Direct carboxylation by the reaction with ethyl chloroformate (1.1 equiv, −78 °C, 15 min) furnishes the corresponding unsaturated ethylester **5b** in 55% isolated yield and an *E*/*Z* ratio of 95:5. Finally, a copper-catalyzed allylation with ethyl 2-(bromomethyl)acrylate [37] (1.5 equiv, −78 to 0 °C, 2 h) affords the triene **5c** in 55% yield and an *E*/*Z* ratio of 99:1 (Scheme 6).

These quenching experiments demonstrate that this new method based on a successive carbocupration and sulfur–lithium exchange allows the stereoselective preparation of various tetrasubstituted alkenes. Since Normant has shown that various alkylcopper species add to alkynyl thioethers [38-40], the use of a bromobiphenyl substituent (R^2) on the sulfur may allow a general stereoselective synthesis of tetra-substituted alkenes.

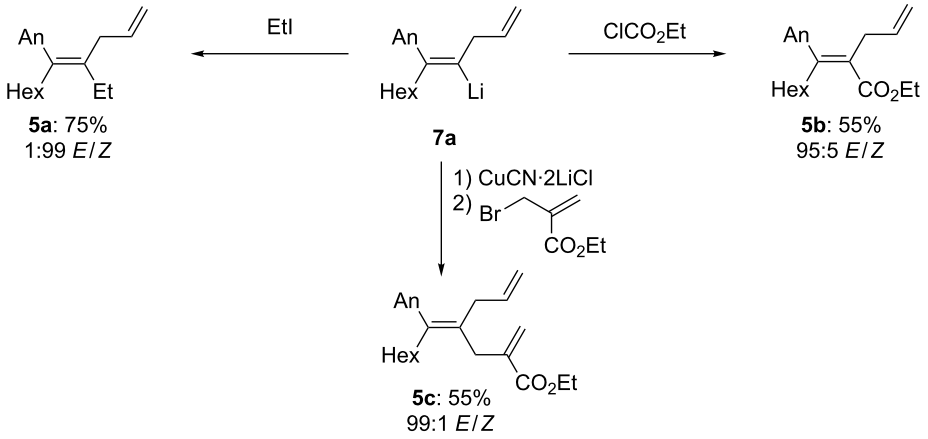
In order to prove that this new sulfur–lithium exchange has further applications in the stereoselective synthesis of alkenes, we prepared the *Z*-alkenyl thioether **12** starting from 2,2'-dibromobiphenyl. Thus, the performance of a double bromine–lithium exchange with BuLi (1.1 equiv, −78 °C, 0.25 h) followed by a quenching with tetramethylthiuram disulfide (1.1 equiv, −78 to 25 °C, 12 h) furnishes the dithiocarbamate **13** in 82% yield. Since the reduction to the free thiol is hard to achieve due to dibenzothiophene formation [41], we performed an in situ deprotection and stereoselective addition to phenylacetylene [42] (1.5 equiv, 1.25 equiv NaOEt, EtOH,



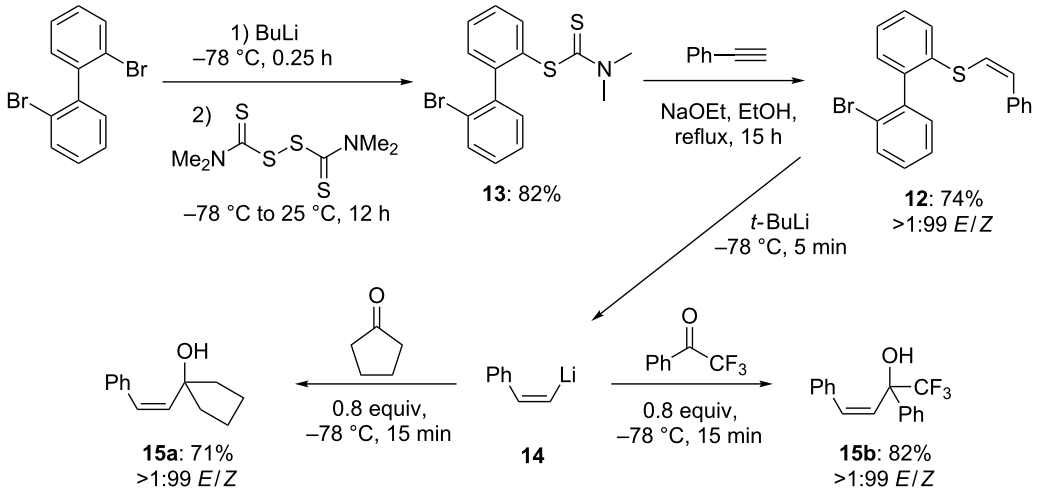
Scheme 4: Carbocupration of the thioether **1a** leading to the tetrasubstituted alkene **4a**.



Scheme 5: Synthesis of the alkenyllithium reagent **7a** by an S–Li exchange.



Scheme 6: Quenching of the alkynyllithium **7a**. (Product ratios and diastereoselectivities were determined by ^{1}H- and 2D-NMR.)



Scheme 7: Synthesis and quenching of *Z*-styryllithium.

reflux, 15 h) yielding the *Z*-alkenyl thioether **12** in 74% yield (Scheme 7).

Treatment of **12** with *t*-BuLi (1.6 equiv, −78 °C, 10 min) provides directly the *Z*-styryllithium **14**, which stereoselectively adds to α,α,α-trifluoroacetophenone (0.8 equiv, −78 °C, 0.5 h) and cyclopentanone (0.8 equiv, −78 °C, 0.5 h) to afford the expected tertiary allylic alcohols **15a**–**b** in 71–82% yield and *E*/*Z* ratios of >1:99.

Conclusion

In summary, we have reported tetrasubstituted olefins with excellent *E*/*Z* ratios using a sequential carbocupration and a new sulfur–lithium exchange involving an alkenyl thioether bearing a 2'-bromobiphenyl substituent, which triggers efficiently the sulfur–lithium exchange. Extension to the stereoselective preparation of Z-styryllithium was shown.

Supporting Information

Supporting Information File 1

Experimental details and characterization data of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-248-S1.pdf]

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Beilstein Journal of Organic Chemistry

Highly stereocontrolled synthesis of *trans*-enediynes via carbocupration of fluoroalkylated diynes

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Letter

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Abstract

Treatment of readily prepared (*Z*)-6-benzyloxy-1,1,1,2-tetrafluoro-6-methyl-2-hepten-4-yne with 1.5 equiv of LHMDS in −78 °C for 1 h gave the corresponding trifluoromethylated diyne in an excellent yield. This diyne was found to be a good substrate for the carbocupration with various higher-ordered cyanocuprates to give the corresponding vinylcuprates in a highly regio- and stereoselective manner. The in situ generated vinylcuprates could react very smoothly with an excess amount of iodine, the vinyl iodides being obtained in high yields. Thus-obtained iodides underwent a very smooth Sonogashira cross-coupling reaction to afford various *trans*-enediynes in high yields.

Introduction

trans-Enediynes (*trans*-hex-3-ene-1,5-diynes), as shown in Figure 1, are well-recognized as one of the most important building blocks because they are frequently utilized for the synthesis of π-conjugated polymers, which have attracted much attention in the fields of electronic and photonic materials science [1-3].

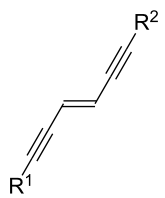
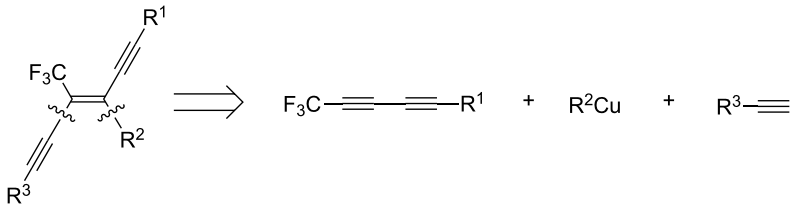


Figure 1: *trans*-Enediyne.

While numerous synthetic approaches to non-fluorinated *trans*-enediynes have been reported so far, there has been quite a limited number studies on the preparation of fluoroalkylated *trans*-enediynes [4-7], although the introduction of fluorine atom(s) into organic molecules very often changes their physical as well as chemical characteristics significantly, resulting in the discovery of new materials with unique physical properties [8-14].

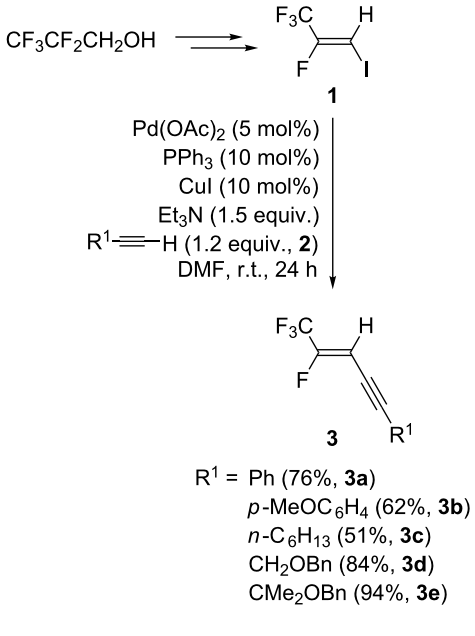


Scheme 1: Synthetic strategy for the preparation of trifluoromethylated diynes.

In this paper we report a convenient and efficient access to trifluoromethylated enediynes by the highly regio- and stereoselective carbocupration reaction of trifluoromethylated diyne with various organocuprates (Scheme 1).

Results and Discussion

Our initial studies began with the preparation of trifluoromethylated diyne derivatives [15-22]. Thus, treatment of 2,3,3,3-tetrafluoro-1-iodo-1-propene (**1**), which could be easily prepared from 2,2,3,3,3-pentafluoropropanol in three steps [23], with 1.2 equiv of terminal alkynes **2** and 1.5 equiv of Et_3N in the presence of 5 mol % of $Pd(OAc)_2$ and 10 mol % each of PPh_3 and CuI in DMF at room temperature for 24 h, gave the corresponding Sonogashira cross-coupling products **3a**–**e** in good to high yields [24-26] (Scheme 2).

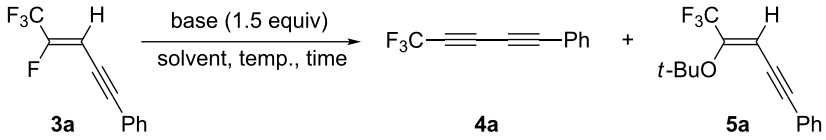


Scheme 2: Preparation of various enynes.

Subsequently, **3a** was subjected to the usual β-elimination conditions according to the literature [23,27-29], i.e., treatment of **3a** with 1.5 equiv of potassium *tert*-butoxide (*t*-BuOK) in THF at room temperature for 2 h. Very surprisingly, the desired trifluoromethylated diyne **4a** was not detected at all and the addition–elimination product **5a** was obtained quantitatively. Therefore, we examined the reaction conditions for the β-elimination of **3a** in detail (Table 1). As shown in Table 1, entries 2 and 3, the reactions with *t*-BuOK in various solvents, such as 1,4-dioxane and ether, were found to be fruitless, leading to a quantitative formation of **5a**. Changing the base from *t*-BuOK to KOH brought about better results (Table 1, entries 4–6). Thus, the reaction with 1.5 equiv of KOH at the reflux temperature of THF produced the desired diyne **4a** in ca. 10%, while no desired product was given at room temperature. On the other hand, a dramatic change could be observed when the amide bases were used. The use of lithium diisopropylamide (LDA) in THF at −78 °C for 2 h resulted in a significant increase of the yield from 10% to 46% (Table 1, entry 7). Switching LDA into lithium hexamethyldisilazide (LHMDS) led to a further improvement of the yield (Table 1, entry 8). Finally, the best yield was obtained when the reaction was carried out in THF at −78 °C for 1 h by using LHMDS. In this case the desired diyne **4a** was generated in 74% ^{19}F NMR yield as a sole product. Unfortunately, **4a** was found to be somewhat thermally unstable, and a partial decomposition was observed in silica-gel column chromatography, **4a** being isolated in very low yield. Additionally, such a partial decomposition of **4a** was also observed even when **4a** was kept in a freezer.

With the thus-obtained optimum reaction conditions, we next investigated the β-elimination reaction of various enynes as described in Table 2. As shown in Table 2, entry 2, changing a phenyl group into an anisyl group in R^1 resulted in a significant increase of the yield from 74% to a quantitative yield. In this case, it was found that **4b** was slightly thermally stable, compared to **4a**, while it could not be isolated in a pure form. In the case of the enyne having an *n*-C_6H_{13} group as R^1, on the other hand, the starting material was not completely consumed, and an inseparable mixture of the desired diyne **4c** and the enyne **3c** was given (Table 2, entry 3). In addition, the reaction proceeded very sluggishly in the enyne having CH_2OBn as R^1,

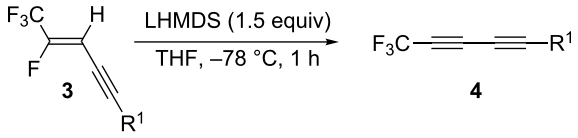
Table 1: Investigation of the reaction conditions.



entry	base	solvent	temp. (°C)	time (h)	yield[a] (% of **4a**)	yield[a] (% of **5a**)	recovery[a] (% of **3a**)
1	*t*-BuOK	THF	rt	2	0	quant.	0
2	*t*-BuOK	1,4-dioxane	rt	2	0	quant.	0
3	*t*-BuOK	Et_2O	rt	2	0	quant.	0
4	KOH	THF	rt	2	0	—	quant.
5	KOH	THF	reflux	2	9	—	83
6	KOH	THF	reflux	2	10	—	47
7	LDA	THF	−78	2	46	—	0
8	LHMDS	THF	−78	2	69	—	0
9	LHMDS	THF	−78	1	74	—	0

[a]Determined by ^{19}F NMR.

Table 2: β-Elimination of various enynes.



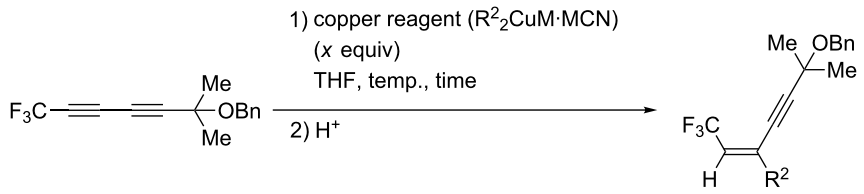
entry	R^1	yield[a] (% of **4**)	recovery[a] (/% of **3**)
1	Ph (**a**)	74	0
2	*p*-$MeOC_6H_4$ (**b**)	quant.	0
3[b]	*n*-C_6H_{13} (**c**)	48	35
4	CH_2OBn (**d**)	3	13
5	CMe_2OBn (**e**)	quant. (95)	0

[a]Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [b]Carried out for 24 h.

and neither **3d** nor **4d** could be obtained in high yields (Table 2, entry 4). Interestingly, the enyne **3e** having a CMe_2OBn group as R^1 was found to be a good substrate, the desired diyne **4e** being obtained quantitatively (Table 2, entry 5). Additionally, **4e** was so thermally stable that it could be obtained in 95% isolated yield after the silica-gel column chromatography.

With the substrate **4e** in hand, our interest was next directed toward the carbocupration reaction of **4e**. First of all, we attempted the investigation of the reaction conditions for the carbocupration reaction of **4e**, as described in Table 3. Thus, treatment of **4e** with 1.2 equiv of higher-ordered cyanocuprate (n-Bu)$_2$CuLi·LiCN, which was prepared from CuCN and 2 equiv of *n*-BuLi, at −78 °C for 2 h, followed by quenching the reaction with saturated aqueous NH_4Cl, gave the corresponding carbocupration product **5** in 46% yield as a sole product (it is well known that the carbocupration reaction of fluoroalkylated alkynes with cuprates proceeds in a highly *cis*-selective manner [30,31]), together with a slight recovery of the starting material (Table 3, entry 1). In this case, the reaction proceeded in a highly regio- and stereoselective manner and the other isomers **6**–**12** were not detected at all (Figure 2). It was especially noteworthy that only the triple bond possessing a CF_3 group, not the triple bond having a CMe_2OBn group, was subjected to the carbocupration reaction. As shown in Table 3, entry 2, raising the reaction temperature from −78 to −45 °C led to a significant increase in the yield. We also examined the reaction with the cuprate prepared from Grignard reagent, *n*-BuMgBr. As

Table 3: Investigation of the reaction conditions in carbocupration.



4e **5**

entry	copper reagent[a] (R^2_2CuM·MCN)	*x* (equiv)	temp. (°C)	time (h)	yield[b] (% of **5**)	recovery[b] (% of **4e**)
1	(*n*-Bu)$_2$CuLi·LiCN	1.2	−78	2	46	7
2	(*n*-Bu)$_2$CuLi·LiCN	1.2	−45	1	61	0
3	(*n*-Bu)$_2$CuMgBr·MgBrCN	1.2	−45	1	38	0
4	(*n*-Bu)$_2$CuMgBr·MgBrCN	1.2	−78	1	44	3
5	(*n*-Bu)$_2$CuMgBr·MgBrCN	1.2	−78	2	44	0
6	(*n*-Bu)$_2$CuMgBr·MgBrCN	1.5	−78	1	85	0
7	(*n*-Bu)$_2$CuMgBr·MgBrCN	1.5	−78	2	57	0

[a]Copper reagents were prepared from 1 equiv of CuCN and 2 equiv of R^2Li or R^2MgBr. [b]Determined by ^{19}F NMR.

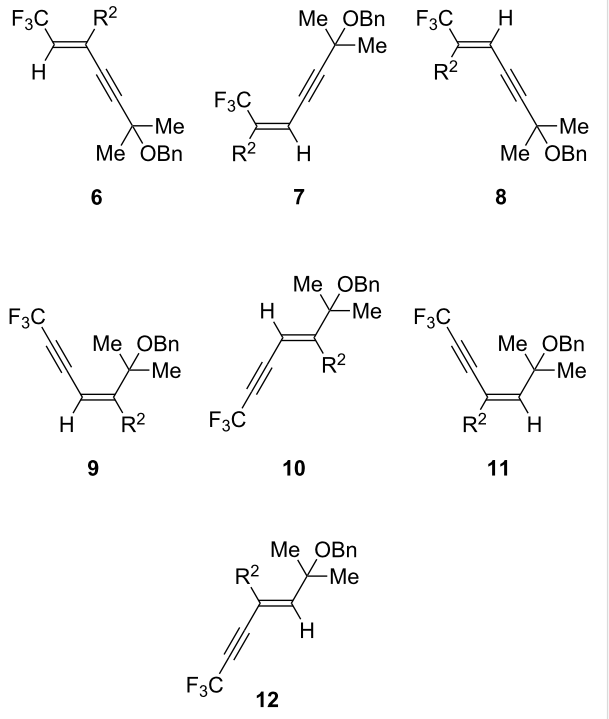


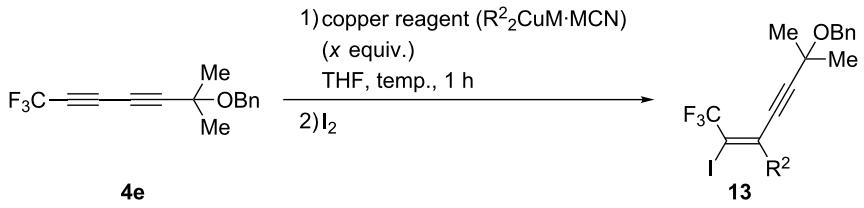
Figure 2: Regio- and stereoisomers.

summarised in Table 3, entries 3–5, a significant decrease of the yield was observed when the reaction was performed by using 1.2 equiv of cuprate. Very interestingly, the use of 1.5 equiv of the higher-ordered cyanocuprate realized the most satisfactory result, the desired product being obtained in 85% yield, though the yield was somewhat eroded in the reaction for 2 h.

With the optimum reaction conditions in hand, we next investigated the carbocupration reaction by using various copper reagents. In all cases, iodine was employed as an electrophile instead of aqueous NH_4Cl. The results are summarised in Table 4. As shown in Table 4, entries 1 and 2, (*n*-Bu)$_2$CuLi·LiCN and Me$_2$CuLi·LiCN could participate in the reaction to give the corresponding iodide **13a**,**b** in good yields. Furthermore, the cuprates prepared from alkyl Grignard reagents, such as *n*-Bu, Me, and cyclohexylmagnesium bromide, reacted smoothly (Table 4, entries 3–5). Switching the cuprate from dialkylcuprate into diarylcuprate did not bring about any influence on the yields at all (Table 4, entries 6 and 7).

A proposed reaction mechanism is outlined in Scheme 3. Based on the accumulated studies on the chemistry of fluoroalkylated alkynes, it appears possible that the copper reagent coordinates to the triple bond proximate to the CF_3 group (**Int-A**), rather than the alternative one (**Int-B**), due to high reactivity of the fluoroalkylated alkyne. Then, Cu^I adds oxidatively to the alkyne to form the intermediate **Int-C,** not **Int-D**. Since a CF_3 group has a very strong electron-withdrawing ability, the CF_3C^{α}—Cu^{III} bond may be stronger than Cu^{III}—C^{β}. (In the hydrometalation and the carbometalation reaction of fluoroalkylated alkynes, the same regioselectivity was observed [32-35].) Accordingly, a transfer of the R^2 group on Cu^{III} to the olefinic

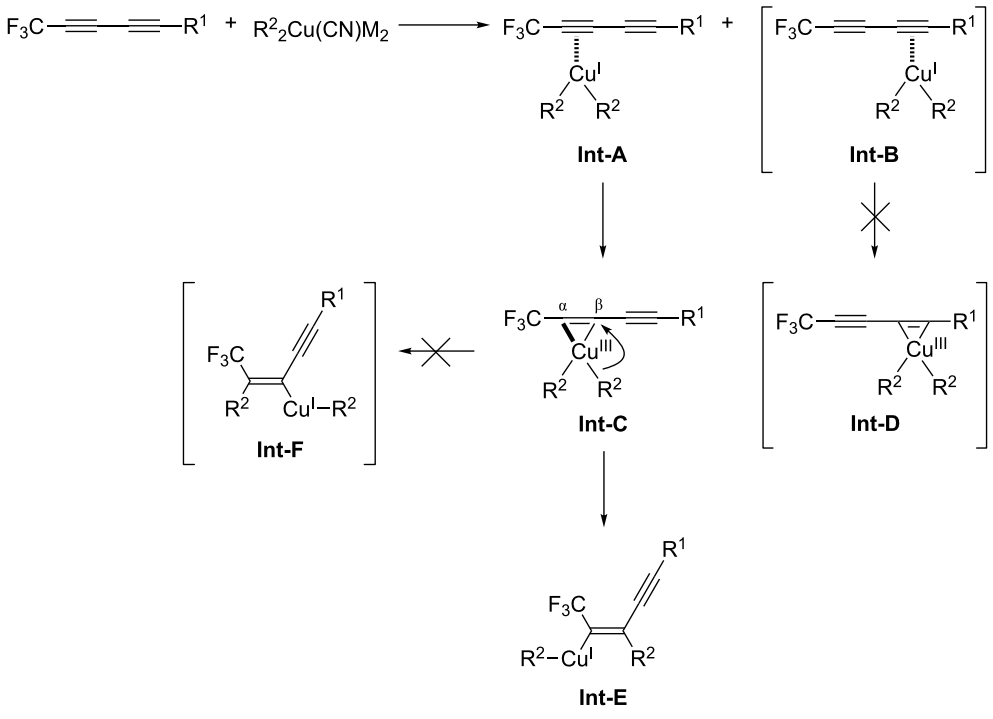
Table 4: Carbocupration with various cuprates.



4e **13**

entry	copper reagent[a] (R^2_2CuM·MCN)	x (equiv)	temp. (°C)	product	yield[b] (% of **13**)
1	(*n*-Bu)$_2$CuLi·LiCN	1.2	−45	**13a**	54
2	Me_2CuLi·LiCN	1.2	−45	**13b**	55
3	(*n*-Bu)$_2$CuMgBr·MgBrCN	1.5	−78	**13a**	60
4	Me_2CuMgBr·MgBrCN	1.5	−78	**13b**	59
5	Cy_2CuMgBr·MgBrCN	1.5	−78	**13c**	44
6	Ph_2CuMgBr·MgBrCN	1.5	−78	**13d**	55
7	(*p*-MeOC$_6$H$_4$)$_2$CuMgBr·MgBrCN	1.5	−78	**13e**	49

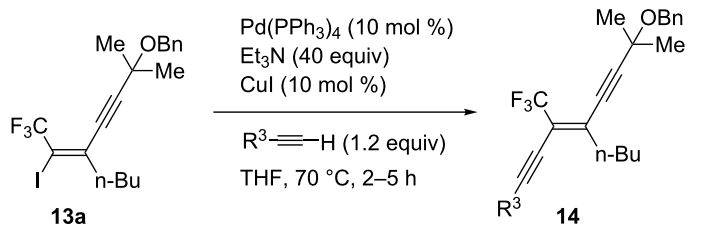
[a]Copper reagents were prepared from 1 equiv of CuCN and 2 equiv of R^2Li or R^2MgBr. [b]Isolated yield.



Scheme 3: A proposed reaction mechanism.

carbon distal to a CF_3 group may take place preferably, with vinylcopper intermediate **Int-E**, not **Int-F**, being produced exclusively. As a result, vinyl iodide **13** can be given in a highly regio- and stereoselective manner.

Finally, we attempted the Sonogashira cross-coupling reaction of the obtained iodide **13a** (Scheme 4). Thus, treatment of **13a** with 1.2 equiv of terminal alkynes and 40 equiv of Et_3N in the presence of 10 mol % each of $Pd(PPh_3)_4$ and CuI in THF at



Scheme 4: Synthesis of *trans*-enediynes. [a]Determind by ^{19}F NMR. Values in parentheses are of isolated yield.

70 °C for 2–5 h gave the corresponding enediynes **14a**–**c** in high to excellent yields. In all cases, other stereoisomers were not detected at all and **14a**–**c** were generated as the sole products in a pure form.

Conclusion

In summary, we have established a convenient as well as efficient access to the trifluoromethylated diyne by Sonogashira cross-coupling reaction of readily accessible 2,3,3,3-tetrafluoro-1-iodo-1-propene (**1**) and the following HF elimination reaction. The thus-obtained CF_3-enediyne could participate in the carbocupration with various higher-ordered cyanocuprates very well to give the corresponding vinyliodides in good yields. Finally, the thus-obtained iodide underwent a smooth Sonogashira cross-coupling reaction to afford the various desired *trans*-enediyne derivatives in high yields.

Supporting Information

Supporting Information File 1

Experimental, characterization details, and NMR spectra of synthesized compounds, **4e**, **13a**–**e**, and **14a**–**c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-249-S1.pdf]

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Intramolecular carbolithiation of *N*-allyl-ynamides: an efficient entry to 1,4-dihydropyridines and pyridines – application to a formal synthesis of sarizotan

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Full Research Paper

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Abstract

We have developed a general synthesis of polysubstituted 1,4-dihydropyridines and pyridines based on a highly regioselective lithiation/6-endo-dig intramolecular carbolithiation from readily available *N*-allyl-ynamides. This reaction, which has been successfully applied to the formal synthesis of the anti-dyskinesia agent sarizotan, further extends the use of ynamides in organic synthesis and further demonstrates the synthetic efficiency of carbometallation reactions.

Introduction

Since the discovery of the carbometallation reaction by Ziegler and Bähr in 1928 [1], this reaction has evolved as a most powerful tool to construct carbon–carbon bonds. An ever increasing number of organometallic species have been shown over the years to be suitable reagents for the carbometallation of various carbon–carbon multiple bonds. Lithium, copper, zinc, magnesium, zirconium, titanium, palladium and other metals are suitable for this transformation and considerable progress has recently been made in this area. Among these systems, the carbometallation of alkynes constitutes a most efficient entry to polysubstituted alkenes, provided that both the regioselectivity and the stereoselectivity can be controlled [2-5]. In this context,

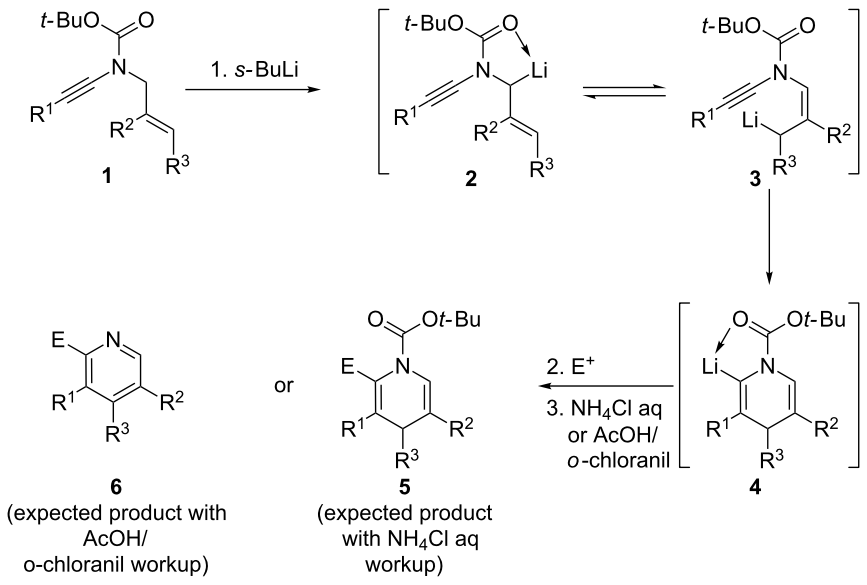
an efficient strategy to control these selectivity issues is the incorporation of a heteroatom directly attached to the triple bond, which can dramatically affect both the regio- and stereochemical outcomes due to the polarization of the triple bond and/or the formation of chelation-stabilized vinylmetal species. The carbometallation of O-, N-, P-, S-, and Si-substituted alkynes has indeed been quite extensively studied and shown to provide most efficient entries to polysubstituted, stereodefined heteroatom-substituted alkenes and has been implemented in remarkably elegant processes [6]. Intramolecular versions are especially attractive and provide most useful entries to highly substituted carbo- and heterocycles.

Based on our recent interest in the chemistry of ynamides [7-18] and inspired by recent reports from Meyer and Cossy [19-21], Marek [22-24] and Lam [25,26] on their carbopalladation, carbocupration and carbozincation, respectively, we decided to study the intramolecular carbolithiation of ynamides, which may provide an interesting entry to highly functionalized 1,4-dihydropyridines [27-29] and pyridines [30-33], most useful building blocks in organic synthesis and medicinal chemistry as well. Our strategy is summarized in Scheme 1 and is based on the following assumptions: According to the remarkable work of the Beak group on the α-lithiation of Boc-protected amines [34-38], *N*-allyl-ynamides **1** should be readily deprotonated to afford a transient chelation-stabilized allyllithium **2** and, provided that a metallotropic equilibrium exists between this intermediate and the less-stable allyllithium **3**, an intramolecular carbometallation may then occur to yield a chelation-stabilized vinyllithium **4** and drive the overall process to the formation of the heterocyclic ring system. Further reaction with an electrophile followed by aqueous workup or hydrolysis under acidic and oxidative conditions would then afford the highly substituted dihydropyridine or pyridine derivatives **5** and **6**, respectively. While there were no examples of such exclusive anionic 6-endo-dig cyclizations reported to the best of our knowledge [39], we felt that the presence of the chelating group on the nitrogen may allow such a selective process and a clean formation of the (dihydro)pyridine ring system. We have indeed demonstrated the efficiency of this strategy [40] and now report in this manuscript a full account on this work as well as the application of our pyridine synthesis to a formal synthesis of the anti-dyskinesia agent sarizotan.

Results and Discussion

Feasibility of the deprotonation/intramolecular carbolithiation

To first evaluate the compatibility of the ynamide moiety with the lithiation step and address potential problems associated with competitive carbolithiation of the activated alkyne, we first reacted *N*-benzyl-ynamide **7** with one equivalent of *sec*-butyllithium and tetramethylethylenediamine (TMEDA) in THF at −78 °C for 15 minutes, followed by the addition of methyl iodide. The corresponding *N*-phenylethyl-ynamide **8** was



Scheme 1: Strategy for the synthesis of (1,4-dihydro)pyridines by deprotonation/intramolecular carbolithiation.

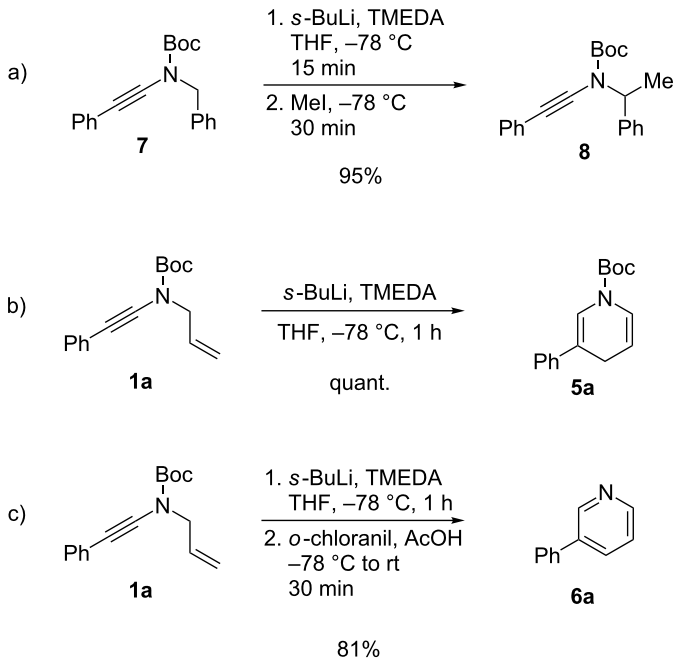
obtained in nearly quantitative yield, therefore demonstrating the compatibility of the ynamide group with the deprotonation step (Scheme 2a), although longer reaction times before the addition of methyl iodide resulted in much lower yields and extensive degradation: The intramolecular carbolithiation of *N*-allyl-ynamides to 1,4-dihydropyridines might therefore be possible, provided that the overall reaction rate is not too slow. To further test this hypothesis, *N*-allyl-ynamide **1a** was reacted under similar reaction conditions and to our delight, a smooth cyclization occurred, the expected 1,4-dihydropyridine **5a** being virtually formed as virtually the sole product (Scheme 2b), a clean reaction being a strict requirement for the development of a general route to 1,4-dihydropyridines devoided of an electron-withdrawing group at C-3, due to the instability of these acid- and oxygen-sensitive molecules. In situ conversion of the intermediate dihydropyridine to the corresponding pyridine by replacing the saturated aqueous ammonium chloride solution, used for the workup, by a combination of acetic acid and *o*-chloranil [41] was equally successful and provided the expected pyridine **6a** in 81% yield (Scheme 2c).

Synthesis of the starting *N*-allyl-ynamides

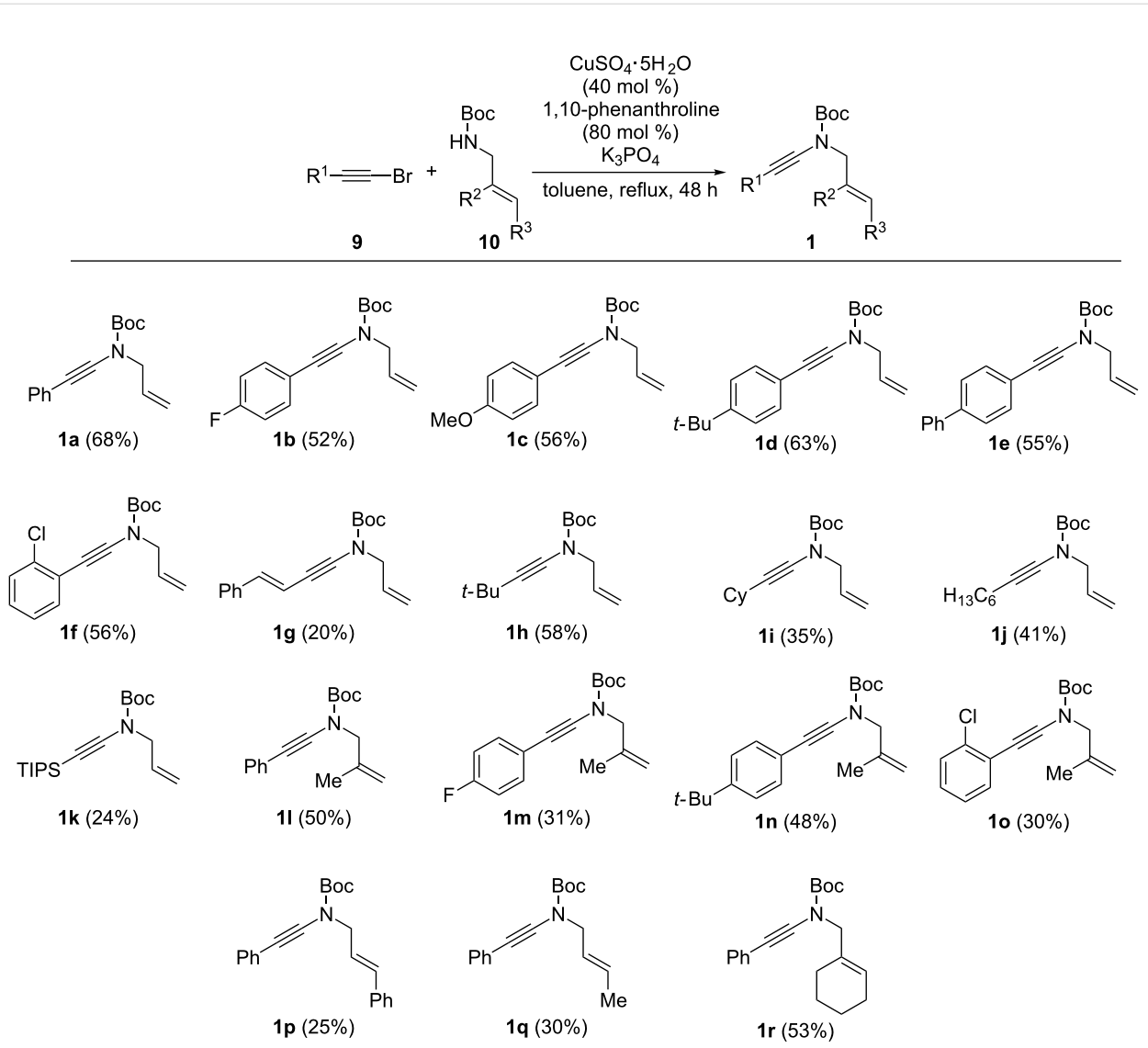
Before moving to the evaluation of the scope and limitations of this intramolecular carbolithiation, we had to prepare a set of ynamides possessing representative substituents on both the ynamide and allyl groups. Among all the methods evaluated, Hsung's second-generation synthesis based on the copper-mediated cross-coupling between bromoalkynes **9** and nitrogen nucleophiles [42] turned out to be the most convenient one, the use of terminal alkynes [43], *gem*-dibromoalkenes [7], potassium alkynyltrifluoroborates [8] or copper acetylides [12] being less efficient when bulky *N*-Boc-allylamines **10** were used as nucleophiles. By using a slightly modified Hsung's procedure, a series of *N*-allyl-ynamides **1** could be readily prepared in acceptable yields using a combination of copper(II) sulfate pentahydrate (40 mol %) and 1,10-phenanthroline (80 mol %) with potassium phosphate in refluxing toluene, the major side reaction observed in all cases being the competitive dimerization of the starting bromoalkynes (Scheme 3).

Intramolecular carbolithiation of *N*-allyl-ynamides to 1,4-dihydropyridines and pyridines: scope and limitations

With this set of ynamides in hand, we next evaluated their cyclization to the corresponding 1,4-dihydropyridines **5** or pyridines **6** using the lithiation/intramolecular carbolithiation sequence. All *N*-allyl-ynamides **1** shown in Scheme 3 were therefore treated with *s*-butyllithium and TMEDA in THF at −78 °C for one hour followed by the addition of an aqueous saturated solution of ammonium chloride (Scheme 4, conditions A) or acetic acid and *o*-chloranil (Scheme 4, conditions B), yielding the corresponding 1,4-dihydropyridines **5** or

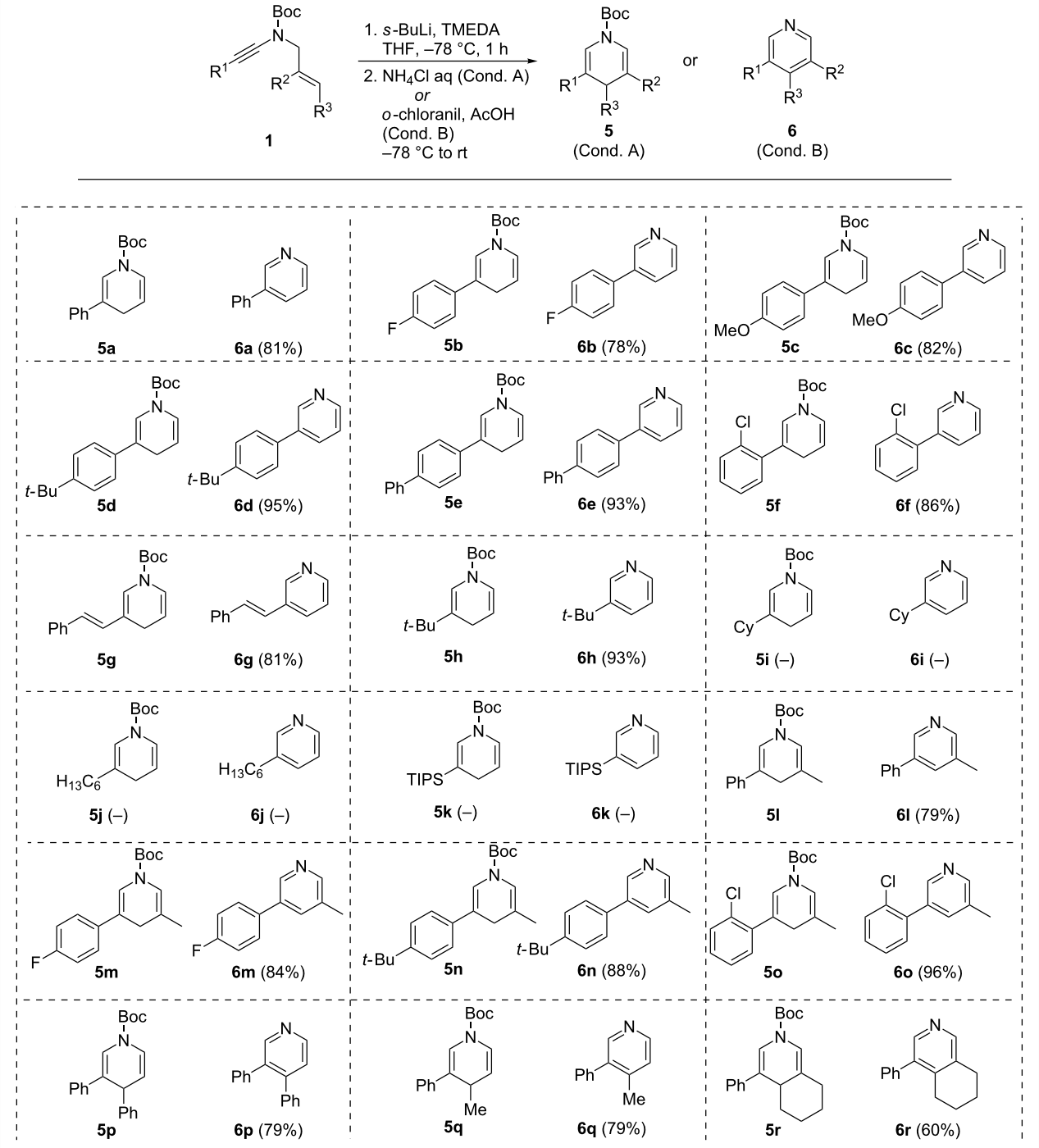


Scheme 2: Feasibility of the deprotonation/intramolecular carbolithiation.



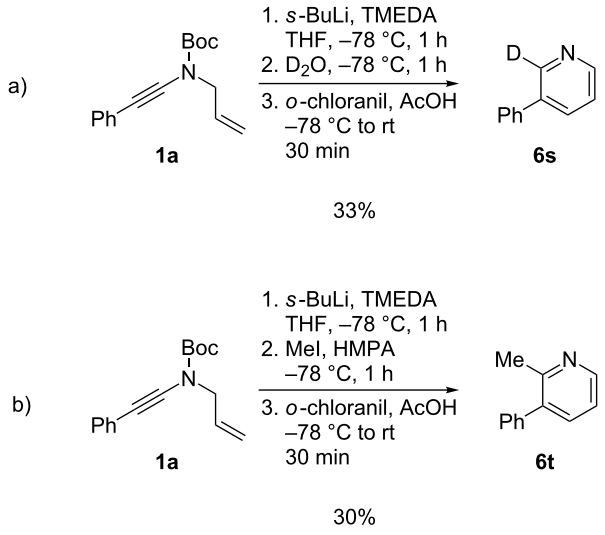
Scheme 3: Synthesis of the starting *N*-allyl-ynamides.

pyridines **6**, respectively. Results from these studies are collected in Scheme 4, yields being indicated only in the pyridine series due to the high sensitivity of the 1,4-dihydropyridine derivatives, which were obtained in virtually pure form in crude reaction mixtures. As evidenced with these results, 3-aryl-1,4-dihydropyridines and pyridines (**5**/**6a**–**f** and **l**–**r**) are readily obtained from the corresponding aryl-substituted *N*-allyl-ynamides regardless of the substitution pattern or the electronic properties of the aromatic ring. The reaction is also efficient in the case of an alkenyl group (**5**/**6g**) and the presence of an alkyl group was, as expected, more problematic due to competitive propargylic lithiation. Indeed, while a *tert*-butyl group was well tolerated (**5**/**6h**), the presence of secondary or primary alkyl chains such as cyclohexyl (**5**/**6i**) or *n*-hexyl (**5**/**6j**) groups did not afford the cyclized products, which could also not be obtained either when starting from a TIPS-protected primary ynamide (**5**/**6k**), the silicon protecting group being readily cleaved under the reaction conditions. The influence of the substitution pattern of the allyl moiety was next carefully examined and substitution at the β-, γ-positions, or both, was well tolerated, yielding the 3,5-disubstituted- (**5**/**6l**–**o**), 3,4-disubstituted- (**5**/**6p**–**q**) and 3,4,5-trisubstituted- (**5**/**6r**) 1,4-dihydropyridines and pyridines in good yields, respectively, compounds that are rather challenging to obtain using other synthetic routes. In addition, the reaction can be performed on a gram-scale with similar efficiency. This was indeed briefly evaluated for the anionic cyclization of ynamide **1a** and the exact same yield of the corresponding pyridine **6a** (81%) was obtained on a gram scale.



Scheme 4: Intramolecular carbolithiation of *N*-allyl-ynamides to 1,4-dihydropyridines and pyridines.

With a chelation-stabilized vinyllithium being formed after the anionic 6-endo-dig cyclization, we next considered the possibility of trapping this vinyllithium with an electrophile, which might allow the introduction of an additional C-2 substituent. *N*-Allyl-ynamide **1a** was therefore cyclized under our standard conditions and then treated with deuterated water (Scheme 5a) or methyl iodide (Scheme 5b) before the acidic and oxidative workup. While the desired 2,3-disubstituted **6s** and **6t** were indeed formed under these conditions, they could only be isolated in modest yields (30–33%), even in the presence of

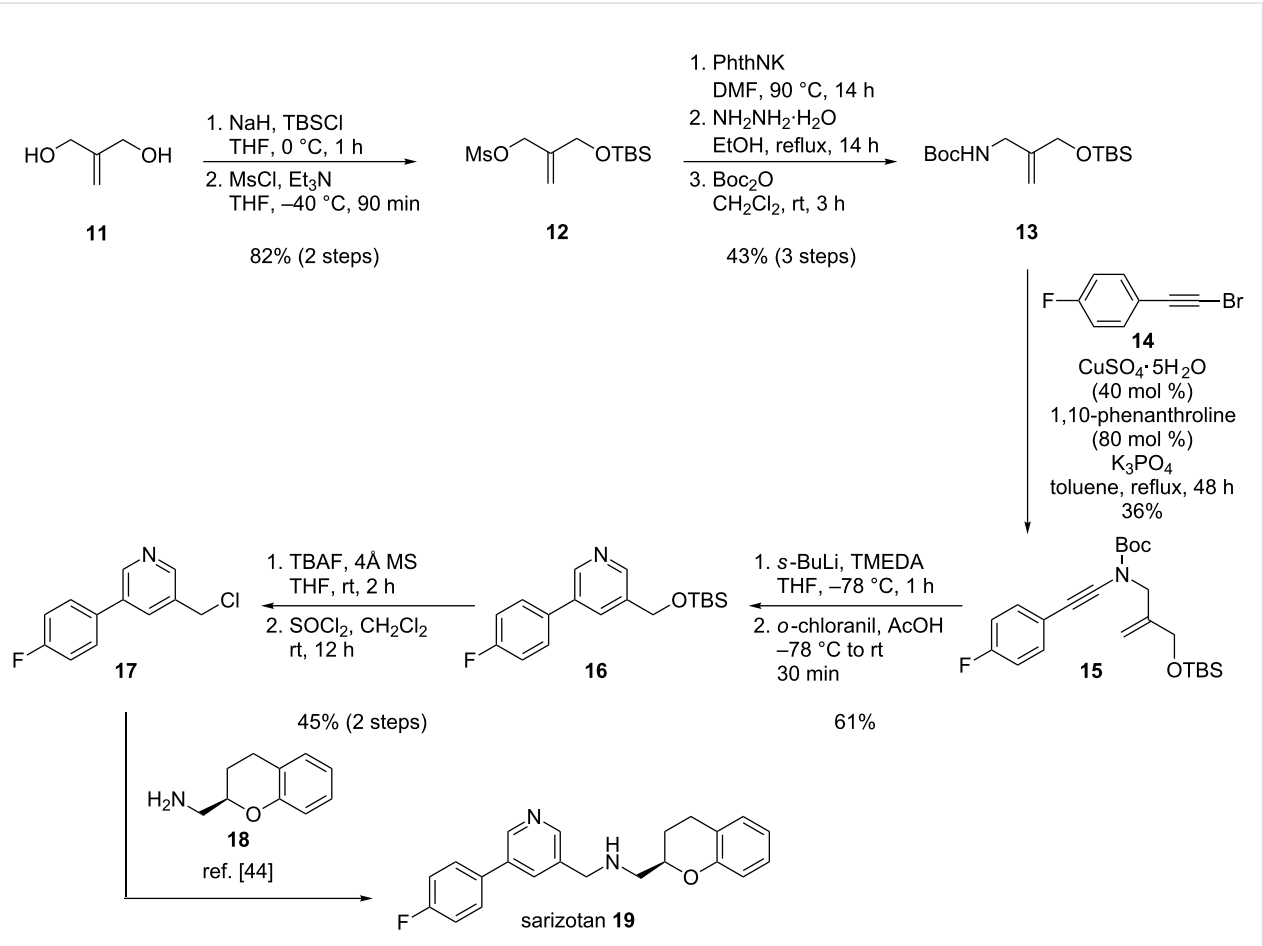


Scheme 5: 2,3-Disubstituted pyridines by trapping of the intermediate metallated 1,4-dihydropyridine.

additional HMPA, which might may constitute the major limitation of our process. Other attempts involving electrophiles such as acid chlorides and allyl bromide or transmetallation with zinc chloride and Negishi cross-coupling were unsuccessful, which does confirm that our deprotonation/carbometallation sequence is not suitable for the preparation of C-2-substituted (1,4-dihydro)pyridines.

Application to a formal synthesis of sarizotan

To further probe the synthetic utility of our pyridine synthesis, we next envisioned its use for the synthesis of the 3,5-disubstituted pyridine core of the antidyskinetic drug, 5-HT_{1A} receptor agonist, dopamine D_2 receptor ligand sarizotan **19** (Scheme 6). The pyridinyl-chroman sarizotan (also called EMD-128130) was originally developed by Merck KGaA in the late 1990's [44] and was found to be a dual selective 5-HT_{1A} receptor agonist and D_2 receptor antagonist displaying a strong efficacy in the reduction of dyskinesia resulting from long-term antiparkinsonian treatment with levodopa [45-50]. Although its development was stopped by Merck KGaA in 2006 after



Scheme 6: Formal synthesis of the anti-dyskinesia agent, 5-HT_{1A} receptor agonist, dopamine D_2 receptor ligand sarizotan.

analysis of data from Phase III clinical trials failed to confirm its efficiency [51], sarizotan is still under intense investigation [52-54] and was recently licensed to Newron Pharmaceuticals for further testing in new indications [55].

Motivated by the high potential of sarizotan and by the clear lack of structure-activity relationship studies on the pyridine core of this bioactive compound [56], we designed an efficient and modular synthesis of the disubstituted pyridine core of sarizotan that should enable the preparation of sarizotan analogues with different substitution on the pyridine ring. This synthesis is shown in Scheme 6 and starts from commercially available 2-methylene-1,3-propanediol (**11**). Mono-protection of this diol as a TBS ether and activation of the remaining alcohol as a mesylate according to previously reported procedures [57,58], gave allylic mesylate **12**, which was next reacted with potassium phthalimide in DMF at 90 °C, affording the corresponding *N*-allylphthalimide. Deprotection of the phthalimide by hydrazinolysis followed by protection of the resulting primary amine as a *tert*-butyl-carbamate gave the Boc-protected amine **13** required for the synthesis of the substrate of the anionic cyclization. Indeed, this amine **13** was engaged in a copper-catalyzed cross-coupling with 1-(bromoethynyl)-4-fluorobenzene (**14**) and gave the corresponding ynamide **15** in a modest, unoptimized 36% yield. This set the stage for the key lithiation/intramolecular carbolithiation/oxidation step for the formation of the pyridine ring. To our delight, treatment of **14** under our optimized conditions (treatment with *s*-butyllithium and tetramethylethylenediamine in THF at −78 °C for one hour followed by addition of acetic acid and *o*-chloranil) smoothly promoted the anionic 6-endo-dig cyclization to the 3,5-disubstituted pyridine **16**, which was isolated in 61% yield. Further deprotection of the primary alcohol with TBAF followed by chlorination with thionyl chloride finally gave the desired chloromethylpyridine **17**, an intermediate used for the preparation of sarizotan **19** at Merck KGaA by coupling of this pyridine fragment **17** with aminomethylchroman **18** [44].

Conclusion

The lithiation/isomerization/6-endo-dig intramolecular carbolithiation sequence from readily available *N*-allylynamides provides an efficient entry to highly substituted 1,4-dihydropyridines and pyridines and has been successfully implemented in a formal synthesis of the anti-dyskinesia agent sarizotan. This new addition to the field of carbometallation reactions extends the chemistry of ynamides and should be useful in heterocyclic and medicinal chemistry as well. Further studies to extend this process to other heteroatom-substituted alkynes and to develop an asymmetric version of our 1,4-dihydropyridines synthesis are in progress and will be reported in due timecourse.

Supporting Information

Experimental details and copies of NMR spectra for all new compounds.

Supporting Information File 1

Experimental.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-250-S1.pdf]

Supporting Information File 2

Copies of ^{1}H and ^{13}C NMR spectra for new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-250-S2.pdf]

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Radical zinc-atom-transfer-based carbozincation of haloalkynes with dialkylzincs

Fabrice Chemla*, Florian Dulong, Franck Ferreira and Alejandro Pérez-Luna*

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Abstract

The formation of alkylidenezinc carbenoids by 1,4-addition/carbozincation of dialkylzincs or alkyl iodides based on zinc atom radical transfer, in the presence of dimethylzinc with β-(propargyloxy)enoates having pendant iodo- and bromoalkynes, is disclosed. Formation of the carbenoid intermediate is fully stereoselective at −30 °C and arises from a formal *anti*-selective carbozincation reaction. Upon warming, the zinc carbenoid is stereochemically labile and isomerizes to its more stable form.

Introduction

The last few years have witnessed a gaining interest in the use of organozinc reagents as nontoxic radical precursors or mediators [1-3]. As part of this development, the so-called radical-polar reactions in which alkylzinc reagents are used as mediators in a radical transformation that affords a new zincated species, have emerged as valuable tools in synthesis. Pivotal to the processes disclosed so far using alkylzinc derivatives is zinc atom radical transfer [4]. In general terms, the reaction involves a radical chain process initiated by the formation of an alkyl radical from the organozinc derivative in the presence of oxygen [5-14]. The newly formed radical then undergoes one or more radical transformations before being reduced by the alkylzinc reagent through homolytic substitution at zinc, producing a new organozinc derivative along with an alkyl radical that sustains a radical chain. Overall, the in situ transformation of simple organozinc reagents into more elaborate ones is thus achieved, and subsequent reaction with electrophiles is possible [15-30].

More specifically, building on well-established addition reactions of carbon-centered radicals to carbon–carbon double and triple bonds, such reactivity has been advantageously employed in the context of carbozincation chemistry [31]. The intramolecular carbozincation of unactivated terminal alkenes following zinc atom transfer processes, including a 5-*exo*-*trig* cyclization step, has been reported. This is, for instance, the case in the for-

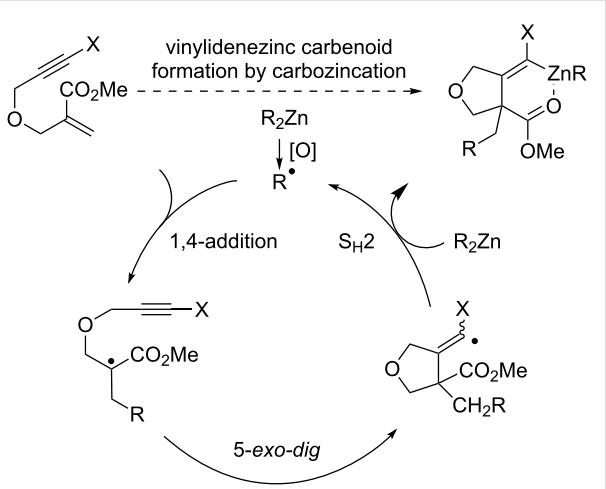
mation of (pyrrolidylmethyl)zinc and (tetrahydrofuranylmethyl)zinc derivatives by reaction of dialkylzinc, organozinc and copper–zinc mixed reagents with (*N*-allyl)aminoenoates [32-34] and β-(allyloxy)enoates [35], in the formation of (pyrrolidonylmethyl)zinc by condensation of dialkylzincs with *N*,*N*-diallylpropiolamide [36], and also in the cyclization of alkenylzinc iodides to cyclopentylmethylzinc iodides, formerly believed to be anionic in nature [4]. Carbozincations of alkynes based on zinc atom transfer have also been disclosed. The reaction of dialkylzincs or of alkyl iodides in the presence of Me_2Zn/O_2 with β-(propargyloxy)enoates entails the intramolecular carbometallation of the pendant alkynes substituted by silyl, alkyl, aryl, alkenyl or amino groups by a 5-exo *dig* radical cyclization step [37,38]. Intermolecular carbozincation of terminal arylacetylenes [39] and of diethyl acetylenedicarboxylate [40] has been achieved by dialkylzinc-mediated radical additions. Worthy of note is that in some cases the zinc-atom-transfer-based carbozincation of alkynes can occur with *anti* selectivity [38,40], and thereby represents a complementary approach to transition-metal-mediated carbozincations, which are generally *syn*-selective [41-46].

To explore further the possibilities offered by zinc atom transfer processes we considered the possibility to prepare alkylidenezinc carbenoids by radical-based carbozincation of haloalkynes. Such carbenoids are multipurpose reagents [47] that are typically prepared from 1,1'-dihaloalkenes, either by lithium/halogen exchange followed by transmetallation with zinc salts or by direct zinc/halogen exchange [48-50]. Alternatively, they can also be prepared efficiently by selective monohalogenation of alkylidene *gem*-bismetallic intermediates [51].

To the best of our knowledge, the preparation of alkylidenezinc carbenoids by the direct carbozincation of haloalkynes has not been reported [52]. As a starting point to develop such an approach, we reasoned that the reaction of dialkylzincs with β-(propargyloxy)enoates bearing pendant haloalkynes would be ideally suited (Scheme 1). On the one hand it would provide a means to control totally the regioselectivity of the radical addition to the haloalkyne, and on the other hand the envisioned zinc atom transfer to an α-halo vinylic radical should be favorable as a result of the presence of the ester moiety. Hereafter, we disclose our findings concerning this reaction.

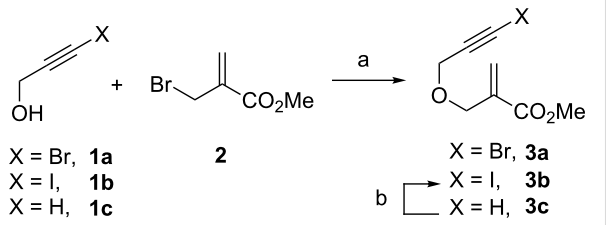
Results and Discussion

β-(Propargyloxy)enoates **3a** and **3b** having a pendant bromoalkyne and an iodoalkyne moiety, respectively, were prepared by condensation of propargylic alcohols **1** with methyl 2-(bromomethyl)acrylate (**2**) (Scheme 2). Enoate **3a** was readily obtained by direct reaction of 3-bromopropargyl alcohol (**1a**).



Scheme 1: Anticipated formation of alkylidene zinc carbenoids by reaction of dialkylzincs with β-(propargyloxy)enoates having pendant haloalkynes.

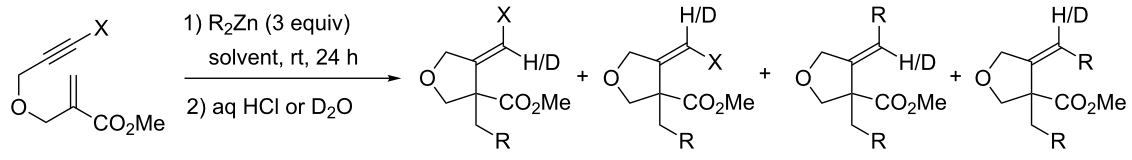
By contrast, the reaction of the iodo analogue **1b** with **2** proved troublesome as it led to inseparable mixtures of the desired enoate **3b** and non-iodinated enoate **3c**. Thus, **3b** was best prepared by iodinating ($AgNO_3$/NIS) the terminal alkyne of enoate **3c** prepared from propargyl alcohol (**1c**) and acrylate **2**.



Scheme 2: Preparation of β-(propargyloxy)enoates having pendant haloalkynes. Reagents and conditions: (a) **2** (1.4 equiv), Et_3N (4 equiv), NaI (10 mol %), CH_2Cl_2, 50 °C, sealed tube, 74% (**3a**), 87% (**3c**); (b) $AgNO_3$ (1.5 equiv), *N*-iodosuccinimide (1.5 equiv), acetone, rt, 53% (**3b**).

According to our previously optimized conditions for the 1,4-addition/carbozincation reaction of dialkylzincs with β-(propargyloxy)enoates [37,38], bromoalkyne **3a** was treated with Et_2Zn at room temperature in Et_2O under an argon atmosphere (Table 1, entry 1). To our delight, following acidic work-up, the expected methylenetetrahydrofuranyl bromide **4aa** was obtained in 43% isolated yield as a mixture of diastereoisomers in a 77:23 *Z*/*E* ratio [53]. Hydrolysis with D_2O evidenced the intermediate formation of an alkylidene zinc carbenoid as deuterated **4aa-D** was produced (Table 1, entry 2). As previously noted in the case of similar 1,4-addition/carbozincation sequences [37,38], deuterium incorporation was nearly quantitative for the *Z* isomer, and much lower for the *E* one. More

Table 1: 1,4-addition/carbozincation of dialkylzincs with β-(propargyloxy)enoates **3** having pendant haloalkynes in the presence of traces of air.[a]



3 (**3a** (X = Br), **3b** (X = I))

(*Z*)-**4** (**4aa** (X = Br, R = Et), **4ba** (X = I, R = Et), **4ab** (X = Br, R = Bu), **4bb** (X = I, R = Bu))

(*E*)-**4** (**4aa** (X = Br, R = Et), **4ba** (X = I, R = Et), **4ab** (X = Br, R = Bu), **4bb** (X = I, R = Bu))

(*Z*)-**5** (**5a** (R = Et), **5b** (R = Bu))

(*E*)-**5** (**5a** (R = Et), **5b** (R = Bu))

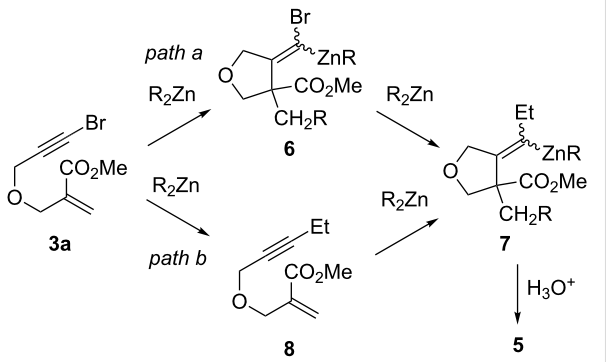
Entry	Enoate	X	Solvent	R	Products (Yield[b] (%) [dr[c] (*Z*/*E*)])
1	**3a**	Br	Et_2O	Et	**4aa** (43 [77:23]); **5a** (40 [79:21])
2	**3a**	Br	Et_2O	Et	**4aa-D**[d] (44 [81(90% D):19(10% D)]); **5a-D**[d] (35 [84(85% D):16(40% D)])
3	**3b**	I	Et_2O	Et	**4ba** (40[e] [98:2]); **5a** (21[e] [82:18])
4	**3a**	Br	Et_2O	*n*-Bu	**4ab** (76 [70:30]); **5b** (7 [nd[f]])
5	**3b**	I	Et_2O	*n*-Bu	**4bb** (58 [98:2])
6	**3a**	Br	CH_2Cl_2	Et	**4aa** (39[d] [78:22]); **5a** (17[d] [91:9])
7	**3a**	Br	CH_2Cl_2	*n*-Bu	**4ab** (37 [76:24]); **5b** (12 [nd][f])

[a]Reaction conditions : R_2Zn (3 equiv), rt, 24 h under Ar atmosphere (see Experimental section).
[b]Combined yield of diastereomers after chromatography unless otherwise noted.
[c]Determined by ^1H NMR analysis of the crude material.
[d]The reaction mixture was quenched with D_2O. The percentage of deuterium incorporation is given in parenthesis for each compound.
[e]Determined by ^1H NMR spectroscopy based on analysis of the crude mixture with biphenyl as internal standard.
[f]Not determined.

unexpectedly, however, 40% of alkylidenetetrahydrofuran **5a**, wherein the bromine atom had been substituted by an ethyl group, was also isolated as a 79:21 *Z*/*E* mixture. Deuterium labeled **5a-D** was produced following hydrolysis with D_2O (Table 1, entry 2), thereby showing that an alkylidenezinc intermediate was being formed in the generation of this side-product under these reaction conditions.

When iodoalkyne **3b** was used, a similar 40% yield of vinylic iodide **4ba** was obtained, but this time exclusively as the *Z* isomer (Table 1, entry 3). **5a** was also produced, but in a lower 21% yield and similar diastereoselectivity (82:18 *Z*/*E* ratio). Significantly lower levels of side-product formation arising from halogen substitution were observed when *n*-Bu_2Zn was used, thus leading to improved results (Table 1, entries 4 and 5). The reaction with bromoalkyne **3a** provided vinylic bromide **4ab** in 76% yield and 70:30 *Z*/*E* ratio and only 7% of **5b**. Better, the reaction with iodoalkyne **3b** afforded exclusively iodide **4bb** in 58% yield and complete diastereoselectivity in favor of the (*Z*) isomer. Formation of substitution side-products was also diminished when CH_2Cl_2 was used as the solvent instead of Et_2O, even though this had little impact on the efficiency and diastereoselectivity of vinyl halide formation (Table 1, entries 6 and 7). Reaction of Et_2Zn with **3a** provided vinyl bromide **4aa** in 39% yield (78:22 *Z*/*E* ratio) and **5a** in 17% yield, while reaction of *n*-Bu_2Zn gave **4ab** in 37% yield (76:24 *Z*/*E* ratio) and **5b** in 12% yield. It is worthy of note that no difference was observed between the different dialkylzincs in this case.

The formation of alkylidenezinc derivatives **7** leading to compounds **5** is intriguing (Scheme 3). A first possible mechanistic route could involve the reaction of zinc carbenoid **6** and the

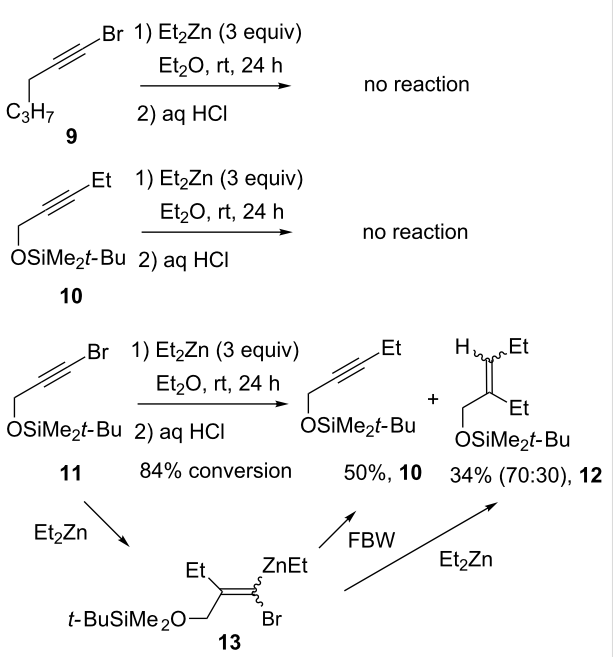


Scheme 3: Possible reaction pathways to account for the formation of product **5**.

excess of dialkylzinc reagent via the intermediate formation of a zincate [48-51] (Scheme 3, path a). The stereoselectivity of such rearrangements is often dependent on the substrate structure, so the diastereopurity of **5** is not necessarily informative about that of **6** [48-51]. An alternative possibility to account for the formation of **7** could be the reaction of the dialkylzinc reagent with enoate **8** arising from a prior substitution of bromoalkyne **3a** with the dialkylzinc reagent (Scheme 3, path b). Both the diastereoselectivity and the levels of deuterium incorporation are very close to those obtained for the reaction of diethylzinc with pure **8** [37], which argues in favor of this mechanistic scenario.

To try to discriminate between these possibilities we conducted some additional test experiments (Scheme 4). In agreement with the general consideration that dialkylzinc reagents do not undergo uncatalyzed cross-coupling reactions with bromoalkynes, no reaction was observed between Et_2Zn and 1-bromohexyne (**9**) [54]. By contrast, bromoalkyne **11** having a silyloxy group at the propargylic position reacted smoothly to afford ethyl-substituted alkyne **10** along with alkene **12**, which had incorporated two ethyl groups. **12** was isolated as a mixture of diastereoisomers in 70:30 dr. The fact that no reaction takes place between pure **10** and Et_2Zn indicates that **12** is not formed by carbozincation. Hence, most likely it is formed by the reaction of Et_2Zn and carbenoid **13** arising from the carbozincation of **11** (Scheme 4). Moreover, if **13** is indeed formed, it would also lead to alkyne **10** following Fritsch–Buttenberg–Wieschell (FBW) rearrangement [55-57]. Since the presence of the oxygen atom in the propargylic position should facilitate the carbometallation reaction [58], this mechanistic pathway provides a plausible explanation for the fact that bromine substitution occurs from α-oxgenated bromoalkyne **11** and not from **9**.

Regarding our 1,4 addition/carbocyclization sequence, these test experiments provide two important pieces of evidence for the behavior of **3a** in the presence of a dialkylzinc. First, β-alkoxy bromoalkynes undergo direct substitution with Et_2Zn to some extent. Second, alkylidenezinc carbenoids react with dialkylzincs to afford the bromine substitution product. Thus, formation of alkylidenezinc compound **7** (and thereby **5**) most probably arises from both depicted mechanistic pathways (paths a and b, Scheme 3). In such a situation, we reasoned that in both possibilities, reducing the reaction time would limit the production of the unwanted side-products by limiting the contact time between the dialkylzinc reagent and either the starting bromoalkyne or the generated zinc carbenoid. Thus, we considered adding air to the reaction media in order to accelerate the oxidation of the dialkylzinc species and therefore radical production (Table 2).

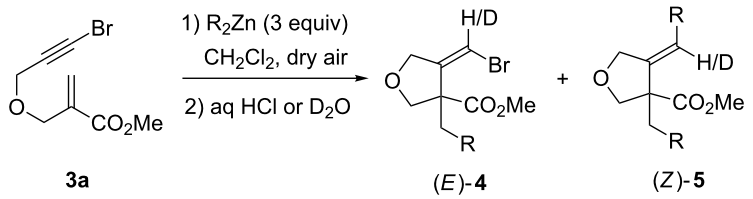


Scheme 4: Test experiments to gain insight into the mechanism of formation of alkylidene zinc intermediate **7**.

A reduced amount of side-product **5** was indeed observed in the reaction of enoate **3a** with Et_2Zn in CH_2Cl_2 at room temperature in the presence of added dry air (Table 2, entry 1). A mixture of vinyl bromide **4aa** and alkene **5a** in a 84:16 ratio and in 69% overall yield was obtained. However the diastereoselectivity of the formation of **4aa** dropped significantly. Lowering the reaction temperature had a highly beneficial impact on the reaction outcome. At 0 °C, the formation of **5a** was totally suppressed, and **4aa** was obtained with a much better diastereoselectivity, though remarkably in favor of the *E* isomer (Table 2, entry 2). At −30 °C, the exclusive and totally diastereoselective formation of (*E*)-**4aa** in excellent 89% isolated yield was obtained (Table 2, entry 3). Hydrolysis with D_2O led to (*E*)-**4aa-D** with 83% deuterium incorporation when either CH_2Cl_2 or DCE were used as solvent (entries 4 and 5), therefore evidencing the intermediate stereoselective formation of an alkylidene zinc carbenoid. Similar results were obtained by using *n*-Bu_2Zn, indicating that the process is quite general (Table 2, entry 6).

The diastereoselectivity of the formation of **4aa** seemed to be dependent not only on the reaction temperature, but also on the total reaction time (compare Table 1, entry 6 and Table 2, entry 1). Suspecting a possible *Z*/*E* isomerization of the alkylidenezinc carbenoid intermediate, we conducted an experiment wherein air was added to a mixture of enoate **3a** and Et_2Zn in CH_2Cl_2 at −30 °C, and the reaction was first kept for 1 h at this temperature and then for 23 h at room temperature (Table 2,

Table 2: 1,4-Addition/carbozincation of dialkylzincs on **3a** in the presence of added air.[a]



3a (*E*)-**4** (*Z*)-**5**

Entry	R	Reaction conditions	Products [ratio]	Yield[b] (%)	dr[c] of product **4** (*E*/*Z*)
1	Et	rt, 1 h	**4aa**/(*Z*)-**5a** [84:16]	69[d]	54:46
2	Et	0 °C, 1 h	**4aa**	93	87:13
3	Et	−30 °C, 1 h	**4aa**	89	>98:2
4	Et	−30 °C, 1 h	**4aa-D**[e]	95[d]	>98(83% D):2
5	Et	−30 °C, 1 h, DCE[f]	**4aa-D**[e]	89	>98(83% D):2
6	Bu	−30 °C, 1 h	**4ab**	93	>98:2
7	Et	−30 °C, 1 h then rt, 24h	**4aa**/(*Z*)-**5a** [78:22]	78[d]	44:56
8	Et	−30 °C, 1 h then rt, 24 h	**4aa-D**[e]/(*Z*)-**5a-D**[g] [78:22]	78[d]	44(<10% D):56(<10% D)

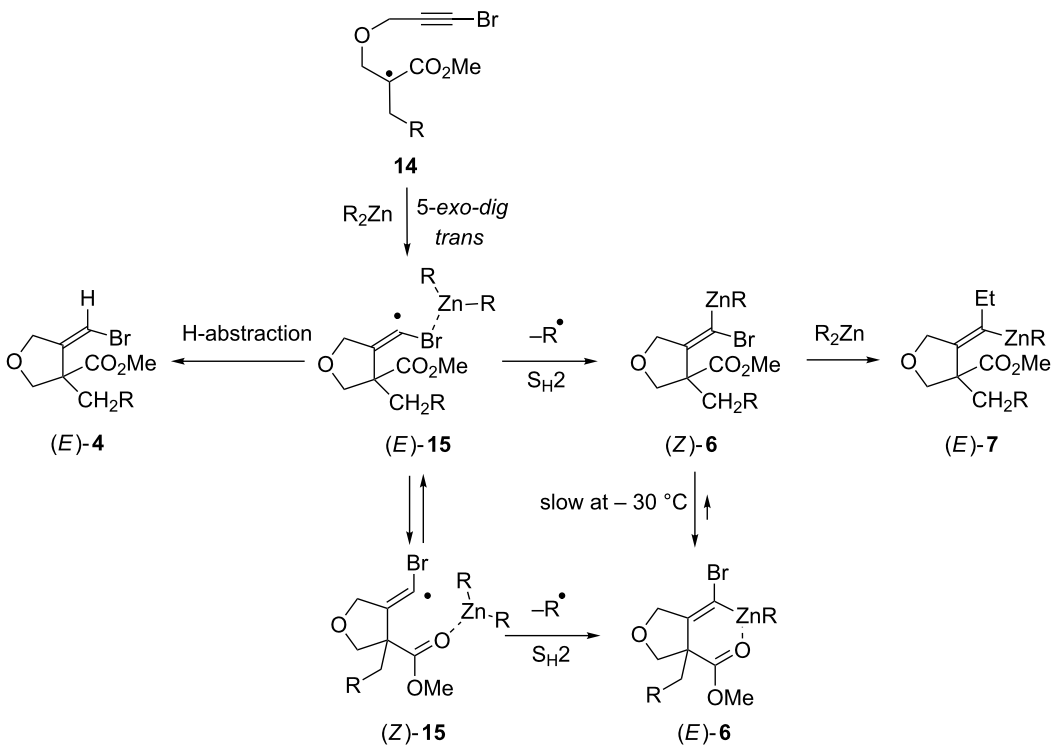
[a]Reaction conditions : R_2Zn (3 equiv), CH_2Cl_2, dry air was bubbled at once into the reaction mixture, which was then kept under Ar atmosphere (see Experimental section).
[b]Combined yield of products after chromatography unless otherwise noted.
[c]Determined by ^1H NMR analysis of the crude material.
[d]Determined by ^1H NMR spectroscopy based on analysis of the crude mixture with biphenyl as the internal standard.
[e]The reaction mixture was quenched with D_2O. The percentage of deuterium incorporation is given in parenthesis for each isomer.
[f]DCE = 1,2-dichloroethane was used as solvent instead of CH_2Cl_2.
[g]30% deuterium incorporation was observed for product **5a-D**.

entry 7). Following acidic quench, very similar results to those noted for the same reaction carried out at room temperature (Table 2, entry 1) were observed. **4aa** was recovered in 61% yield as a 56:44 mixture of isomers along with alkene (*Z*)-**5a** in 22% yield. It is worthy to note that very low levels of deuterium incorporation were observed in this case.

These results have a three-fold consequence. First, they indicate that *Z*/*E* isomerization of the alkylidenezinc carbenoid occurs between −30 °C and room temperature. Second, it demonstrates that alkene **5a** can be formed by the reaction between the zinc carbenoid and Et_2Zn (Scheme 3, path a), and that in such a case the transformation is stereoselective. Third, when oxygen is introduced into the reaction media, the alkylidenezinc carbenoid is eventually demetallated upon standing at room temperature.

The different results obtained for the 1,4-addition/carbozincation of enoates having pendant bromoalkynes are consistent with our anticipated zinc atom radical transfer mechanism (Scheme 1) and can be rationalized according to the following scenario (Scheme 5). The process involves the initial 1,4-addition of radical R to the starting enoate and the subsequent 5-*exo*-*dig* cyclisation of enoxy radical **14** to provide α-bromovinyl radical **15** of *E* geometry. Substitution by electron-withdrawing groups slows down *E* to *Z* isomerization of vinylic radicals, and therefore, due to the presence of the bromine atom, interconversion of (*E*)-**15** into (*Z*)-**15** should not be fast. Thus, (*E*)-**15** reacts by Zn atom transfer prior to its equilibration to provide stereoselectively carbenoid (*Z*)-**6** [59] and to some extent by H-atom transfer to give reduced bromoalkene (*E*)-**4** [60]. Upon warming, (*Z*)-**6** isomerizes to its more stable isomer (*E*)-**6** wherein the zinc atom is coordinated intramolecularly to the adjacent ester. To a minor extent, reaction with the excess dialkylzinc present in the reaction media provides alkylidenezinc (*E*)-**7** stereoselectively. Note, however, that in the case where reactions are conducted at room temperature, *E*/*Z* equilibration of the intermediate radical **15** should be faster and zinc atom transfer from (*Z*)-**15** may also contribute to the formation of (*E*)-**6**.

Two situations are next to be distinguished. Under the conditions involving excess air, carbenoid **6** is protonated in the reaction media (even though we have not identified the proton source). It is possible that protonation occurs prior to full *E* to *Z* isomerization and vinyl bromide **4** is obtained in low diastereoselectivity. Under the conditions involving only a trace of air, after 24 h at room temperature, carbenoid **6** is still present and



Scheme 5: Mechanistic rationale for the reaction of dialkylzincs with β-(propargyloxy)enoate **3a**.

total *Z* to *E* isomerization has occurred. The reason why vinyl bromide **4** is only isolated with moderate diastereoselectivity following hydrolysis, is that (*E*)-**4**, formed from (*E*)-**15** by H-abstraction, is present from the start.

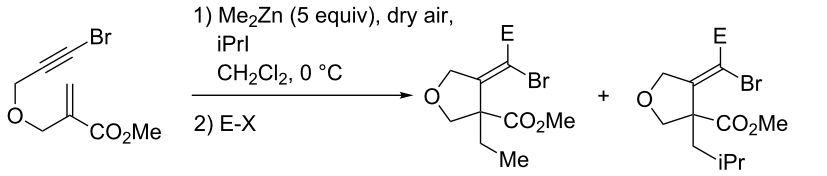
We finally considered the prospect to carry out the carbozincation of bromoalkynes using a combination of an alkyl iodide and dimethylzinc (Table 3). Towards this end, we first treated enoate **3a** with Me_2Zn, following our previously reported optimized conditions for the 1,4-addition/carbozincation of β-(propargyloxy)enoates with Me_2Zn [38], which proceeds in CH_2Cl_2 at 0 °C and under continuous introduction of dry air over a period of 1 h (Table 3, entry 1). After acidic quench, vinylic bromide (*E*)-**4ac** [61] was isolated in 77% yield as a single diastereoisomer. The stereoselective formation of an alkylidenezinc carbenoid intermediate was this time evidenced by treating the reaction mixture with iodine (Table 3, entry 2). Vinylic dihalide **16** was isolated in 64% yield, again as a single *Z* diastereoisomer. Thus, Me_2Zn showed a similar reactivity to its higher homologues Et_2Zn and *n*-Bu_2Zn, with the additional advantage that no direct formation of vinyl bromide (*E*)-**4ac** by hydrogen abstraction was observed.

In the presence of 5 equiv iPrI, a mixture of two (diastereomerically pure) compounds **4ad** and **4ac** in 87:13 ratio was observed. Incorporation of the iPr moiety was therefore the major reaction pathway. The competitive addition of a Me group could be reduced by increasing the amount of iPrI to 10 equiv (Table 3, entries 3 and 4). However, in this case, significant amounts of vinylic dihalide **17** were also isolated. Thus, if large amounts of iodide are used, radical iodine atom transfer between iPrI and the α-bromovinylic radical **15** resulting from the cyclization step (Scheme 5) becomes competitive with the desired zinc atom transfer and hampers the carbozincation process.

Conclusion

In conclusion, we have shown that β-(propargyloxy)enoates having pendant iodo- and bromoalkynes undergo a 1,4-addition/carbozincation sequence by reaction with dialkylzincs or with alkyliodides in the presence of dimethylzinc. The sequence involves a radical chain mechanism initiated by air and provides the proof of concept that alkylidenezinc carbenoids can be prepared by carbozincation based on zinc atom transfer. In the disclosed process, we have demonstrated that the formation of a bromocarbenoid intermediate is fully stereoselective at −30 °C and arises from a formal *anti*-selective carbozincation reaction. Upon warming, the zinc carbenoid is stereochemically labile and isomerizes to its more stable form. In the absence of added air, no decomposition of the carbenoid intermediate is observed at room temperature for at least 24 h. Deuterium labeling and iodolysis experiments evidence that the zinc carbenoids

Table 3: Me_2Zn-mediated 1,4-addition/carbozincation of alkyl iodides with **3a** in the presence of added air.[a]



3a

4ac (E = H) **4ad** (E = H)
4ac-D (E = D) **4ad-D** (E = D)
16 (E = I) **17** (E = I)

Entry	iPrI (equiv)	E-X	Yield[b] (%)	Products [ratio]
1	0	H_2O	77	**4ac**[c]
2	0	I_2	64	**16**
3[d]	5	H_2O	59	**4ad**/**4ac** [87:13]
4[d]	10	H_2O	87	**4ad**/**4ac**/**17** [75:6:19]
5[d]	10	D_2O	75	**4ad-D**/**4ac-D**/**17** [75 (95% D):6 (95% D):19]

[a]Reaction conditions: Me_2Zn (5 equiv), iPrI (equiv), CH_2Cl_2, 0 °C, 20 mL dry air was bubbled during 1 h into the reaction mixture via a syringe pump.
[b]Combined yield of isolated products after chromatography unless otherwise noted.
[c]The product was contaminated with ~10% of product resulting from the addition of the dichloromethyl radical (**4ae**, R = $CHCl_2$).
[d]3 equiv Me_2Zn were used.

prepared under such reactions can act as typical nucleophiles and should, thus, be well-suited for subsequent functionalization [47-51]. Furthermore, as indicated with the formation of some side-products observed during this work, they should also react readily as electrophiles toward organometallic nucleophiles and undergo intramolecular nucleophilic substitution reactions [47-51].

Experimental

Experiments involving organometallic compounds were carried out in dried glassware under a positive pressure of dry Ar. All solvents were distilled to remove stabilizers and dried with a MBRAUN Solvent Purification System SPS-800. *n*-Bu_2Zn (Fluka, ~1 N in heptane), Et_2Zn (Aldrich, 1.0 M in hexanes), Me_2Zn (Aldrich, 1.0 M in heptane) and all other reagents were of commercial quality and were used without purification. ^1H NMR, ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer fitted with BBFO probe with Z gradient. Chemical shifts are reported in δ relative to an internal standard of residual chloroform (δ 7.27 for ^1H NMR and 77.16 for ^{13}C NMR). IR spectra were recorded with an ATR diamond spectrophotometer. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95.

General Procedure 1. Reaction of *n*-Bu_2Zn and Et_2Zn with β-(propargyloxy)enoates 3a and 3b having pendant haloalkynes in the presence of a trace amount of air (Table 1): Under argon, to a stirred solution of β-(propargyloxy)enoate (0.2 mmol) in Et_2O (1 mL) at room temperature was added R_2Zn (0.6 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was hydrolyzed with an aqueous solution of HCl (1 M, 10 mL). The layers were separated, the aqueous one being extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by flash chromatography (pentane/ether).

General Procedure 2. Reaction of *n*-Bu_2Zn and Et_2Zn with β-(propargyloxy)enoate 3a in the presence of added air (Table 2): Under argon, to a stirred solution of β-(propargyloxy)enoate **3a** (0.2 mmol) in CH_2Cl_2 (2 mL) at −30 °C was added R_2Zn (0.6 mmol). Air (2 mL) was bubbled at once into the solution via a syringe fitted with a $CaCl_2$ guard and the reaction mixture was stirred at −30 °C for 1 h. CH_2Cl_2 (20 mL) and an aqueous solution of HCl (1 M, 10 mL) were added to quench the reaction. The layers were separated, the aqueous one being extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product.

(*Z*)-Methyl 4-(bromomethylene)-3-propyltetrahydrofuran-3-carboxylate ((*Z*)-4aa): Prepared according to general procedure 1 from enoate **3a** (50 mg, 0.2 mmol) and Et_2Zn (0.6 mL, 1.0 M in hexanes, 0.6 mmol). Purification by flash chromatography with pentane/ether (95:05) as eluent gave the title compound ((*Z*)-**4aa**) (19 mg, 33%) as a colorless oil. IR (neat):

2958, 1730, 1434, 1219, 1072, 938, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (t, *J* = 2.7 Hz, 1H), 4.42 (d(AB system), *J* = 9.1 Hz, 1H), 4.40 (d br, *J* = 2.9 Hz, 2H), 3.84 (d(AB system), *J* = 9.1 Hz, 1H), 3.74 (s, 3H), 1.90 (m, 1H), 1.68 (m, 1H), 1.24 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 146.6, 100.4, 75.7, 72.8, 58.5, 52.6, 39.5, 18.8, 14.2; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{10}H_{15}O_3BrNa$: 285.00968; found: 285.00990.

(*E*)-Methyl 4-(bromomethylene)-3-propyltetrahydrofuran-3-carboxylate ((*E*)-4aa): Prepared according to general procedure 2 from enoate **3a** (47 mg, 0.2 mmol) and Et_2Zn (0.6 mL, 1.0 M in hexanes, 0.6 mmol). The title compound ((E)-**4aa**) was isolated pure (47 mg, 89%) as a colorless oil and did not require further purification. IR (neat): 2960, 2873, 1769, 1730, 1433, 1217, 1122, 1074, 968, 938, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (t, *J* = 1.9 Hz, 1H), 4.39 (dd(ABX system), *J* = 12.7, 1.9 Hz, 1H), 4.32 (dd(ABX system), *J* = 12.7, 1.8 Hz, 1H), 4.12 (d(AB system), *J* = 8.9 Hz, 1H), 3.97 (d(AB system), *J* = 8.9 Hz, 1H), 3.74 (s, 3H), 2.13 (td, *J* = 13.5, 4.6 Hz, 1H), 1.90 (dt, *J* = 12.5, 4.4 Hz, 1H), 1.50–1.30 (m, 1H), 1.30–1.25 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 146.7, 98.5, 78.3, 73.8, 58.3, 52.7, 34.7, 17.9, 14.8; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{10}H_{15}O_3BrNa$: 285.0097; found: 285.0091.

(*Z*)-Methyl 4-(iodomethylene)-3-pentyltetrahydrofuran-3-carboxylate ((*Z*)-4bb): Prepared according to general procedure 1 from enoate **3b** (40 mg, 0.14 mmol) and Bu_2Zn (0.42 mL, ~1 N in heptane, 0.42 mmol). Purification by flash chromatography with pentane/ether (80:20) as eluent gave the title compound ((*Z*)-**4bb**) (28 mg, 58%) as a colorless oil. IR (neat): 2951, 2925, 2856, 1731, 1434, 1230, 1073, 939, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (t, *J* = 2.6 Hz, 1H), 4.49 (d(AB system), *J* = 9.1 Hz, 1H), 4.31 (d br, *J* = 2.6 Hz, 2H), 3.90 (d(AB system), *J* = 9.1 Hz, 1H), 3.74 (s, 3H), 1.90 (m, 1H), 1.66 (m, 1H), 1.40–1.20 (m, 6H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 152.4, 76.5, 76.2, 71.3, 59.7, 52.7, 37.3, 32.0, 25.1, 22.5, 14.1.

(*E*)-Methyl 4-(bromomethylene)-3-pentyltetrahydrofuran-3-carboxylate ((*E*)-4ab): Prepared according to general procedure 2 from enoate **3a** (47 mg, 0.2 mmol) and Bu_2Zn (0.6 mL, ~1 N in heptane, 0.6 mmol). The title compound ((E)-**4ab**) was isolated pure (55 mg, 93%) as a colorless oil and did not require further purification. IR (neat): 2955, 2927, 2856, 1771, 1733, 1433, 1260, 1230, 1217, 1122, 1074, 936, 910, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (t, *J* = 1.9 Hz, 1H), 4.39 (dd(ABX system), *J* = 12.7, 2.0 Hz, 1H), 4.32 (dd(ABX system), *J* = 12.7, 1.8 Hz, 1H), 4.12 (d(AB system), *J* = 8.9 Hz, 1H), 3.97 (d(AB system), *J* = 8.9 Hz, 1H), 3.74 (s, 3H), 2.15 (td, *J* = 13.7, 4.2 Hz, 1H), 1.91 (dt, *J* = 12.2, 4.4 Hz, 1H), 1.50–1.20 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 146.7, 98.6, 78.3, 73.9, 58.2, 52.7, 32.5, 32.4, 24.1, 22.7, 14.3; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{12}H_{19}O_3BrNa$: 313.0410; found: 313.0413.

(*E*)-Methyl 4-(bromomethylene)-3-ethyltetrahydrofuran-3-carboxylate ((*E*)-4ac) (Table 3, entry 1): Under argon, to a stirred solution of β-(propargyloxy)enoate **3a** (46 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added Me_2Zn (1 mL, 1.0 M in heptane, 1.0 mmol). Air (20 mL) was slowly introduced over 1 h into the solution via a syringe pump by using a syringe fitted with a $CaCl_2$ guard. The reaction mixture was then stirred at 0 °C for 1 h. CH_2Cl_2 (5 mL) was then added, and the reaction was hydrolyzed with an aqueous solution of HCl (1 M, 5 mL). The layers were separated, the aqueous one being extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/ether 80:20) afforded the title compound ((E)-**4ac**) (38 mg, 77%) as a colorless oil. IR (neat): 2953, 1767, 1731, 1638, 1229, 1138, 1034, 936, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (t, *J* = 1.9 Hz, 1H), 4.41 (dd(ABX system), *J* = 12.7, 1.9 Hz, 1H), 4.33 (dd(ABX system), *J* = 12.7, 1.9 Hz, 1H), 4.13 (d(AB system), *J* = 8.9 Hz, 1H), 3.98 (d(AB system), *J* = 8.9 Hz, 1H), 3.75 (s, 3H), 2.21 (m, 1H), 2.00 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 146.4, 98.5, 77.9, 73.8, 58.5, 52.6, 25.2, 8.9; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_9H_{13}O_3BrNa$: 270.99403; found: 270.99477.

(*E*)-Methyl 4-(bromomethylene)-3-isobutyltetrahydrofuran-3-carboxylate ((*E*)-4ad) (Table 3, entry 4): Under argon, to a stirred solution of β-(propargyloxy)enoate **3a** (47 mg, 0.2 mmol) and iPrI (0.2 mL, 2.0 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added Me_2Zn (0.6 mL, 1.0 M in heptane, 0.6 mmol). Air (20 mL) was slowly introduced over 1 h into the solution via a syringe pump by using a syringe fitted with a $CaCl_2$ guard. The reaction mixture was then stirred at 0 °C for 1 h. CH_2Cl_2 (5 mL) was then added and the reaction was hydrolyzed with an aqueous solution of HCl (1 M, 5 mL). The layers were separated, the aqueous one being extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/ether 50:50) afforded the title compound ((*E*)-**4ad**) (36 mg, 65%) as a colorless oil. IR (neat): 2953, 2870, 1732, 1640, 1230, 1126, 1073, 937, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (t, *J* = 1.9 Hz, 1H), 4.40 (d, *J* = 1.9 Hz, 2H), 4.15 (d(AB system), *J* = 8.9 Hz, 1H), 4.02 (d(AB system), *J* = 8.9 Hz, 1H), 3.74 (s, 3H), 2.05 (m, 2H), 1.77 (m, 1H), 0.96 (d, *J* = 8.4 Hz,

3H), 0.95 (d, J = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 146.9, 98.6, 78.0, 73.6, 58.1, 52.5, 40.5, 24.9, 24.5, 24.4; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{11}H_{17}O_3BrNa$: 299.02533; found: 299.02606.

(*Z*)-Methyl 4-(bromoiodomethylene)-3-ethyltetrahydrofuran-3-carboxylate (16) (Table 3, entry 2): Under argon, to a stirred solution of β-(propargyloxy)enoate **3a** (45 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added Me_2Zn (1 mL, 1.0 M in heptane, 1.0 mmol). Air (20 mL) was slowly introduced over 1 h into the solution via a syringe pump by using a syringe fitted with a $CaCl_2$ guard. The reaction mixture was then stirred at 0 °C for 1 h. A solution of I_2 (330 mg, 1.3 mmol) in THF (1 mL) was then added at the same temperature, and the mixture was stirred for 1 h. CH_2Cl_2 (10 mL) followed by an aqueous solution of $Na_2S_2O_3$ (10%) were added. The layers were separated, the aqueous one being extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with HCl (1 M) (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/ether 80:20) afforded the title compound **16** (46 mg, 64%) as a pale yellow oil. IR (neat): 2947, 2878, 1730, 1630, 1432, 1236, 1081, 941 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d(AB system), J = 14.0 Hz, 1H), 4.27 (d(AB system), J = 14.0 Hz, 1H), 4.24 (d(AB system), J = 8.8 Hz, 1H), 4.15 (d(AB system), J = 8.8 Hz, 1H), 3.75 (s, 3H), 2.21 (m, 1H), 1.95 (m, 1H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 152.4, 80.1, 79.5, 60.9, 52.8, 41.2, 25.5, 9.0; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_9H_{12}O_3BrINa$: 396.89067; found: 396.89159.

(*Z*)-Methyl 4-(bromoiodomethylene)-3-isobutyltetrahydrofuran-3-carboxylate (17) (Table 3, entry 4): The title compound was obtained as a side-product following the above-described procedure for the preparation of (*E*)-**4ad.** It could not be isolated pure after column chromatography, but characteristic NMR spectroscopic data were obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d(AB system), J = 14.0 Hz, 1H), 4.29 (d(AB system), J = 14.0 Hz, 1H), 4.24 (d(AB system), J = 8.9 Hz, 1H), 4.21 (d(AB system), J = 8.9 Hz, 1H), 3.75 (s, 3H), 2.10 (dd, J = 14.5, 6.8 Hz, 1H), 1.95 (dd, J = 14.5, 5.0 Hz, 1H), 1.81 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 152.9, 80.3, 79.8, 58.3, 52.7, 41.9, 40.7, 24.7, 24.5, 23.8.

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53. The *Z* configuration for the major isomer was determined by NOE experiments on isolated pure (*Z*)-**4aa**. An NOE signal (3%) was observed between the vinylic proton and the protons of the methylene group of the propyl chain α to the ester.
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    Zn-atom radical transfer is facilitated by coordination to a Lewis base. In the present case, the bromine atom may be coordinated to the dialkylzinc reagent and thereby activates it towards homolytic substitution. For a similar proposed coordination involving SmI_2, see this reference.
60. Even though the H-donor has not been identified, competitive H-atom transfer is a frequent side-reaction in the 1,4-addition/cyclization reaction of dialkylzincs with β-(propargyloxy)enoates, see references [37] and [38].
61. The stereochemical assignment was done on the basis of the comparison of the NMR data of **4ac** and **4aa**. Among others, the chemical shift (δ = 6.17 ppm) and coupling constant of the vinylic proton (*J* = 1.9 Hz) are indicative of the *E*-configuration.

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Recent advances in transition-metal-catalyzed intermolecular carbomagnesiation and carbozincation

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Review

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Abstract

Carbomagnesiation and carbozincation reactions are efficient and direct routes to prepare complex and stereodefined organomagnesium and organozinc reagents. However, carbon–carbon unsaturated bonds are generally unreactive toward organomagnesium and organozinc reagents. Thus, transition metals were employed to accomplish the carbometalation involving wide varieties of substrates and reagents. Recent advances of transition-metal-catalyzed carbomagnesiation and carbozincation reactions are reviewed in this article. The contents are separated into five sections: carbomagnesiation and carbozincation of (1) alkynes bearing an electron-withdrawing group; (2) alkynes bearing a directing group; (3) strained cyclopropenes; (4) unactivated alkynes or alkenes; and (5) substrates that have two carbon–carbon unsaturated bonds (allenes, dienes, enynes, or diynes).

Introduction

Whereas direct transformations of unreactive carbon–hydrogen or carbon–carbon bonds have been attracting increasing attention from organic chemists, classical organometallic reagents still play indispensable roles in modern organic chemistry. Among the organometallic reagents, organomagnesium and organozinc reagents have been widely employed for organic synthesis due to their versatile reactivity and availability. The most popular method for preparing organomagnesium and organozinc reagents still has to be the classical Grignard method [1], starting from magnesium or zinc metal and organic halides [2-7]. Although the direct insertion route is efficient and versatile, stereocontrolled synthesis of organomagnesium or organozinc reagents, especially of alkenyl or alkyl derivatives, is always difficult since the metal insertion process inevitably passes through radical intermediates to lose stereochemical information [5,8]. Halogen–metal exchange is a solution for the stereoselective synthesis [9-13]. However, preparation of the corresponding precursors can be laborious when highly func-

tionalized organometallic species are needed. Thus, many organic chemists have focused on carbometalation reactions that directly transform simple alkynes and alkenes to structurally complex organometallics with high stereoselectivity.

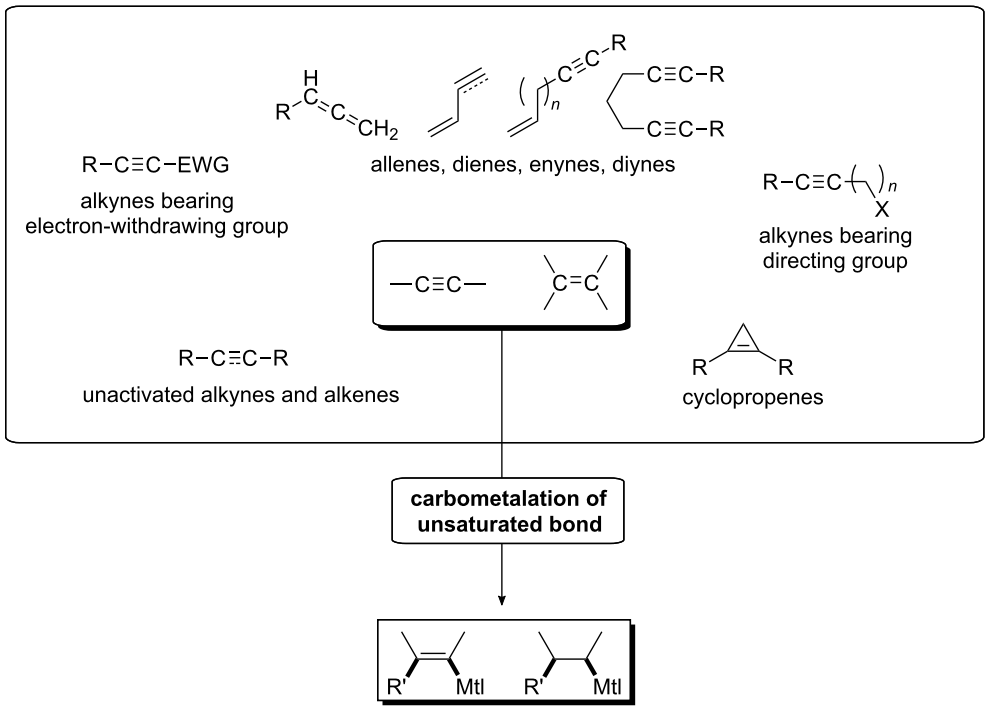
In general, carbon–carbon multiple bonds are unreactive with organomagnesium and organozinc reagents. Hence, limited substrates and reagents could be employed for uncatalyzed intermolecular carbometalation. Naturally, many groups envisioned transition-metal-catalyzed carbometalation reactions that directly convert alkynes and alkenes to new organomagnesium and organozinc reagents [14-33]. The resulting organomagnesium and organozinc intermediates have versatile reactivity toward various electrophiles to provide multisubstituted alkenes and alkanes. Thus, carbomagnesiation and carbozincation reactions are highly important in organic synthesis. Although intramolecular carbomagnesiation and -zincation [15] and intermolecular carbocupration with stoichiometric copper reagents has been well established [14,18,25], catalytic intermolecular carbomagnesiation and carbozincation are still in their infancy.

This article includes the advances in transition-metal-catalyzed intermolecular carbomagnesiation and carbozincation reactions that have been made in the past 15 years, promoting the development of these potentially useful technologies. The contents are categorized by the substrates (Scheme 1): (1) alkynes bearing an electron-withdrawing group; (2) alkynes bearing a directing group; (3) cyclopropenes; (4) unactivated alkynes or alkenes; and (5) substrates that have two carbon–carbon unsaturated bonds (allenes, dienes, enynes, or diynes).

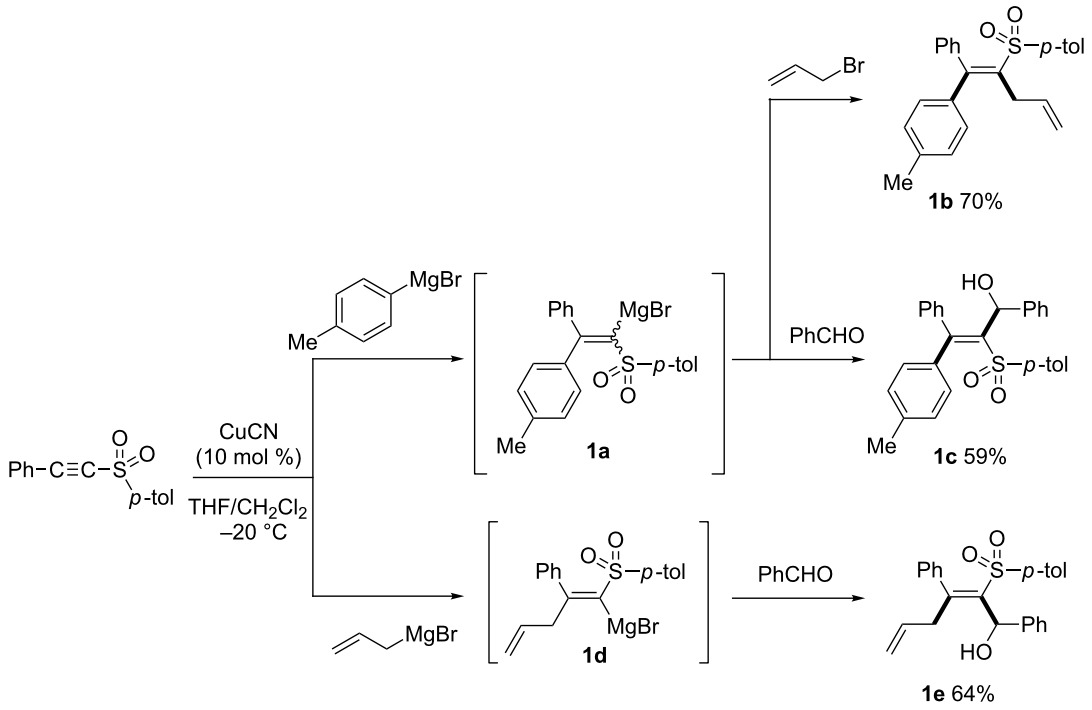
Review

Carbomagnesiation and carbozincation of electron-deficient alkynes

Since conjugate addition reactions of organocuprates with alkynyl ketones or esters have been well established [14,34-37], alkynes bearing an electron-withdrawing group other than carbonyl have been investigated recently [25,38]. The Xie, Marek, and Tanaka groups have been interested in copper-catalyzed carbometalation of sulfur-atom-substituted alkynes, such as alkynyl sulfones, sulfoxides, or sulfoximines as electron-deficient alkynes. Xie reported a copper-catalyzed carbomagnesiation of alkynyl sulfone to give the corresponding alkenylmagnesium intermediates (Scheme 2) [39,40]. Interestingly, the stereochemistry of the products was nicely controlled by the organomagnesium reagents and electrophiles employed. The reaction with arylmagnesium reagents provided alkenylmagnesium intermediate **1a**. The reaction of **1a** with allyl bromide provided *syn*-addition product **1b** in 70% yield while the reaction with benzaldehyde afforded *anti*-addition product **1c** in



Scheme 1: Variation of substrates for carbomagnesiation and carbozincation in this article.



Scheme 2: Copper-catalyzed arylmagnesiation and allylmagnesiation of alkynyl sulfone.

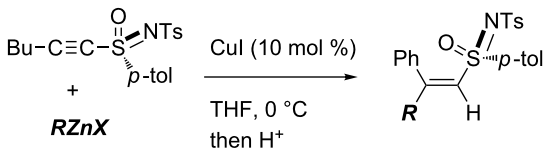
59% yield. In contrast, allylmagnesiated intermediate **1d** reacted with benzaldehyde to give *syn*-addition product **1e** stereoselectively.

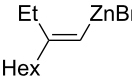
Marek reported copper-catalyzed carbometalation of alkynyl sulfoximines and sulfones using organozinc reagents of mild reactivity [41]. Various organozinc reagents can be used, irrespective of the identity of the organic groups, preparative protocols, and accompanying functional groups (Table 1). Similarly, Xie reported ethyl- or methylzincation of alkynyl sulfones [42] and Tanaka reported carbozincation of alkynyl sulfoxides [43,44].

Marek discovered efficient methods for the stereoselective synthesis of multisubstituted allylic zinc intermediates **1f** from alkynyl sulfoxides with organomagnesium or -zinc reagents (Scheme 3) [45,46]. It is noteworthy that they applied their chemistry to the preparation of various allylic metals [24,25,47-53] or enolates [54] from simple alkynes by carbocupration reactions.

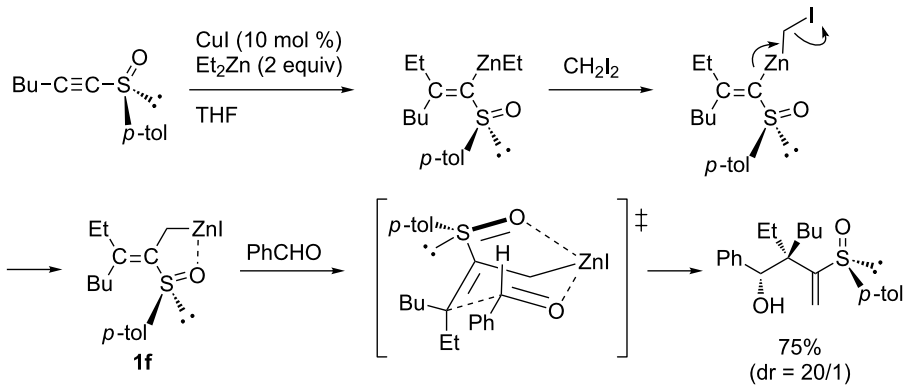
Not only copper but also rhodium can catalyze carbometalation reactions. Hayashi applied carborhodation chemistry [55-58] to the reactions of aryl alkynyl ketones with arylzinc reagents, which provided enolates of indanones (Scheme 4) [59]. Phenylrhodation of **1g** first proceeds to form **1A**. A subsequent intramolecular 1,4-hydrogen shift gives **1B**, which smoothly undergoes an intramolecular 1,4-addition to yield **1C**. Finally, transmetalation from the phenylzinc reagent to rhodium enolate **1C** affords zinc enolate **1h**, which reacts with allyl bromide to give **1i** in 60% yield.

Table 1: Copper-catalyzed carbozincation of alkynyl sulfoximines.

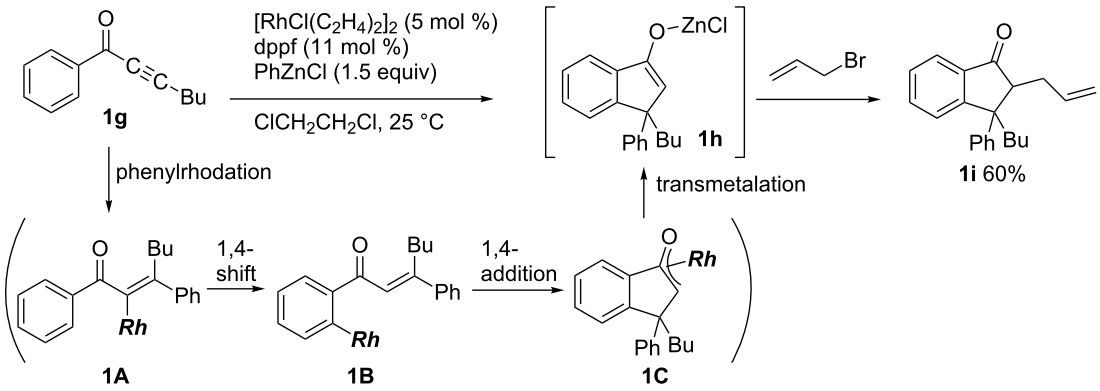


Entry	***RZnX***	Yield
1	Et_2Zn	82%
2	EtZnI[a]	90%
3	OctZnI[b]	55%
4	EtZnBr[c]	75%
5	iPrZnBr[c]	80%
6	PhZnBr[c]	85%
7	$MeOCO(CH_2)_3ZnI$[b]	55%
8		72%

[a]Prepared from Et_2Zn and I_2. [b]Prepared from the corresponding alkyl iodide and zinc dust. [c]Generated from the corresponding Grignard reagent and $ZnBr_2$. [d]Prepared from the corresponding vinyl iodide by iodine–lithium exchange and followed by transmetalation with $ZnBr_2$.



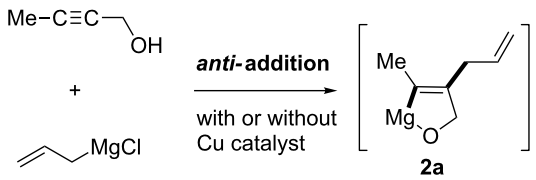
Scheme 3: Copper-catalyzed four-component reaction of alkynyl sulfoxide with alkylzinc reagent, diiodomethane, and benzaldehyde.



Scheme 4: Rhodium-catalyzed reaction of aryl alkynyl ketones with arylzinc reagents.

Carbomagnesiation and carbozincation of alkynes bearing a directing group

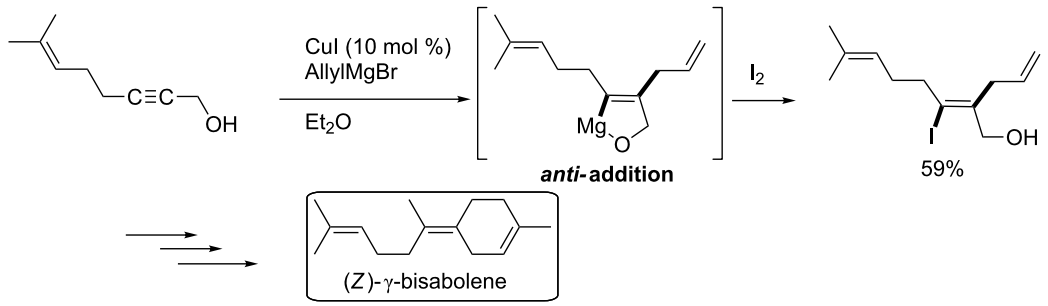
Directing groups have been utilized in successful carbometalation with high regio- and stereoselectivity. Classically, hydroxy groups on propargylic alcohols are used in uncatalyzed carbomagnesiation (Scheme 5) [60,61]. This addition proceeded in an *anti* fashion to give intermediate **2a**. The trend is the same in copper-catalyzed reactions of wide scope [62]. In 2001, Negishi applied copper-catalyzed allylmagnesiation to the total synthesis of (*Z*)-γ-bisabolene (Scheme 6) [63].



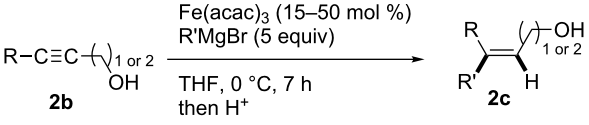
Scheme 5: Allylmagnesiation of propargyl alcohol, which provides the *anti*-addition product.

Recently, Ready reported an intriguing iron-catalyzed carbomagnesiation of propargylic and homopropargylic alcohols **2b** to yield *syn*-addition intermediates **2c** with opposite regioselectivity (Scheme 7) [64]. They assumed that the key organo-iron intermediate **2A** underwent oxygen-directed carbometalation to afford **2B** or **2C** (Scheme 8). Further transmetalation of vinyl-iron intermediate **2B** or **2C** with R′MgBr yielded the corresponding vinylmagnesium intermediate **2D**. Therefore, selective synthesis of both regioisomers of allylic alcohols can be accomplished by simply choosing transition-metal catalysts (Cu or Fe). Methyl-, ethyl-, and phenylmagnesium reagents could be employed for the reaction.

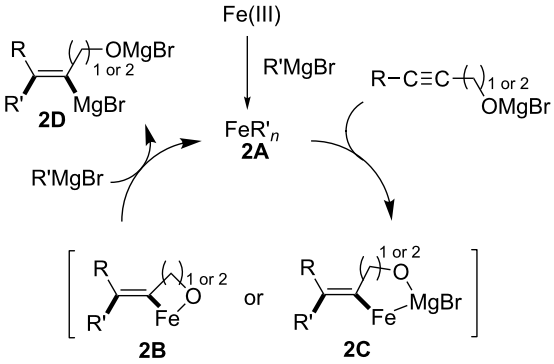
Aside from the examples shown in Scheme 5 and Scheme 6, alkynes that possess a directing group usually undergo *syn*-addition. Oshima reported manganese-catalyzed regio- and stereoselective carbomagnesiation of homopropargyl ether **2d** leading to the formation of the corresponding *syn*-addition product **2e** (Scheme 9) [65]. The reaction of [2-(1-propynyl)phenyl]-methanol (**2f**) also proceeded in a *syn* fashion (Scheme 10) [66-68].



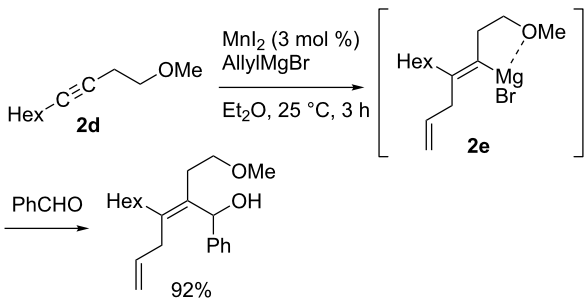
Scheme 6: Negishi's total synthesis of (*Z*)-γ-bisabolene by allylmagnesiation.



Scheme 7: Iron-catalyzed *syn*-carbomagnesiation of propargylic or homopropargylic alcohol.

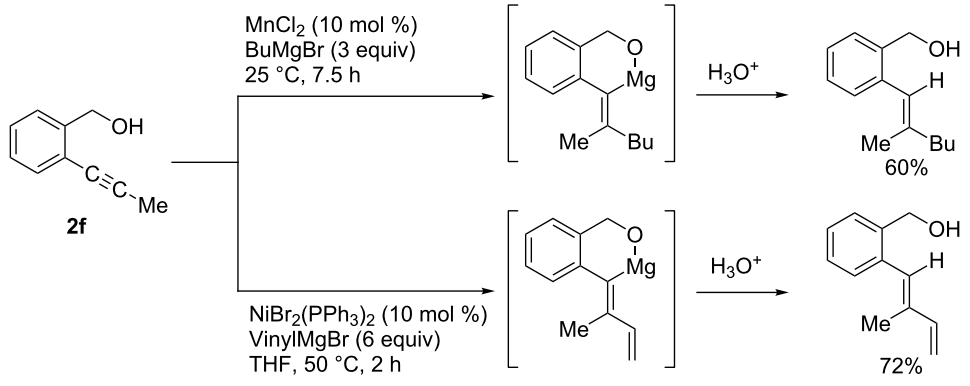


Scheme 8: Mechanism of iron-catalyzed carbomagnesiation.

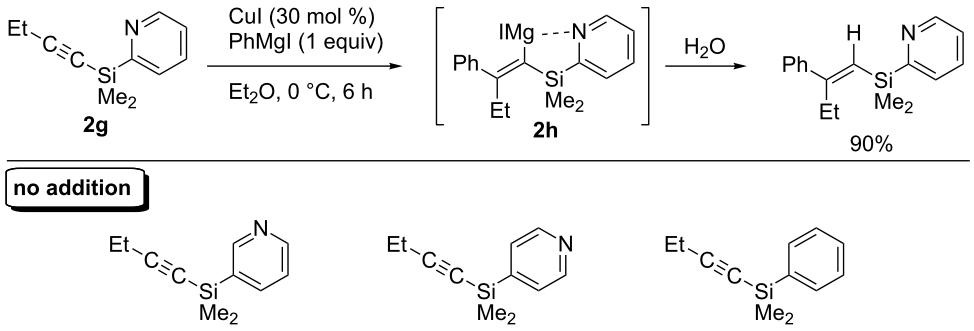


Scheme 9: Regio- and stereoselective manganese-catalyzed allylmagnesiation.

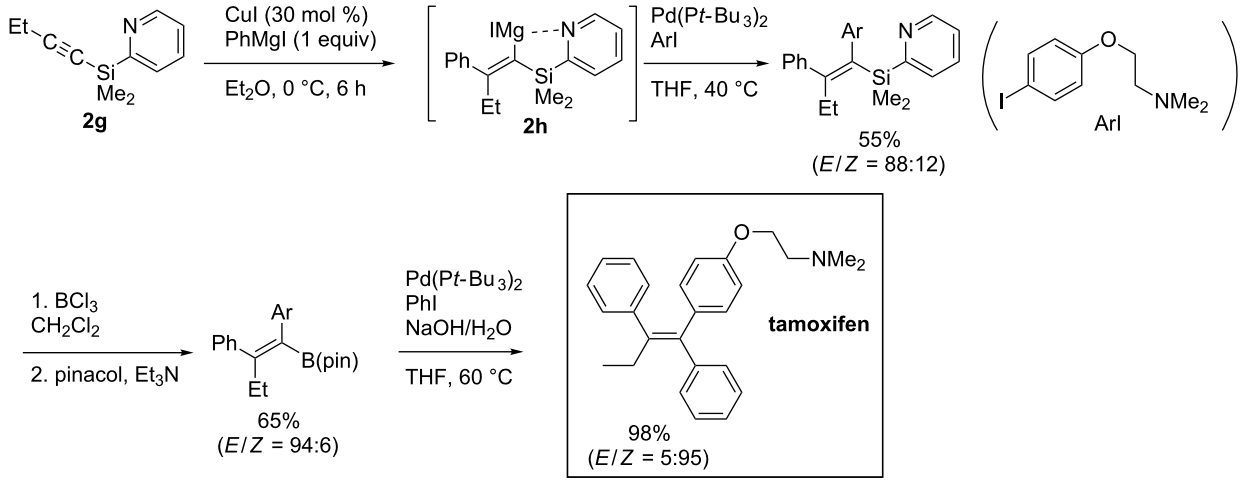
In 2003, Itami and Yoshida revealed a concise synthesis of tetrasubstituted olefins from (2-pyridyl)silyl-substituted alkynes. The key intermediate **2h** was prepared by copper-catalyzed arylmagnesiation of **2g**, in which the 2-pyridyl group on silicon efficiently worked as a strong directing group (Scheme 11) [69]. Furthermore, they accomplished a short and efficient synthesis of tamoxifen from **2g** (Scheme 12). Notably, the synthetic procedure is significantly versatile and various tamoxifen derivatives were also prepared in just three steps from **2g**.



Scheme 10: Vinylation and alkylation of arylacetylene-bearing hydroxy group.



Scheme 11: Arylmagnesiation of (2-pyridyl)silyl-substituted alkynes.



Scheme 12: Synthesis of tamoxifen from **2g**.

The directing effect dramatically changed the regioselectivity in the reactions of oxygen- or nitrogen-substituted alkynes. Carbocupration of these alkynes generally gives the vicinal product **2D** (copper locates at the β-position to the O or N) (Scheme 13, path A) [14,70-73]. On the other hand, the reversed regioselectivity was observed in the carbocupration of *O*-alkynyl carbamate and *N*-alkynyl carbamate, in which carbonyl groups worked as a directing group to control the regioselectivity to afford **2E** (Scheme 13, path B) [25,74-76].

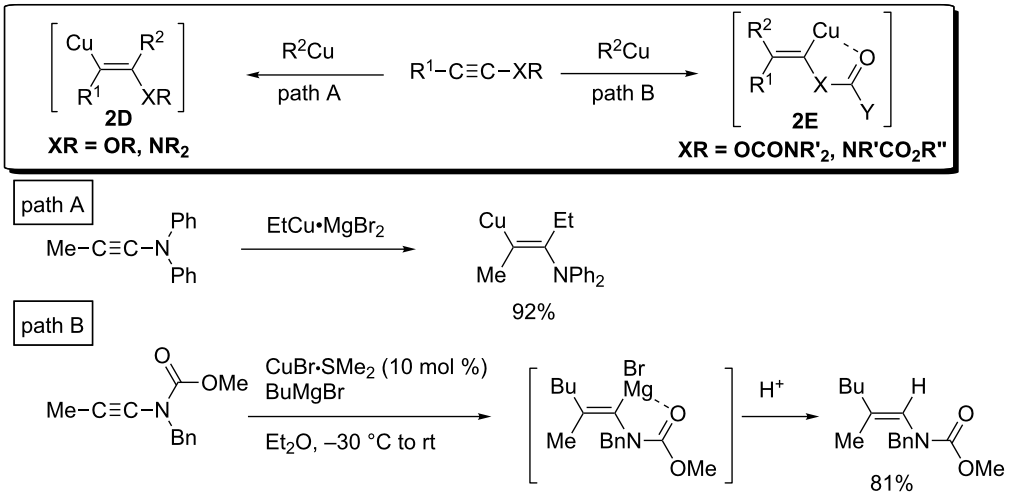
In 2009, Lam reported the rhodium-catalyzed carbozincation of ynamides. The reaction smoothly proceeded under mild conditions to provide the corresponding intermediate **2i** regioselectively (Scheme 14) [77,78]. A wide variety of ynamides and organozinc reagents could be used for the reaction (Table 2).

Yorimitsu and Oshima reported an interesting transformation of ynamides to nitriles by a carbomagnesiation/aza-Claisen rearrangement sequence (Scheme 15) [79,80].

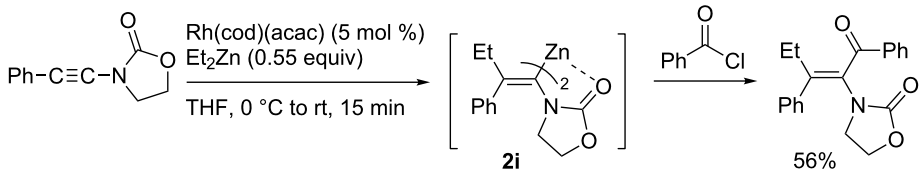
Carbomagnesiation and carbozincation of cyclopropenes

Increasing the reactivity of alkynes and alkenes is another strategy to achieve intermolecular carbometalation reactions. For example, strained alkenes are highly reactive toward carbometalation. The reactions of cyclopropenes took place without the aid of a metal catalyst (Scheme 16) [81].

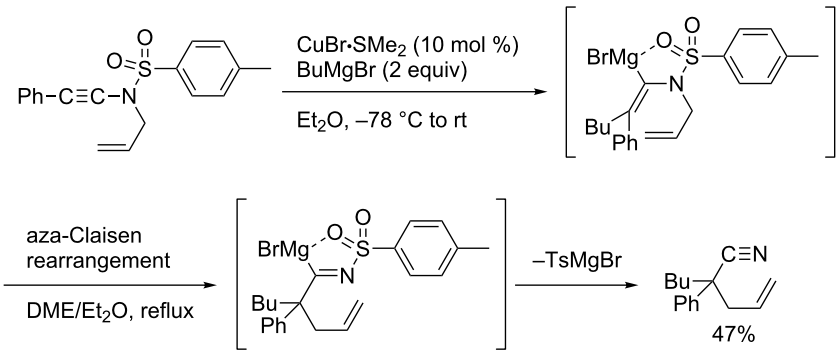
Nakamura and co-workers discovered that an addition of iron salt enhanced the carbometalation of cyclopropenone acetal with organomagnesium and -zinc species (Scheme 17) and applied the reaction to enantioselective carbozincation



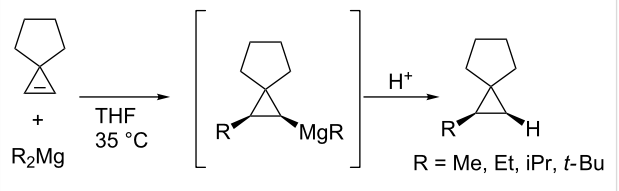
Scheme 13: Controlling regioselectivity of carbocupration by attaching directing groups.



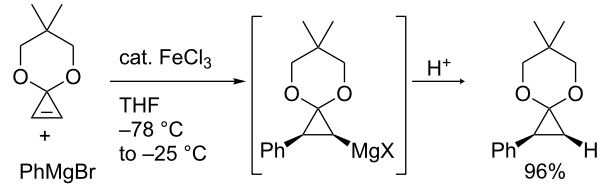
Scheme 14: Rhodium-catalyzed carbozincation of ynamides.



Scheme 15: Synthesis of 4-pentenenitriles through carbometalation followed by aza-Claisen rearrangement.

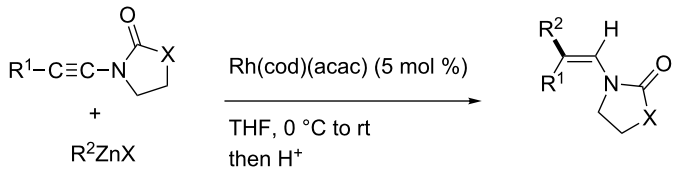


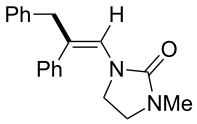
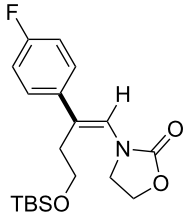
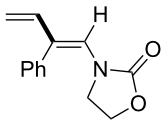
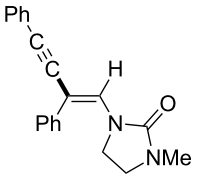
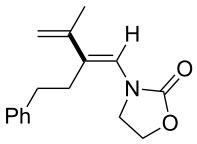
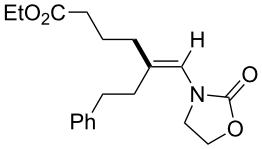
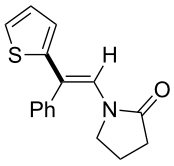
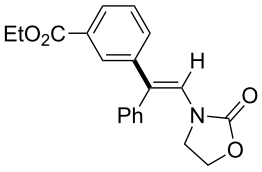
Scheme 16: Uncatalyzed carbomagnesiation of cyclopropenes.



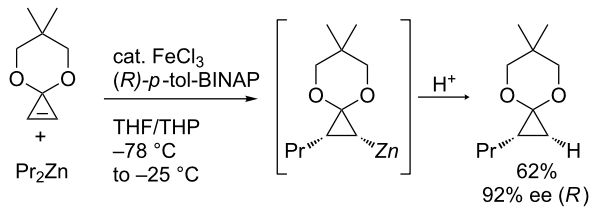
Scheme 17: Iron-catalyzed carbometalation of cyclopropenes.

Table 2: Scope of rhodium-catalyzed carbozincation of ynamide.



Reagent	Product	Yield [%]	Reagent	Product	Yield [%]
Bn_2Zn		71	$(p\text{-}FC_6H_4)_2Zn$		84
$(vinyl)_2Zn$		66	$(phenylethynyl)_2Zn$		60
$(2\text{-propenyl})_2Zn$		47	$EtO_2C(CH_2)_3ZnBr$		54
$(2\text{-thienyl})_2Zn$		66	$m\text{-}EtO_2CC_6H_4ZnI$		58

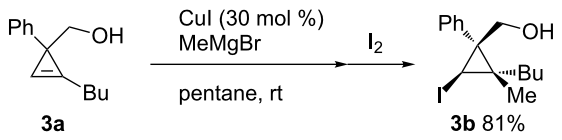
(Scheme 18) [82,83]. The scope was wide enough to use phenyl-, vinyl-, and methylmagnesium reagents or diethylzinc and dipentylzinc reagents. It is noteworthy that the reaction in the absence of the iron catalyst did not proceed at low temperature and gave a complex mixture at higher temperature (up to 65 °C).



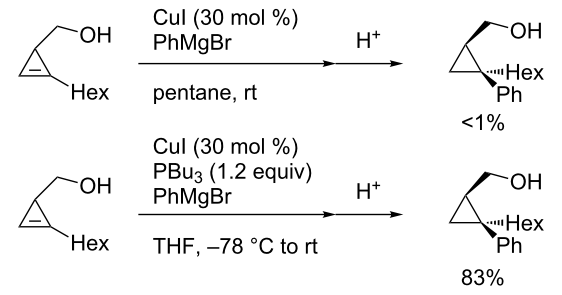
Scheme 18: Enantioselective carbozincation of cyclopropenes.

A hydroxymethyl group also showed a significant directing effect in the copper-catalyzed reaction of cyclopropene **3a** with methylmagnesium reagent to afford **3b** with perfect stereoselectivity (Scheme 19) [84]. Not only methylmagnesium reagents but also vinyl- or alkynylmagnesium reagents could be employed. Although the arylation reaction did not proceed under the same conditions (Scheme 20, top), the addition of tributylphosphine and the use of THF as a solvent enabled the stereoselective arylmagnesiation with high efficiency (Scheme 20, bottom) [85]. Similarly, carbocupration reactions of 1-cyclopropenylmethanol and its derivatives using the directing effect of the hydroxymethyl group are also known [86-89].

Notably, Fox reported the enantio- and stereoselective carbomagnesiation of cyclopropenes without the addition of transition metals (Scheme 21) [90]. The key to successful reactions

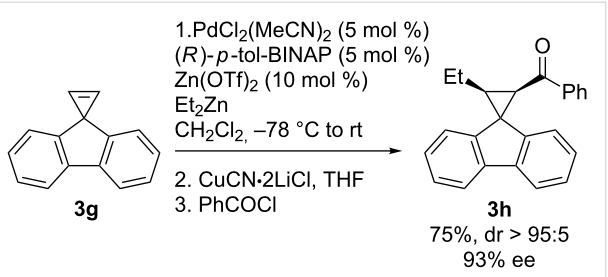


Scheme 19: Copper-catalyzed facially selective carbomagnesiation.



Scheme 20: Arylmagnesiation of cyclopropenes.

is the addition of aminoalcohol **3c** and 1 equiv of methanol. In 2009, Fox et al. improved their copper-catalyzed carbometalation reactions of cyclopropenes by using functional-group-tolerable organozinc reagents (Scheme 22) such as dimethyl-, diethyl-, diphenyl-, diisopropyl-, and divinylzinc reagents [91]. Treatment of cyclopropene **3d** with dimethylzinc in the presence of a catalytic amount of copper iodide afforded organozinc intermediate **3e** and finally **3f** after protonolysis. In 2012, Fox reported the stereoselective copper-catalyzed arylzincation of cyclopropenes with a wider variety of arylzinc reagents [92]. The organozinc reagents were prepared by iodine/magnesium

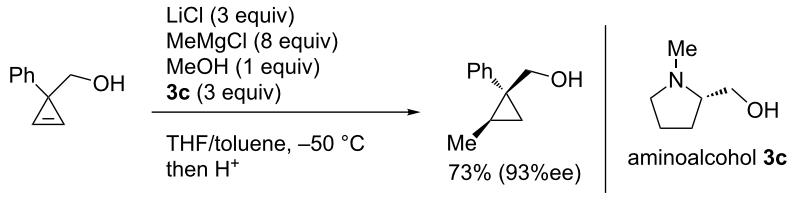


Scheme 23: Enantioselective ethylzincation of cyclopropenes.

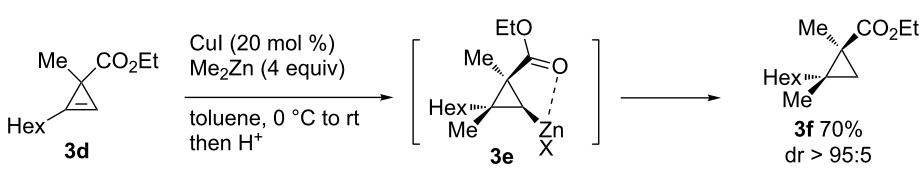
exchange and the subsequent transmetalation to zinc, and then used directly in one pot (Table 3).

Lautens reported enantioselective carbozincation of alkenes using a palladium catalyst with a chiral ligand (Scheme 23) [93]. Treatment of **3g** with diethylzinc in the presence of catalytic amounts of palladium salt, (*R*)-tol-BINAP, and zinc triflate and subsequent quenching with benzoyl chloride afforded **3h** in 75% yield with 93% ee. The addition of zinc triflate may help the formation of a more reactive cationic palladium(II) species. Under similar conditions, Lautens also reported palladium-catalyzed carbozincation of oxabicycloalkenes [94].

Terao and Kambe reported two types of intriguing ring-opening carbomagnesiations of a methylenecyclopropane that proceed through site-selective carbon–carbon bond cleavage (Scheme 24) [95]. The reaction pathways depended on the reagents used, i.e., the reaction with a phenylmagnesium reagent provided **3i** whereas the reaction with a vinylmagne-

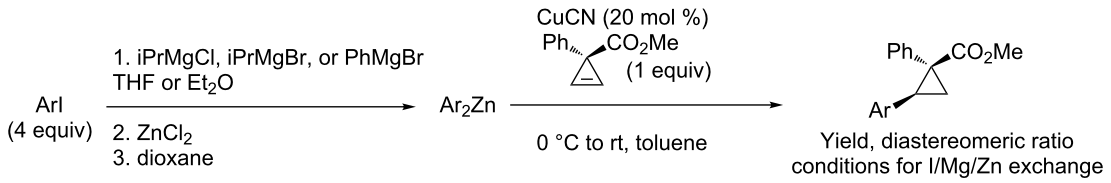


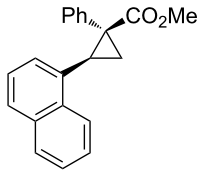
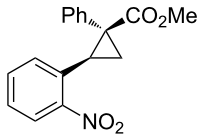
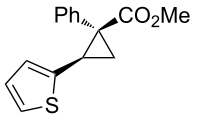
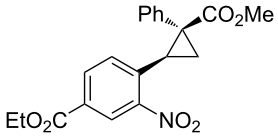
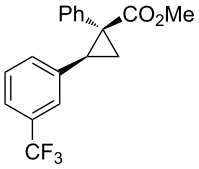
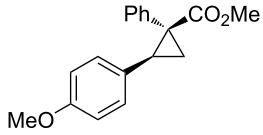
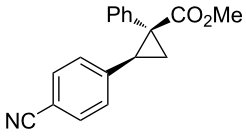
Scheme 21: Enantioselective methylmagnesiation of cyclopropenes without catalyst.

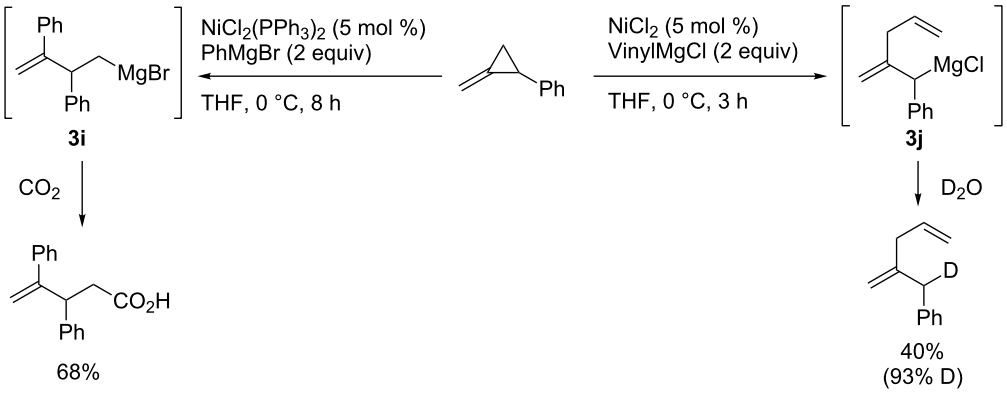


Scheme 22: Copper-catalyzed carbozincation.

Table 3: Sequential I/Mg/Zn exchange and arylzincation of cyclopropenes.

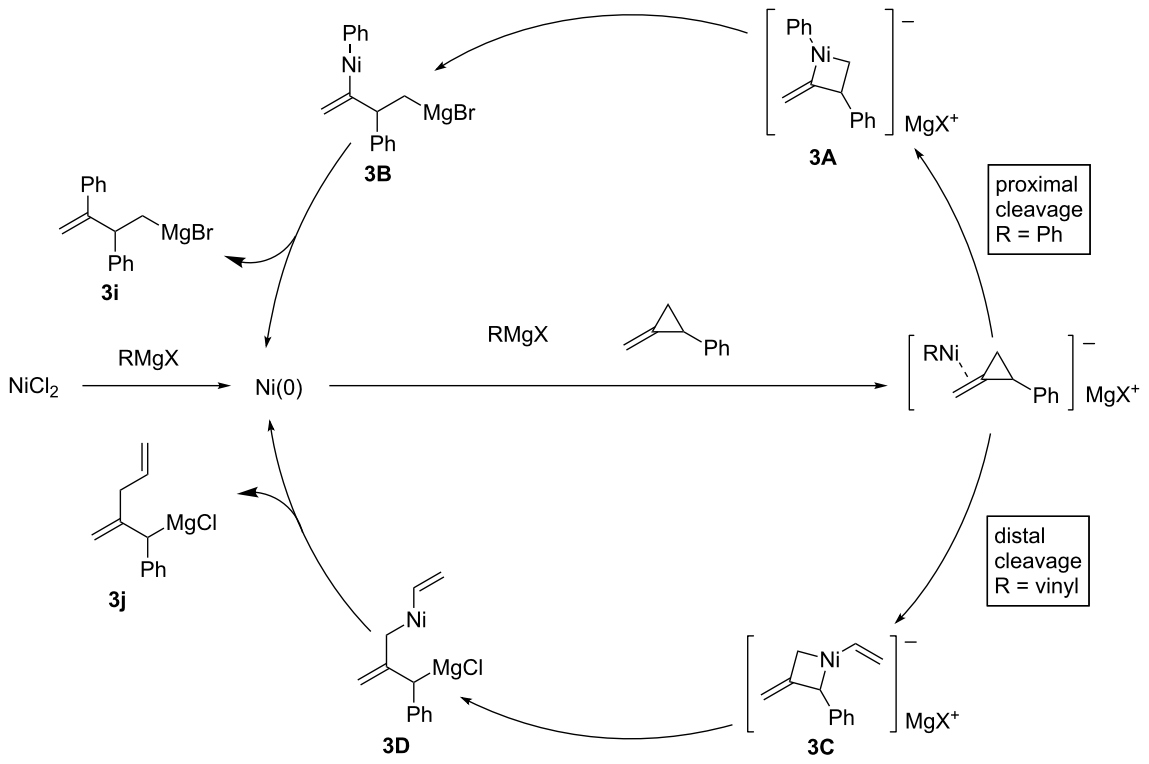


Reaction step 1.	Product	Yield [%] (dr)	Reaction step 1.	Product	Yield [%] (dr)
iPrMgCl, Et_2O, rt		81 (>95:5)	PhMgBr, THF, −35 °C		62 (95:5)
iPrMgCl, THF, −35 °C		69 (>95:5)	PhMgBr, THF, −40 °C		61 (>95:5)
iPrMgCl, Et_2O, −35 °C		70 (>95:5)	iPrMgBr, THF, rt		60 (88:12)
iPrMgCl, THF, −35 °C		55 (91:9)			



Scheme 24: Nickel-catalyzed ring-opening aryl- and alkenylmagnesiation of a methylenecyclopropane.

sium reagent gave **3j**. The reaction mechanisms are shown in Scheme 25. They proposed that the carbon–carbon bond cleavage happened prior to the carbometalation reactions, which is different from other ring-opening reactions of cyclopropenes [96,97] where carbometalation is followed by carbon–carbon bond cleavage. Firstly, the oxidative addition of methylenecyclopropane to the reduced nickel(0) may yield **3A** or **3C**. The subsequent isomerization would proceed to form **3B** or **3D**, respectively, and then reductive elimination would afford the corresponding organomagnesium intermediate **3i** or **3j**.



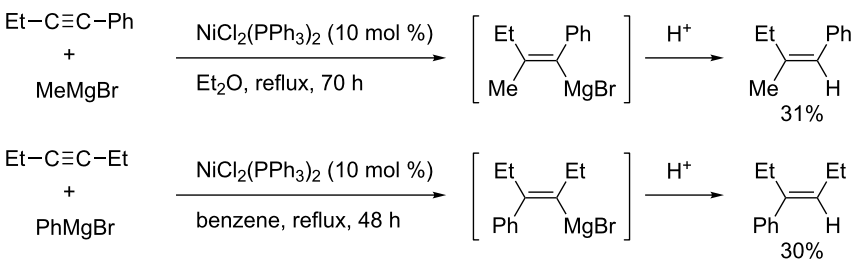
Scheme 25: Reaction mechanism.

Carbomagnesiation and carbozincation of unfunctionalized alkynes and alkenes

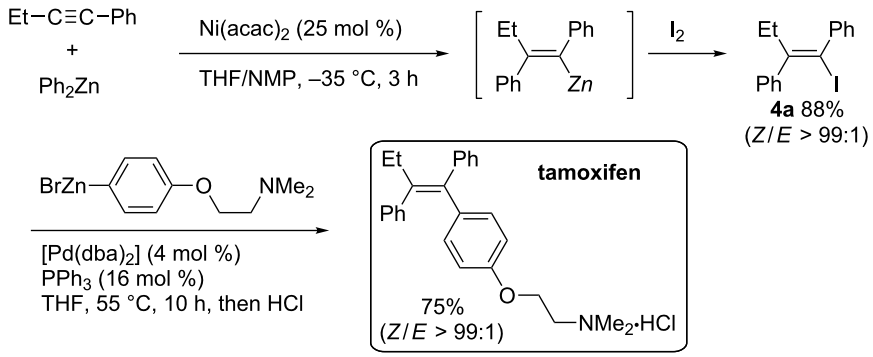
Carbomagnesiation and carbozincation of simple alkynes has been a longstanding challenge. In 1978, Duboudin reported nickel-catalyzed carbomagnesiation of unfunctionalized alkynes, such as phenylacetylenes and dialkylacetylenes (Scheme 26) [98]. Although this achievement is significant as an intermolecular carbomagnesiation of unreactive alkynes, the scope was fairly limited and yields were low.

In 1997, Knochel reported nickel-catalyzed carbozincation of arylacetylenes (Scheme 27) [99,100]. The reaction smoothly proceeded at –35 °C and exclusively produced tetrasubstituted (*Z*)-alkene **4a** in high yield. Not only diphenylzinc reagent but also dimethyl- and diethylzinc reagents were employed. Chemists at the Bristol-Myers Squibb company developed a scalable synthesis of (*Z*)-1-bromo-2-ethylstilbene (**4b**), a key intermediate of a selective estrogen-receptor modulator, using the modified Knochel's carbozincation method (Scheme 28) [101]. It is noteworthy that the modified nickel-catalyzed reaction could be performed at 20 °C to afford 57 kg of the corresponding phenylated product (58% yield) from 44 kg of 1-phenyl-1-butyne.

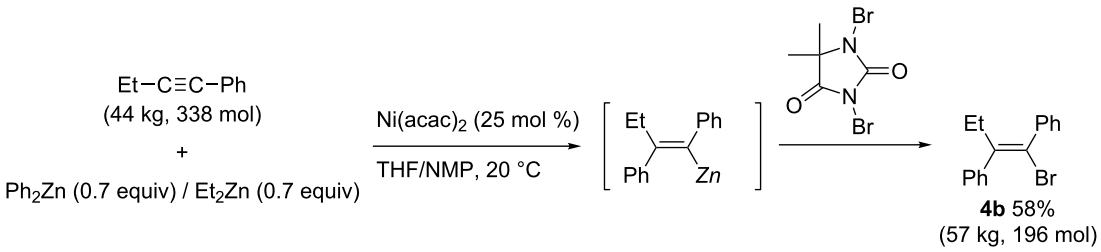
Oshima reported manganese-catalyzed phenylmagnesiation of a wide range of arylacetylenes (Table 4) [102]. Notably, directing groups, such as *ortho*-methoxy or *ortho*-amino groups, facilitated the reaction (Table 4, entries 2 and 3 versus entry 4).



Scheme 26: Nickel-catalyzed carbomagnesiation of arylacetylene and dialkylacetylene.

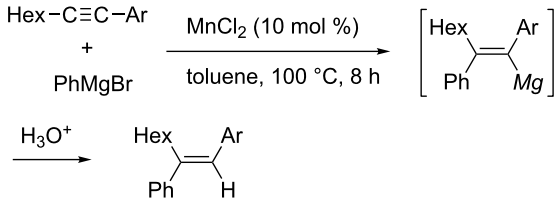


Scheme 27: Nickel-catalyzed carbozincation of arylacetylenes and its application to the synthesis of tamoxifen.



Scheme 28: Bristol-Myers Squibb's nickel-catalyzed phenylzincation.

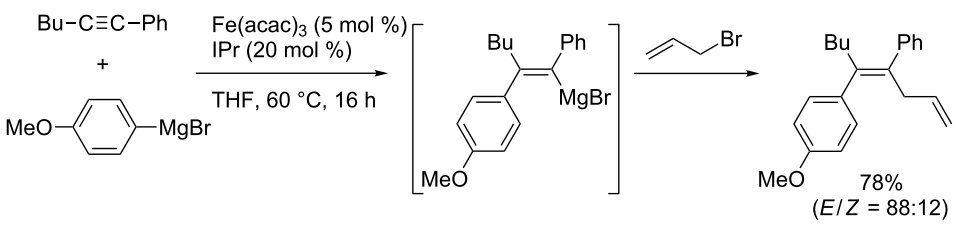
Table 4: Manganese-catalyzed arylmagnesiation of arylacetylenes.



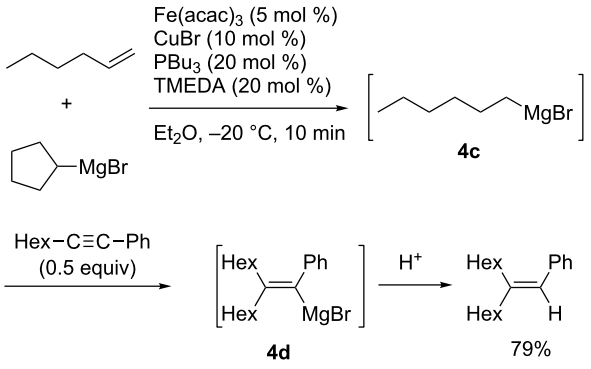
Entry	Ar	Yield
1	Ph	66%
2	*o*-$Me_2NC_6H_4$	94%
3	*o*-$MeOC_6H_4$	80%
4	*p*-$MeOC_6H_4$	38%
5	*o*-FC_6H_4	47%

Recently, iron and cobalt have been regarded as efficient catalysts for carbometalation of simple alkynes. Shirakawa and Hayashi reported that iron salts could catalyze arylmagnesiation of arylacetylenes in the presence of an *N*-heterocyclic carbene (NHC) ligand (Scheme 29) [103].

In 2012, Shirakawa and Hayashi reported iron/copper cocatalyzed alkene–Grignard exchange reactions and their application to one-pot alkylmagnesiation of alkynes (Scheme 30) [104]. The exchange reactions proceeded through a β-hydrogen elimination–hydromagnesiation sequence to generate **4c**. The alkylmagnesiation reactions of 1-phenyl-1-octyne with **4c** provided the corresponding alkylated products **4d** exclusively without contamination by the hydromagnesiated products of alkynes. In contrast, Nakamura reported the iron-catalyzed hydromagnesiation of diarylacetylenes and diynes with ethyl-



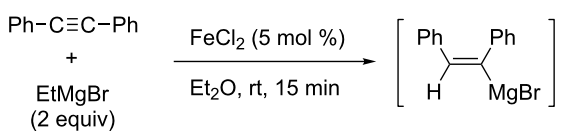
Scheme 29: Iron/NHC-catalyzed arylmagnesiation of aryl(alkyl)acetylene.



Scheme 30: Iron/copper-cocatalyzed alkylmagnesiation of aryl(alkyl)acetylenes.

magnesium bromide as a hydride donor without forming alkylated products (Scheme 31) [105].

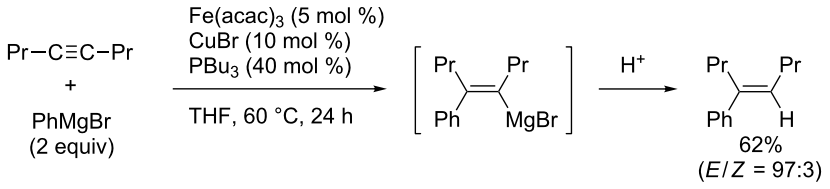
As shown in Scheme 32, carbomagnesiation of dialkylacetylene provided the corresponding arylated product only in low yield. Although Negishi reported ethylzincation [106], allylzincation [107], and methylalumination [108] with a stoichiometric amount of zirconium salt, the examples of transition-metal-catalyzed carbometalation of dialkylacetylenes were



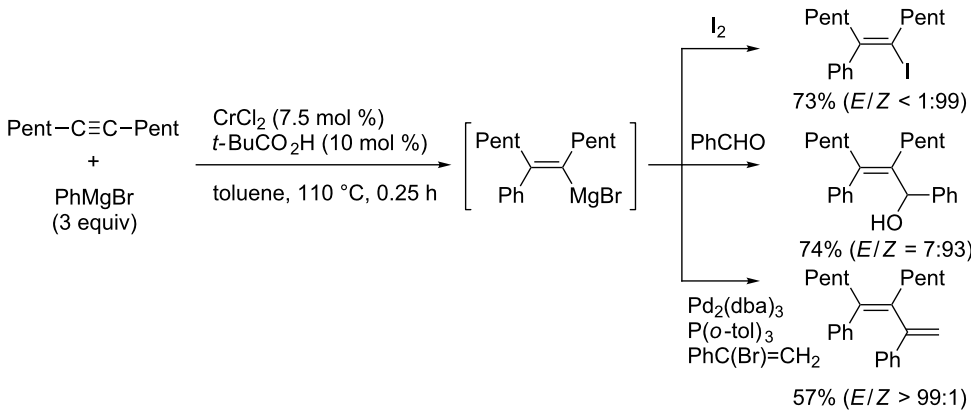
Scheme 31: Iron-catalyzed hydrometalation.

limited only to carboboration [109,110] and carbostannylation [111]. In 2005, Shirakawa and Hayashi reported iron/copper-cocatalyzed arylmagnesiation of dialkylacetylenes [112]. This is the first successful catalytic carbomagnesiation of dialkylacetylenes. Note that Ilies and Nakamura reported iron-catalyzed annulation reactions of various alkynes, including dialkylacetylenes with 2-biphenylylmagnesium reagents to form phenanthrene structures [113].

In 2007, Yorimitsu and Oshima reported that chromium chloride could catalyze the arylmagnesiation of simple alkynes [114]. They found that the addition of a catalytic amount of pivalic acid dramatically accelerated the reaction (Table 5). Although the reason for the dramatic acceleration is not clear, the reaction provided various tetrasubstituted alkenes efficiently with good stereoselectivity (Scheme 33).

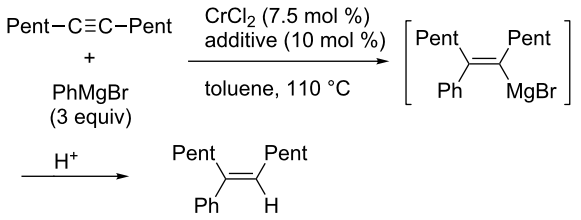


Scheme 32: Iron/copper-cocatalyzed arylmagnesiation of dialkylacetylenes.



Scheme 33: Chromium-catalyzed arylmagnesiation of alkynes.

Table 5: Acceleration effect of additive on chromium-catalyzed arylmagnesiation.

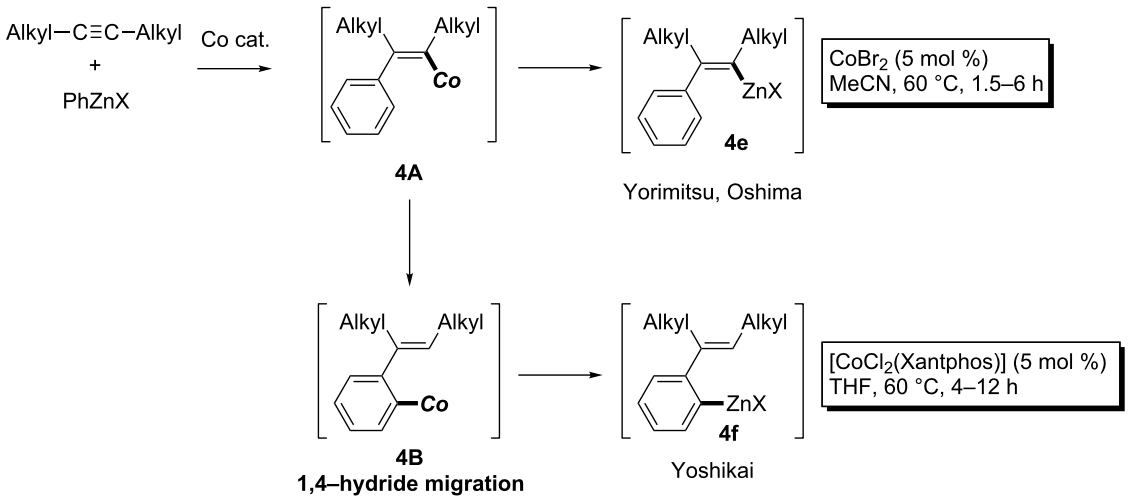


Entry	Additive	Time	Yield (*E*/*Z*)
1	None	18 h	81% (91:9)
2	MeOH	2 h	77% (95:5)
3	$MeCO_2H$	0.25 h	79% (>99:1)
4	$PhCO_2H$	0.25 h	81% (>99:1)
5	***t*-BuCO$_2$H**	**0.25 h**	**87% (>99:1)**

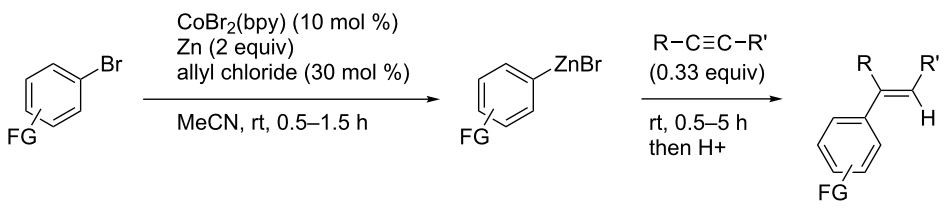
A more versatile arylmetalation of dialkylacetylenes using arylzinc reagents in the presence of a cobalt catalyst was then reported by Yorimitsu and Oshima (Scheme 34, top) [115]. Treatment of dialkylacetylenes with arylzinc reagents in acetonitrile in the presence of a catalytic amount of cobalt bromide afforded the corresponding arylated intermediate **4e**. Further study by Yoshikai revealed that the use of Xantphos as a ligand totally changed the products [116]. Smooth 1,4-hydride migration from **4A** to **4B** happened to provide organozinc **4f** (Scheme 34, bottom). The versatile 1,4-migration reactions were widely applicable for the 1,2-difunctionalization of arenes.

In 2012, Gosmini reported similar cobalt-catalyzed arylzincation reactions of alkynes, which provided tri- or tetrasubstituted alkenes with high stereoselectivity [117]. Their catalytic system was dually efficient: the simple $CoBr_2$(bpy) complex worked as a catalyst not only for arylzincation but also for the formation of arylzinc reagents (Scheme 35).

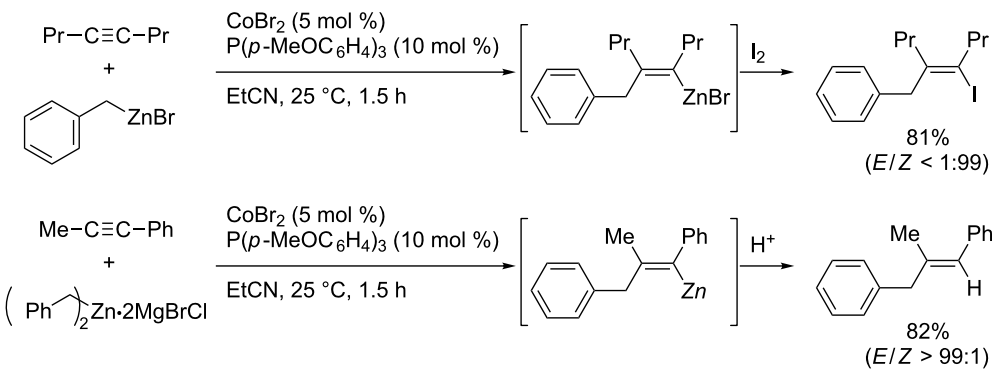
Yorimitsu and Oshima also accomplished benzylzincation of simple alkynes to provide allylbenzene derivatives in high yields (Scheme 36) [118]. For the reactions of simple dialkylacetylenes, benzylzinc bromide was effective (Scheme 36, top). On the other hand, dibenzylzinc reagent was effective for the



Scheme 34: Cobalt-catalyzed arylzincation of alkynes.



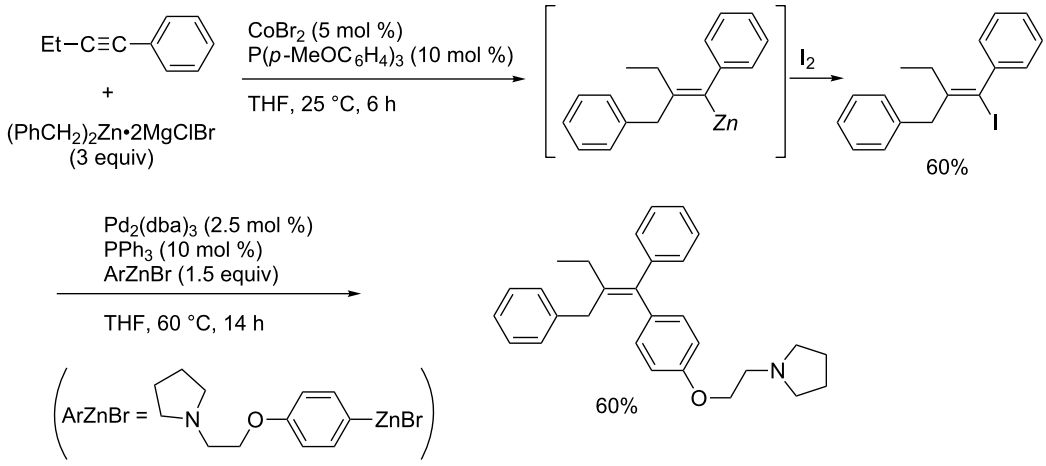
Scheme 35: Cobalt-catalyzed formation of arylzinc reagents and subsequent arylzincation of alkynes.



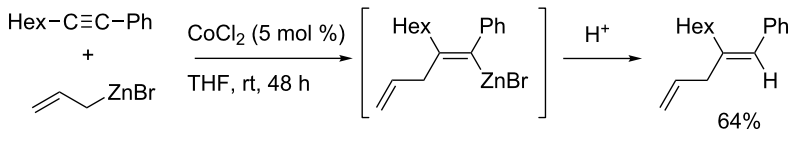
Scheme 36: Cobalt-catalyzed benzylzincation of dialkylacetylene and aryl(alkyl)acetylenes.

reactions of aryl(alkyl)acetylenes (Scheme 36, bottom). They applied the reaction toward the synthesis of an estrogen-receptor antagonist (Scheme 37). Although the cobalt-catalyzed allylzincation reactions of dialkylacetylenes resulted in low yield, the reactions of arylacetylenes provided various tri- or tetrasubstituted styrene derivatives (Scheme 38) [119,120].

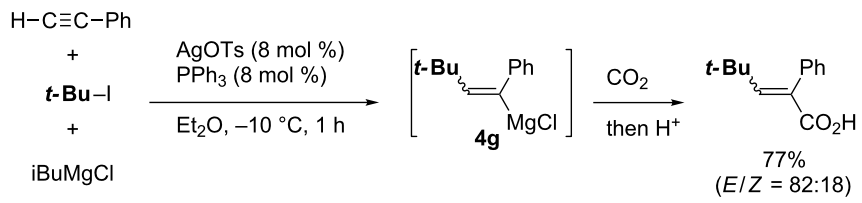
Kambe reported a rare example of silver catalysis for carbomagnesiation reactions of simple terminal alkynes (Scheme 39) [121,122]. They proposed that the catalytic cycle (Scheme 40) would be triggered by the transmetalation of AgOTs with iBuMgCl to afford isobutylsilver complex **4C**. Complex **4C** would react with *tert*-butyl iodide to generate *tert*-butylsilver



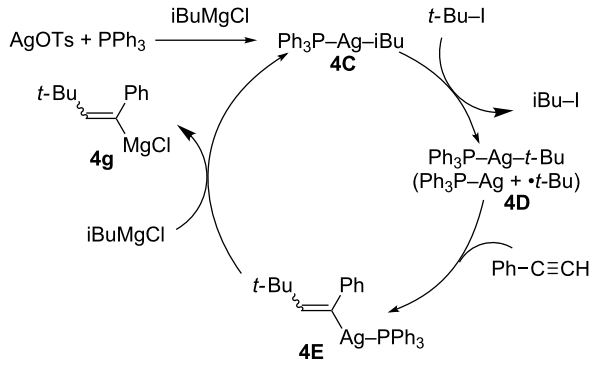
Scheme 37: Synthesis of estrogen receptor antagonist.



Scheme 38: Cobalt-catalyzed allylzincation of aryl-substituted alkynes.



Scheme 39: Silver-catalyzed alkylmagnesiation of terminal alkyne.

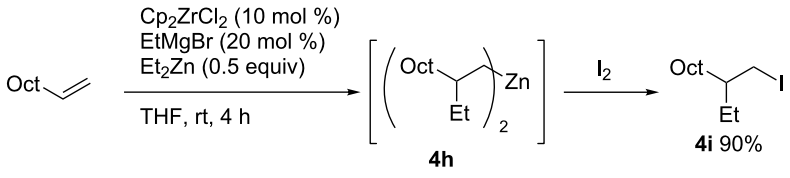


Scheme 40: Proposed mechanism of silver-catalyzed alkylmagnesiation.

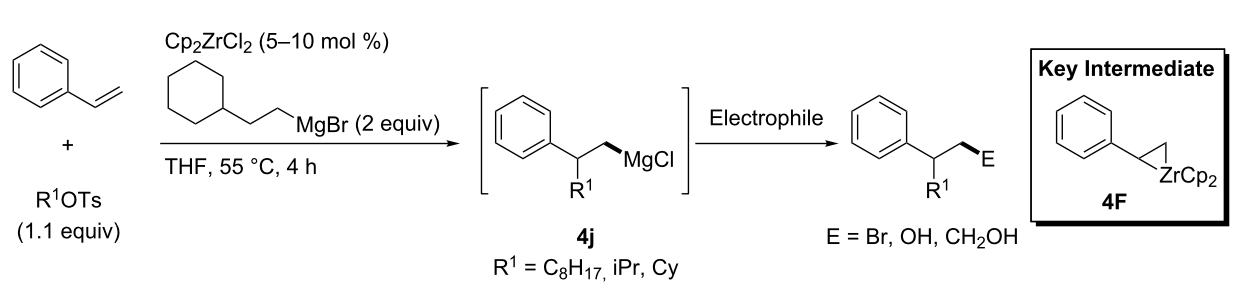
intermediate **4D**. Carbometalation of terminal alkynes with **4D**, probably by addition of a *t*-Bu radical, would yield vinylsilver **4E**. Finally, transmetalation with iBuMgCl would give the corresponding vinylmagnesium intermediate **4g**. Due to the intermediacy of radical intermediates, the carbomagnesiation is not stereoselective.

In 2000, Negishi reported zirconium-catalyzed ethylzincation of 1-decene to provide dialkylzinc intermediate **4h** (Scheme 41) [123]. Intermediate **4h** reacted with iodine to provide alkyl iodide **4i** in 90% yield. The carbozincation reaction is cleaner and affords the corresponding products in high yields compared with the reported carbomagnesiation reactions [124-129].

Hoveyda reported zirconium-catalyzed alkylmagnesiation reactions of styrene in 2001 by using primary or secondary alkyl tosylates as alkyl sources [130]. The reactions proceeded through zirconacyclopropane **4F** as a key intermediate to provide the corresponding alkylmagnesium compounds **4j**, which could be employed for further reactions with various electrophiles (Scheme 42).



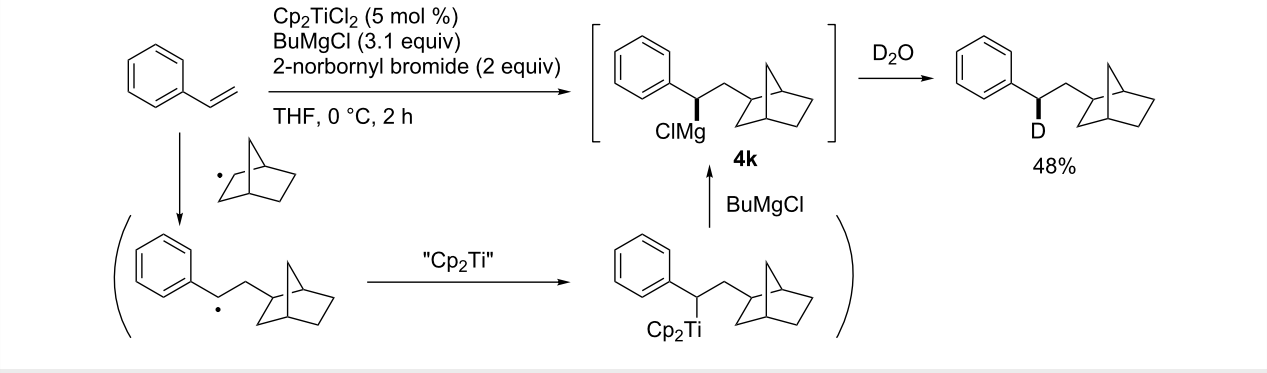
Scheme 41: Zirconium-catalyzed ethylzincation of terminal alkenes.



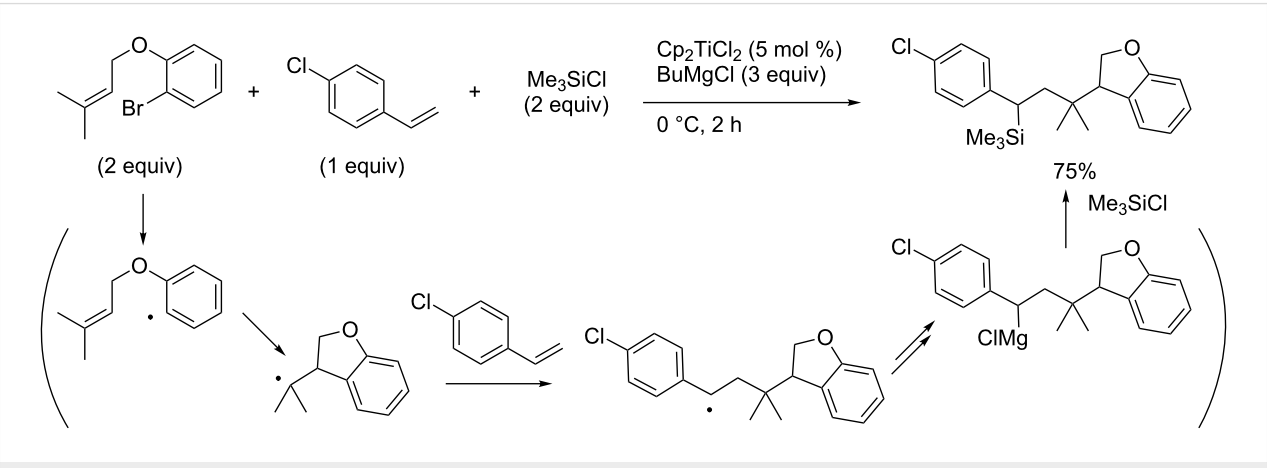
Scheme 42: Zirconium-catalyzed alkylmagnesiation.

In 2004, Kambe reported titanocene-catalyzed carbomagnesiation, which proceeded through radical intermediates not metallacyclopropanes (Scheme 43) [131]. As a result, Hoveyda's zirconium-catalyzed reactions provided homobenzylmagnesium intermediates **4j**, while Kambe's titanium-catalyzed reactions afforded benzylmagnesium intermediates **4k**. Kambe applied the titanocene-catalyzed reaction to a three-component coupling reaction involving a radical cyclization reaction (Scheme 44).

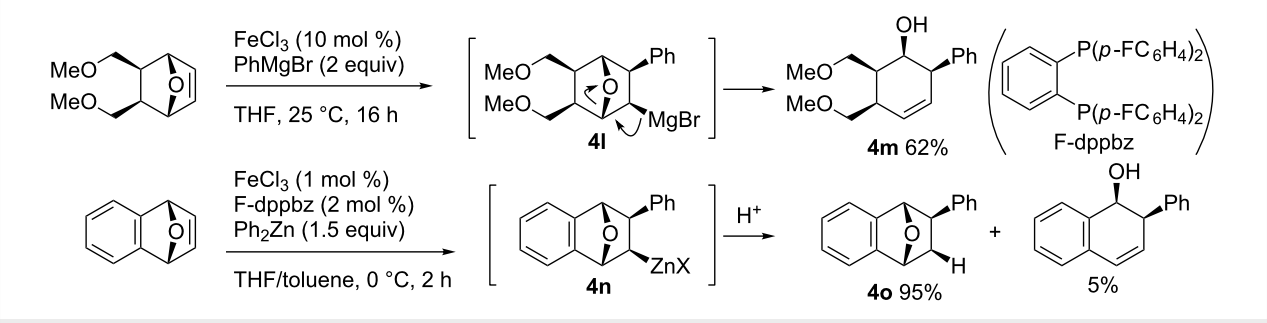
Under Nakamura's iron-catalyzed carbometalation reaction conditions (shown in Scheme 17), the reaction of oxabicyclic alkenes provided ring-opened product **4m** through a carbomagnesiation/elimination pathway (Scheme 45, reaction **4l** to **4m**) [82]. In contrast, the use of the 1,2-bis(diphenylphosphino)benzene (dppbz) ligand efficiently suppressed the elimination pathway to provide the corresponding carbozincation product **4o** in high yield (Scheme 45, reaction **4n** to **4o**) [132].



Scheme 43: Titanium-catalyzed carbomagnesiation.



Scheme 44: Three-component coupling reaction.



Scheme 45: Iron-catalyzed arylzincation reaction of oxabicyclic alkenes.

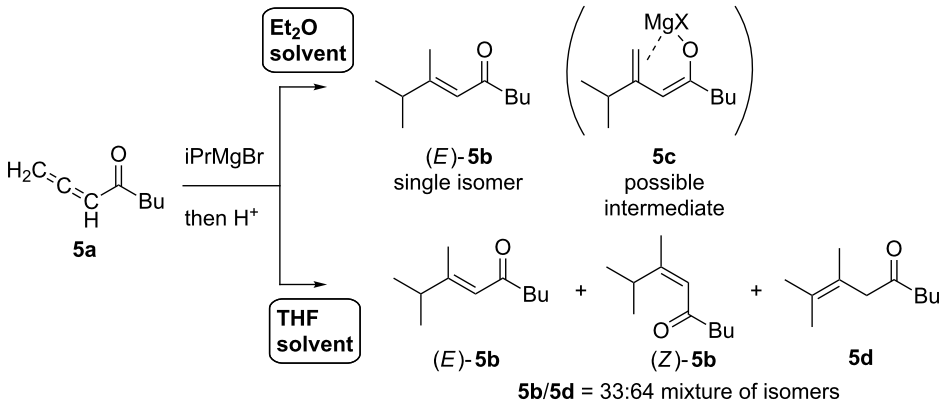
Carbomagnesiation and carbozincation of allenes, dienes, enynes, and diynes

Interesting transformations were accomplished by the carbometalation of allenes, dienes, enynes, and diynes, since the resulting organometallic species inherently have additional saturation for further elaboration.

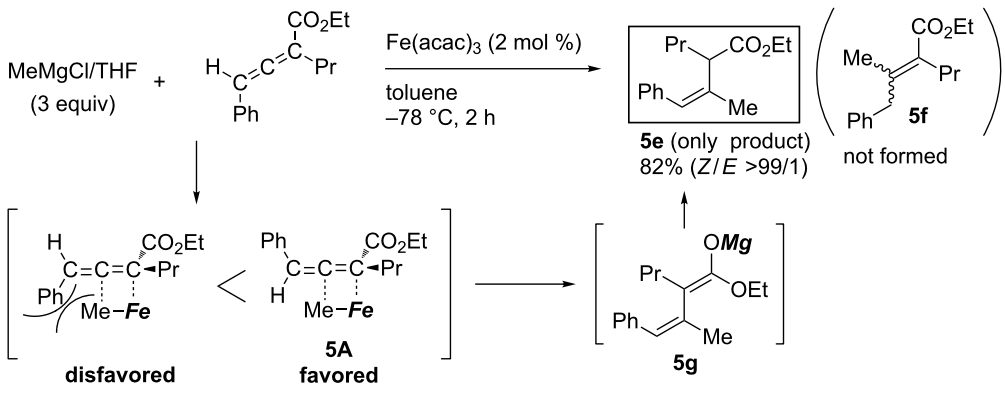
In 2002, Marek reported the reaction of allenyl ketones **5a** with organomagnesium reagents in the absence of a catalyst [133]. The reaction yielded α,β-unsaturated ketone (*E*)-**5b** as a single isomer in ether solution, while a mixture of isomers **5b** and **5d** was obtained in THF solution (Scheme 46). They proposed that the reason for the selectivity would be attributed to intermediate **5c**, which could stably exist in the less coordinative ether solution.

Using an iron catalyst dramatically changed the trend of the addition product. Ma reported that treatment of a 2,3-allenoate with methylmagnesium reagent in the presence of a catalytic amount of iron catalyst exclusively gave the corresponding product **5e** (Scheme 47) [134]. Not only primary alkylmagnesium reagents but also secondary alkyl-, phenyl-, and vinylmagnesium reagents could be employed. Notably, α,β-unsaturated ester **5f** was not formed and the reaction was highly *Z*-selective. Ma explained that transition state **5A** would be favored because of the sterics to form intermediate **5g**. Independently, Kanai and Shibasaki reported copper-catalyzed enantioselective alkylative aldol reactions starting from 1,2-allenoate and dialkylzinc [135], which may proceed through carbometalation intermediates **5B** (Scheme 48).

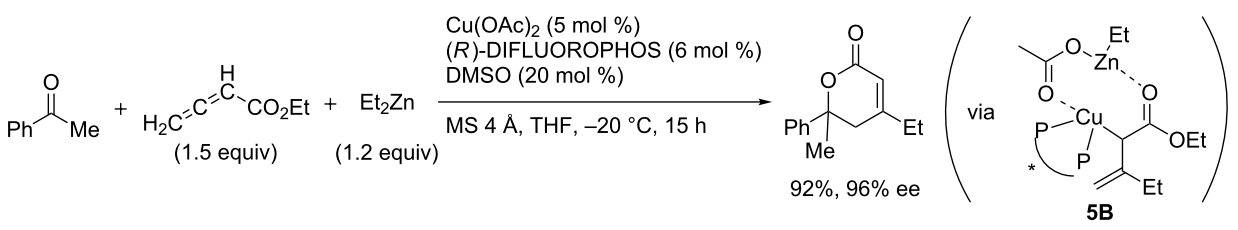
Yorimitsu and Oshima reported a rhodium-catalyzed arylzincation of simple terminal allenes that provided allylic zinc intermediates **5h** (Scheme 49) [136]. The resulting allylic zinc intermediates **5h** reacted with various electrophiles with high regio- and stereoselectivity. Thus, the reactions were applied to the synthesis of stereodefined skipped polyene **5i** via iterative arylzincation/allenylation reactions (Scheme 50).



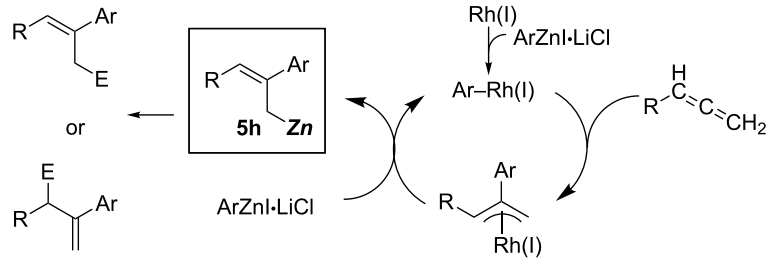
Scheme 46: Reaction of allenyl ketones with organomagnesium reagent.



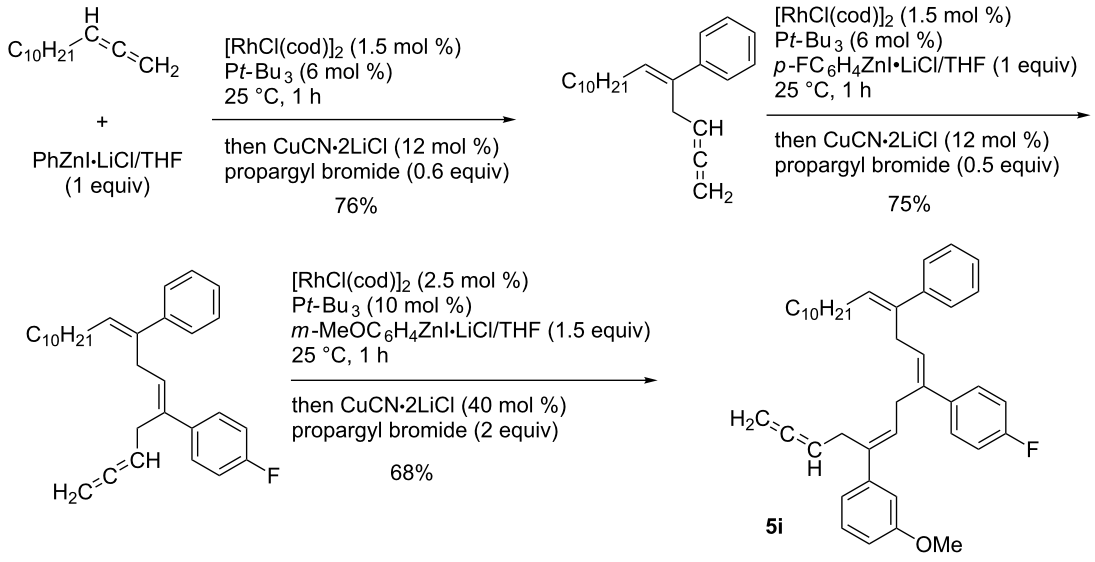
Scheme 47: Regio- and stereoselective reaction of a 2,3-allenoate.



Scheme 48: Three-component coupling reaction of 1,2-allenoate, organozinc reagent, and ketone.



Scheme 49: Proposed mechanism for a rhodium-catalyzed arylzincation of allenes.

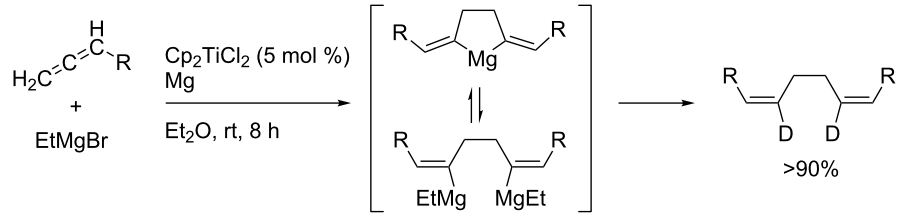


Scheme 50: Synthesis of skipped polyenes by iterative arylzincation/allenylation reaction.

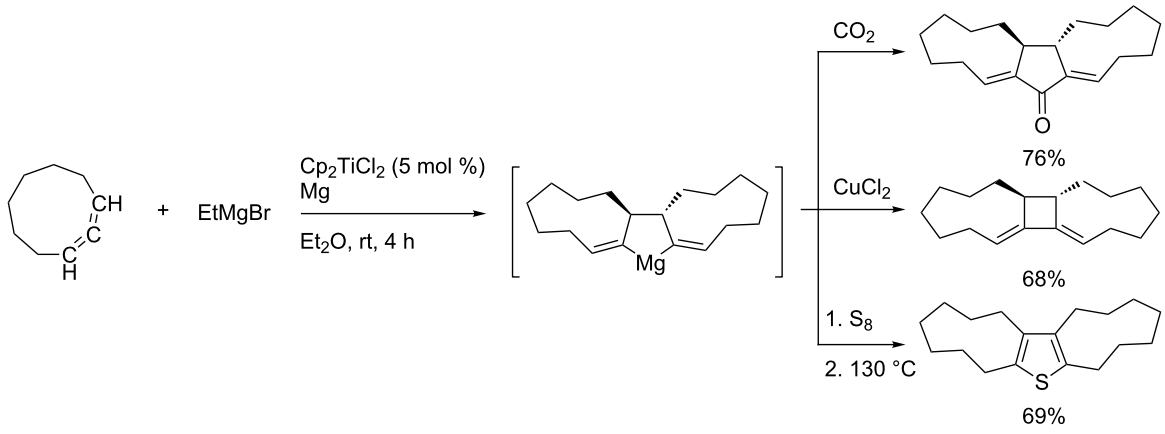
Zirconium-catalyzed dimerization of 1,2-dienes in preparation for the synthesis of useful 1,4-diorganomagnesium compounds from 1,2-dienes (Scheme 51) and its application to the synthesis of tricyclic compounds (Scheme 52) was reported [137-143].

Manganese-catalyzed regioselective allylmetalation of allenes was reported (Scheme 53) [144]. The regioselectivity of the manganese-catalyzed addition reaction was opposite to that of the rhodium-catalyzed reactions, and vinylmagnesium intermediates were formed.

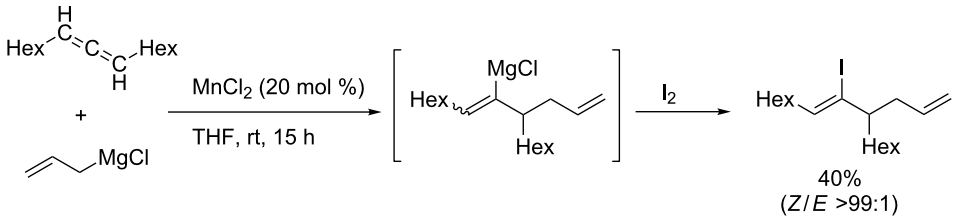
Although titanium-catalyzed allylmagnesiation of isoprene was reported in the 1970s, the scope of the reagents was limited to the allylic magnesium reagents [145,146]. Recently, Terao and Kambe reported copper-catalyzed regioselective carbomagnesiation of dienes and enynes using *sec*- or *tert*-alkylmagnesium reagents (Scheme 54) [147]. They assumed that the active



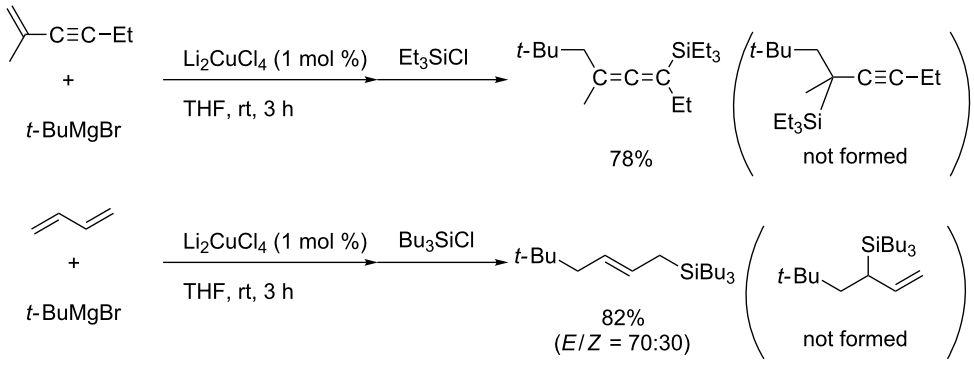
Scheme 51: Synthesis of 1,4-diorganomagnesium compound from 1,2-dienes.



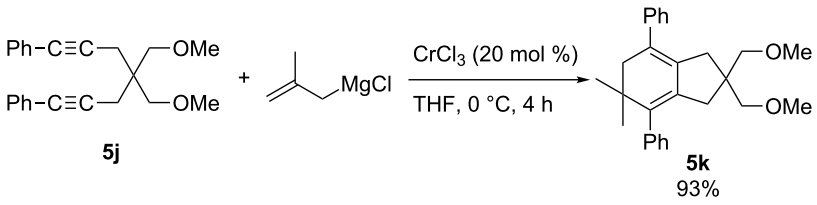
Scheme 52: Synthesis of tricyclic compounds.



Scheme 53: Manganese-catalyzed allylmagnesiation of allenes.



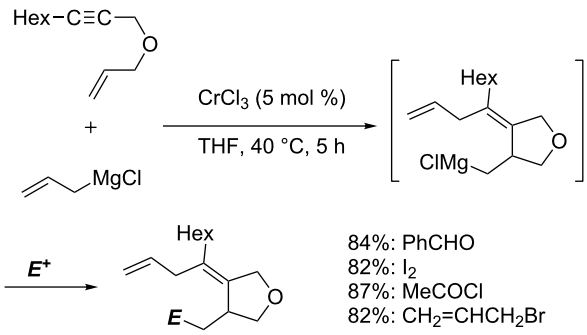
Scheme 54: Copper-catalyzed alkylmagnesiation of 1,3-dienes and 1,3-enynes.



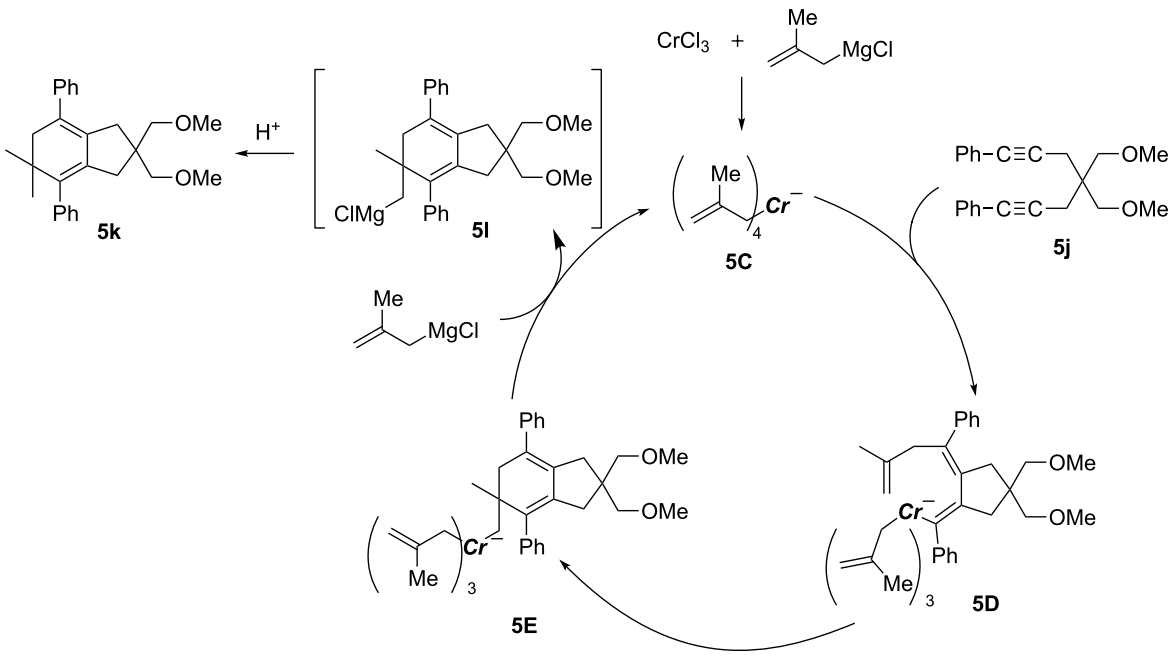
Scheme 55: Chromium-catalyzed methallylmagnesiation of 1,6-diynes.

species were organocuprates and that the radical character of carbocupration enabled bulky *sec*- or *tert*-alkylmagnesium reagents to be employed.

Chromium-catalyzed carbomagnesiation of 1,6-diyne (Scheme 55) [148] and 1,6-enyne (Scheme 56) [149] also provided interesting organomagnesium intermediates through cyclization reactions [150]. Treatment of 1,6-diyne **5j** with methallylmagnesium reagent in the presence of chromium(III) chloride afforded bicyclic product **5k** in excellent yield. In the proposed mechanism, the chromium salt was firstly converted to chromate **5C** by means of 4 equiv of methallylmagnesium reagent (Scheme 57). After the carbometalation followed by cyclization onto another alkyne moiety, vinylic organochromate **5D** would be then formed. Subsequent intramolecular carbochromation would provide **5E**, and finally transmetalation with methallylmagnesium reagent would give **5l** efficiently. The reaction of 1,6-enyne also proceeded through a tetraallylchromate complex as an active species (Scheme 56). However, the second cyclization did not take place.



Scheme 56: Chromium-catalyzed allylmagnesiation of 1,6-enynes.



Scheme 57: Proposed mechanism of the chromium-catalyzed methallylmagnesiation.

Conclusion

We have summarized the progress in transition-metal-catalyzed carbomagnesiation and carbozincation chemistry that has been made in the past 15 years. Despite the significant advances, there remains room for further improvements with regards to the scope of reagents, selectivity of the reaction, and information about the mechanisms, especially for alkenes as substrates. Further studies will surely provide powerful routes for functionalized multisubstituted alkenes and alkanes from simple alkynes and alkenes with high regio-, stereo-, and ultimately enantioselectivity.

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Inter- and intramolecular enantioselective carbolithiation reactions

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Review

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Abstract

In this review we summarize recent developments in inter- and intramolecular enantioselective carbolithiation reactions carried out in the presence of a chiral ligand for lithium, such as (−)-sparteine, to promote facial selection on a C=C bond. This is an attractive approach for the construction of new carbon–carbon bonds in an asymmetric fashion, with the possibility of introducing further functionalization on the molecule by trapping the reactive organolithium intermediates with electrophiles.

Introduction

The carbolithiation reaction has attracted considerable interest among synthetic organic chemists, as it offers an attractive pathway for the efficient construction of new carbon–carbon bonds by addition of an organolithium reagent to nonactivated alkenes or alkynes, with the possibility of introducing further functionalization on the molecule by trapping the reactive organolithium intermediates with electrophiles. Several reviews have covered the synthetic applications of this kind of reaction [1-8].

When alkenes are used, up to two contiguous stereogenic centers may be generated, which may be controlled by using chiral ligands for lithium, thus opening new opportunities for their application in asymmetric synthesis. The naturally occurring alkaloid (−)-sparteine, which has been until recently inexpensive and commercially available, is the most widely used chiral ligand in enantioselective carbolithiation reactions. These reactions can be carried out either in an inter- or intramolecular fashion, though only a few examples have been described, due to the difficulty of enantiofacial differentiation for a nonactivated alkene. The intramolecular version has found application in the synthesis of both carbocycles and heterocycles, with a high degree of regio- and stereoselectivity in the formation of five-membered rings, although its application to larger rings is still not general.

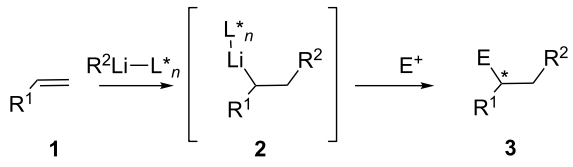
The present review will survey some recent advances in the application of inter- and intramolecular enantioselective carbolithiation reactions. The review will not attempt to provide

exhaustive coverage of the literature, but it is intended to focus on examples in which a stereogenic center is created in the chiral-ligand-mediated carbolithiation reaction of achiral substrates.

Review

Intermolecular carbolithiation reactions

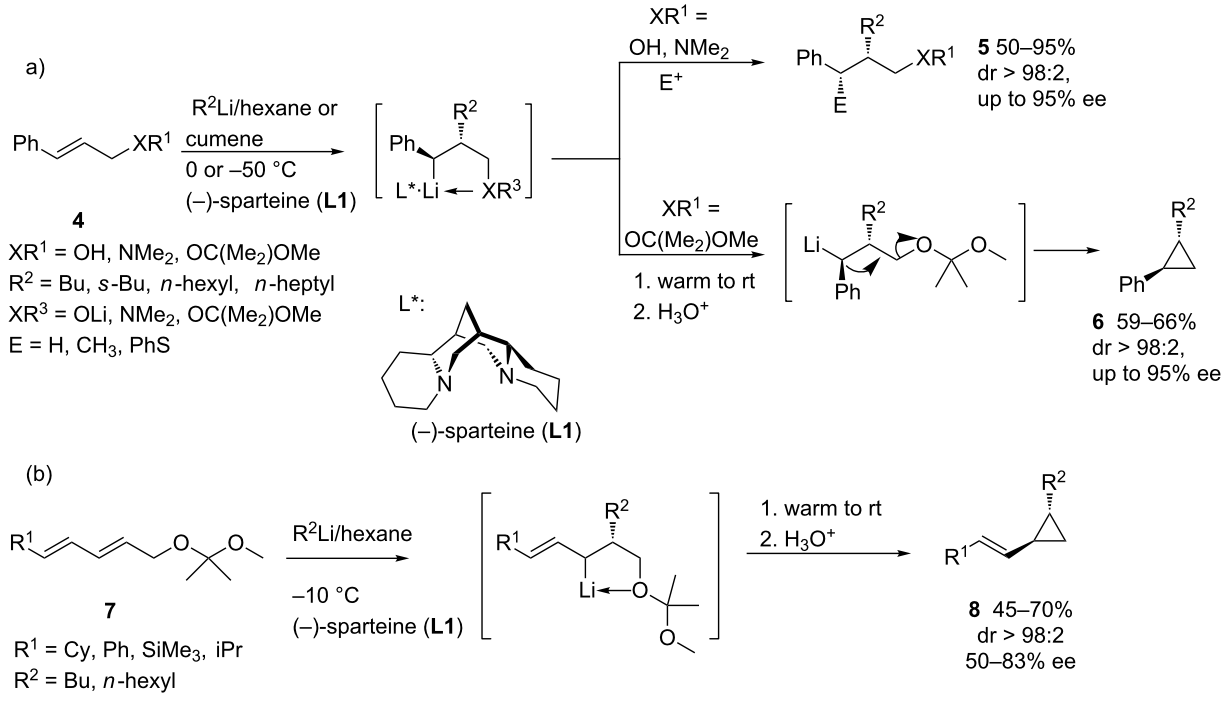
Enantioselective versions of intermolecular carbolithiation reactions can be carried out under the influence of a chiral ligand for lithium (L^*_n) to promote facial selection on a carbon–carbon double bond, though only a few examples have been described, due to the difficulty of enantiofacial differentiation for an nonactivated alkene. Besides, a major concern for the synthetic use of intermolecular carbolithiation reactions is the polymerization of the intermediate organolithium **2**. Thus, successful examples have been developed for substrates with substituents on the alkene that may stabilize the resulting organolithium in different ways, to avoid this polymerization (Scheme 1).



Scheme 1: Intermolecular carbolithiation.

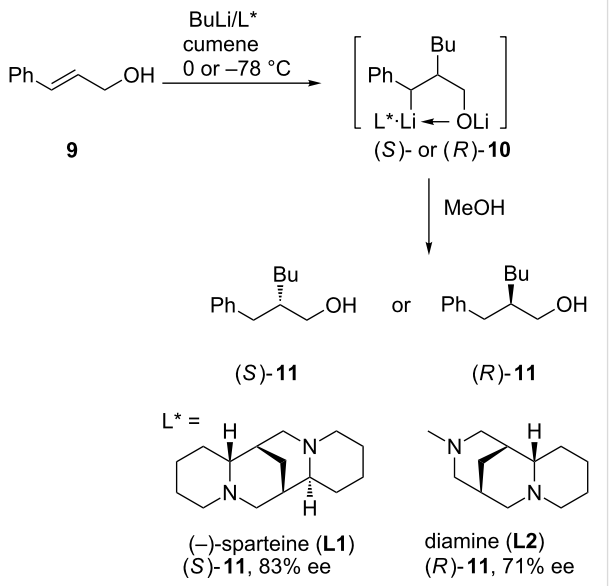
The first examples of intermolecular enantioselective carbolithiations of styrene derivatives were reported by Normant and Marek [9], taking advantage of the complex-induced proximity effect (CIPE). Thus, the addition of primary and secondary alkyllithiums to (*E*)- and (*Z*)-cinnamyl alcohols and amines **4** in the presence of stoichiometric or substoichiometric amounts of (−)-sparteine (**L1**) led to the corresponding alkylated products **5** in high enantiomeric excess (Scheme 2a). The chiral benzylic organolithium intermediates, which are stabilized by coordination with a Lewis-basic substituent, react with different electrophiles in a highly diastereoselective manner. On the other hand, when acetals derived from cinnamyl alcohols are used as substrates, cyclopropanes **6** can be obtained in high enantiomeric excess by warming the reaction mixture to room temperature, since the resulting benzyllithium intermediates undergo 1,3-elimination [10]. In a similar fashion, the asymmetric carbolithiation of dienyl systems **7** can also be carried out with alkyllithiums in the presence of substoichiometric amounts of (−)-sparteine, thus obtaining *trans*-disubstituted vinylcyclopropanes **8** in moderate to good enantiomeric excesses (Scheme 2b) [11].

More recently, enantioselective carbolithiation of cinnamyl alcohol has been reinvestigated by using (+)-sparteine surrogates, such as diamine **L2** [12]. The best results are obtained by the treatment of cinnamyl alcohol (**9**) with the complex of butyllithium/diamine **L2** in cumene at 0 °C, obtaining alcohol



Scheme 2: Carbolithiation of cinnamyl and dienyl derivatives.

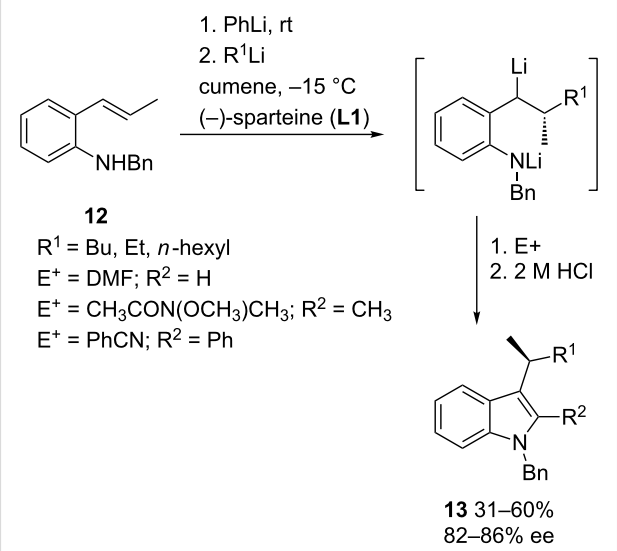
(*R*)-**11** in 71% yield with 71% ee (Scheme 3). This is essentially opposite to the enantioselectivity obtained previously with (−)-sparteine **L1** (82% yield, 83% ee in favor of (*S*)-**11**) [10].



Scheme 3: Carbolithiation of cinnamyl alcohol.

Substituted styrene derivatives also undergo efficient enantioselective carbolithiation in the presence of chiral diamines, when there are electron-donating groups (e.g., methoxy and dialkylamino) at the *ortho*- or *para*-positions of the benzene ring to stabilize the intermediate benzyllithiums, thus deactivating the double bond towards organolithium addition and avoiding polymerization. Thus, the (−)-sparteine-mediated enantioselective intermolecular carbolithiation of (*E*)-*N*-benzyl-2-(prop-1-enyl)aniline (**12**) and subsequent trapping of the intermediate organolithium with a suitable electrophile, followed by an in situ ring closure and dehydration generates the substituted indoles **13** with high enantioselectivities (enantiomeric excess up to 86%) (Scheme 4). Different functional groups can be introduced at the C-2 position of the indoles by varying the electrophile [13,14]. The procedure has also been extended to the synthesis of chiral aromatics and heteroaromatics, such as isoquinolines or benzofurans, though lower yields and ee were obtained [15].

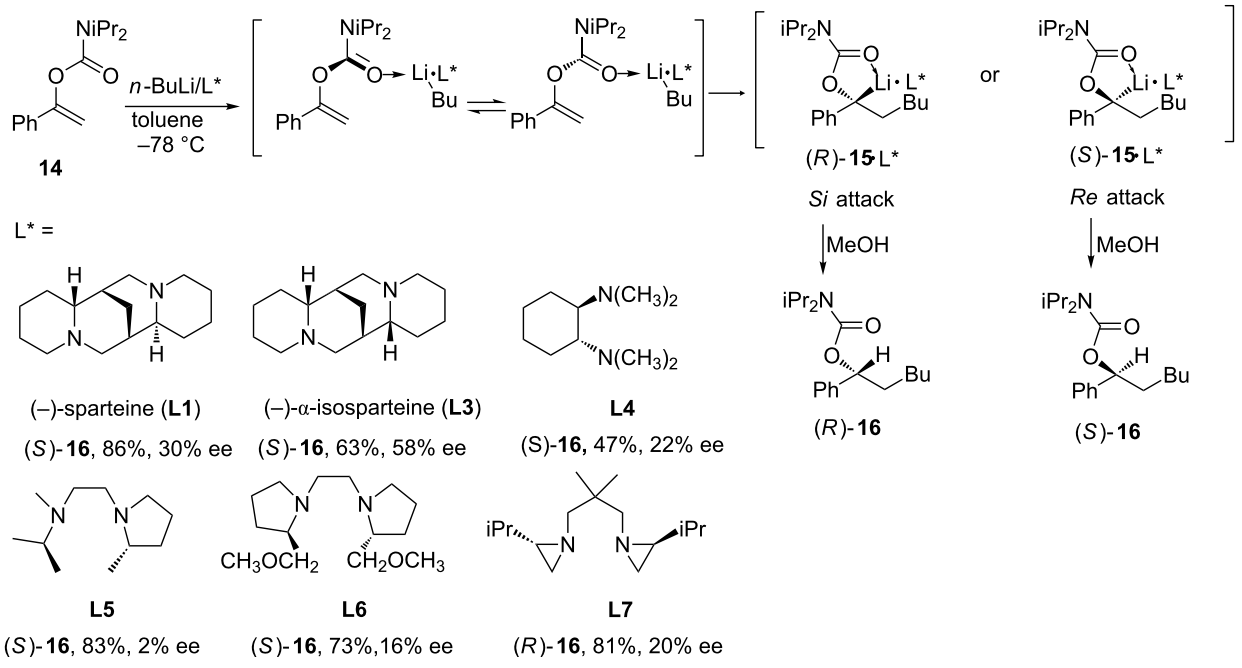
On the other hand, α-aryl *O*-(α-arylalkenyl) carbamates (α-carbamoyloxy-substituted styrenes) such as **14** undergo facile intermolecular carbolithiation reactions, via secondary α-carbamoyloxybenzyllithiums **15**, in the presence of chiral diamines, such as (−)-sparteine (**L1**) or (−)-α-isosparteine (**L3**), but only with moderate enantiofacial differentiation. The best results are obtained with unsubstituted alkenes (vinyl carba-



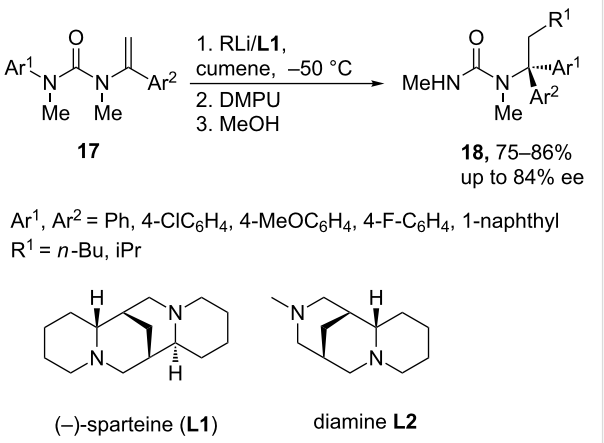
Scheme 4: Carbolithiation of styrene derivatives.

mates) by using butyllithium/(−)-α-isosparteine (up to 58% ee) (Scheme 5) [16]. The enantiofacial differentiation can be explained through the formation of the complexed conformers by the coordination of the organolithium and the chiral ligand, which will react with the double bond in an intramolecular *syn*-addition to form benzyllithium derivatives **15**. These secondary α-carbamoyloxybenzyllithiums are configurationally stable and can be trapped. The authors assume that the problem of these enantioselective carbolithiations is due to the interconversion of the conformers, formed by coordination of *n*-BuLi and the chiral ligand, being too slow, and that the energetic barriers are of the magnitude of the activation energies of the competing diastereomorphic addition steps.

In the presence of (–)-sparteine (**L1**), *N*-alkenyl-*N*-arylureas **17** undergo addition of organolithiums to generate stabilized benzyllithiums, in which a N to C aryl transfer occurs by using DMPU as an additive to accelerate the aryl migration [17], probably by favoring the formation of solvated ion pairs [18]. Thus, this tandem enantioselective carbolithiation–rearrangement of vinylic ureas bearing an *N*-aryl group leads to the formation of two new carbon–carbon bonds with control of the absolute configuration, providing enantiomerically enriched amine derivatives **18** with a quaternary stereogenic center in the alpha position to the nitrogen atom (Scheme 6) [19]. The stereochemical outcome is explained taking into account that both protonation and aryl migration are stereochemically retentive, while carbolithiation is *syn* selective. The reactions begin with an asymmetric carbolithiation, in which the (−)-sparteine-complexed organolithium attacks the *Re* enantiotopic face of the alkene to form a stereodefined organolithium formed under kinetic control. On the other hand, the use of (+)-sparteine



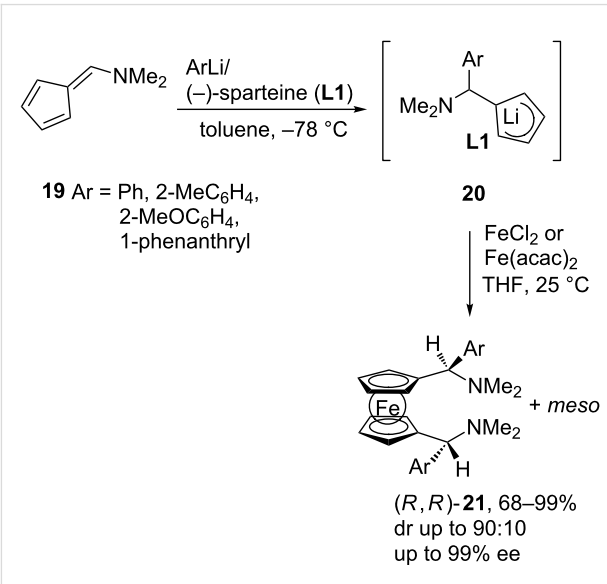
Scheme 5: Carbolithiation of α-aryl *O*-alkenyl carbamates.



Scheme 6: Carbolithiation-rearrangement of *N*-alkenyl-*N*-arylureas.

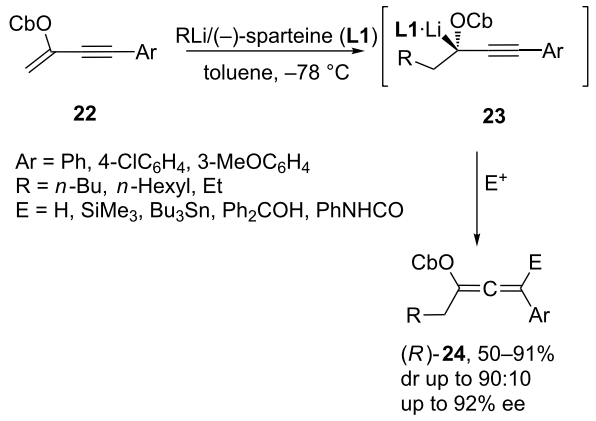
surrogate **L2** as a chiral ligand allows the synthesis of the products with the opposite absolute configuration, even when using THF as solvent [19].

The carbolithiation reaction of 6-(*N*,*N*-dimethylamino)fulvene (**19**) with aryllithiums can be carried out in an enantioselective fashion in the presence of (−)-sparteine (**L1**). Thus, addition of the aryllithiums (generated from the corresponding aryl bromides and lithium metal) to **19** occurs cleanly at −78 °C in toluene, and the resulting chiral cyclopentadienyllithiums **20** are transformed into ferrocenes **21** by treatment with $FeCl_2$ or $Fe(acac)_2$ (Scheme 7). The enantiomeric excess of the ferrocenes is very high, up to 91% ee for those containing one chiral side chain and 99% ee or higher for those containing two chiral side chains, one on each of the cyclopentadienyl ring [20]. The chiral ferrocenes obtained are versatile synthetic intermediates that can be converted into various types of chiral ferrocene derivatives through diastereoselective *ortho*-lithiation [21].



Scheme 7: Carbolithiation of *N*,*N*-dimethylaminofulvene.

Some years ago, the concept of flash chemistry was proposed, involving fast chemical synthesis by using flow microreactors, which enabled the use of highly reactive intermediates before they decompose [22-25]. Thus, Yoshida [26] demonstrated that the addition of aryllithiums, generated by halogen–lithium exchange, to conjugated enynes bearing an appropriate directing group occurs with complete regioselectivity and in good yields. More recently, they applied this concept to avoid the epimerization of reactive intermediates, which has allowed them to carry out the enantioselective version of the above procedure. Thus, the use of a flow microreactor system has allowed the enantioselective carbolithiation of conjugated enynes, followed by the reaction with electrophiles to give enantioenriched chiral allenes. By high-resolution control of the residence time, the epimerization of a configurationally unstable chiral organolithium intermediate **23** could be suppressed. Using this method, *n*-butyllithium reacts with enynes **22** in the presence of chiral ligands, and the resulting organolithiums can be trapped with different electrophiles to afford allenes **24** with complete regioselectivity and good yields. The best ee is obtained when there is a carbamoyloxy group (CbO) as directing group in the substrate with (−)-sparteine (**L1**) as the chiral ligand (Scheme 8) [27].

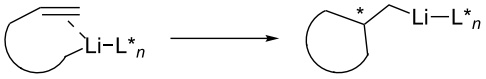


Scheme 8: Carbolithiation of enynes.

Despite the success achieved in the procedures described above, stoichiometric use of chiral ligands is usually required. However, recently a general catalytic methodology for the enantioselective intermolecular addition of alkyllithiums has been reported, though it implies transmetalation to copper complexes. In this case, the use of a copper-base chiral catalytic system allows carbon–carbon bond formation by allylic alkylation with alkyllithiums, with high enantioselectivities and high functional-group tolerance [28,29]. This process may open new interesting applications in organolithium chemistry, though it is beyond the scope of this review.

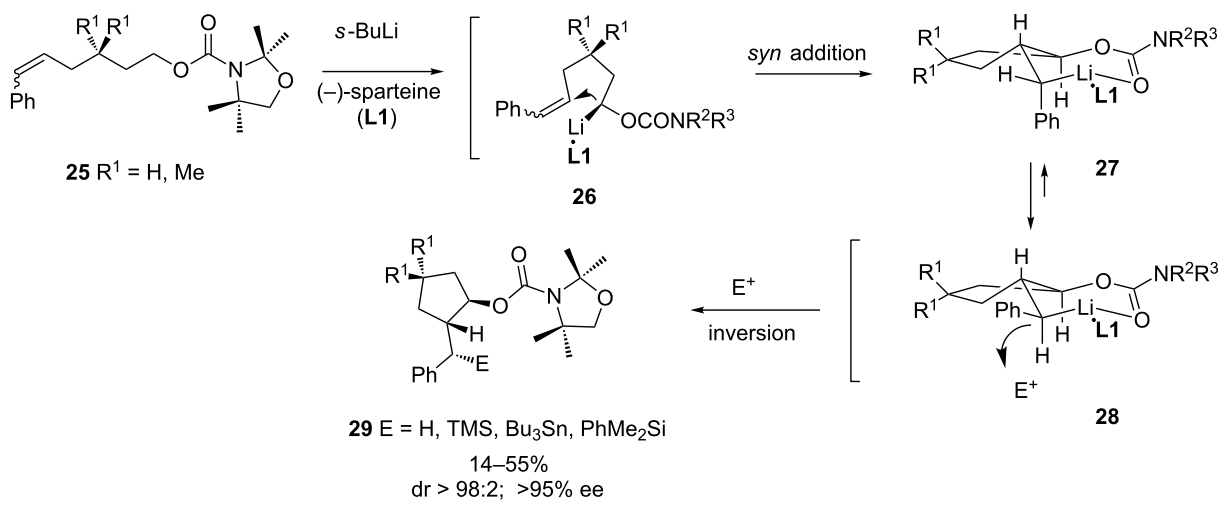
Intramolecular carbolithiation reactions

In the intramolecular carbolithiation of alkenes the highly reactive organolithium species has to be selectively generated in the presence of the internal alkene. Several approaches have been used for this purpose, such as halogen–lithium exchange, tin–lithium exchange, selenium–lithium exchange or reductive lithiation [1-8]. Once the organolithium has been generated, the intramolecular carbolithiation reaction usually takes place with high stereochemical control, as a consequence of a rigid transition state in which the lithium atom is coordinated to the remote π-bond [30-32]. This high stereocontrol has allowed the synthesis of enantiomerically pure carbocycles and heterocycles through diastereoselective cyclization of chiral nonracemic substrates [33-38]. Additionally, the internally coordinated organolithium would have two additional sites available for coordination with a chiral bidentate ligand. Thus, enantioselective versions of intramolecular carbolithiation reactions can also be carried out under the influence of a chiral ligand for lithium (Scheme 9).



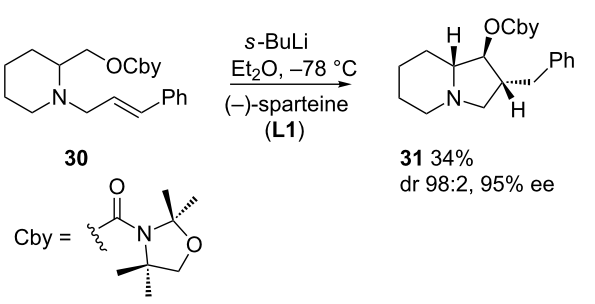
Scheme 9: Intramolecular carbolithiation.

However, the first examples reported of asymmetric intramolecular carbolithiation reactions using alkyllithiums took advantage of the (−)-sparteine-mediated enantioselective deprotonation reaction of carbamates [39]. Thus, achiral (*Z*)- or (*E*)-6-phenyl-hex-5-enylcarbamates **25** can be cyclized with *sec*-butyllithium in the presence of (−)-sparteine (**L1**) at −78 °C giving *trans*-substituted cyclopentanes **29** in high diastereo- and enantioselectivity. The primary benzyllithium intermediates are also diastereoselectively substituted by different electrophiles creating a third consecutive stereogenic center (Scheme 10) [40]. The stereochemical outcome is explained assuming that the (−)-sparteine-mediated enantioselective deprotonation leads to an (*S*)-configurated (α-carbamoyloxy)alkyllithium intermediate **26**. Then, the cycloisomerization occurs through a *syn* addition to the π-bond to give a stabilized benzyllithium **27**, which epimerizes to a more stable benzyllithium **28**, due to the equatorial position of the phenyl substituent, which is subsequently trapped by electrophiles with inversion. This proposal is supported by the fact that both *E*- and *Z*-alkenes led to the same diastereomers. This procedure has been further extended to 4-functionalized 6-phenyl-hex-5-enylcarbamates [41]. Following a similar approach, deprotonation of racemic (carbamoyloxy)methyl-*N*-cinnamylpiperidine **30** with *s*-butyllithium/(−)-sparteine (**L1**), and subsequent anionic 5-*exo*-*trig* cyclization, leads to indolizidine **31** with high diastereomeric



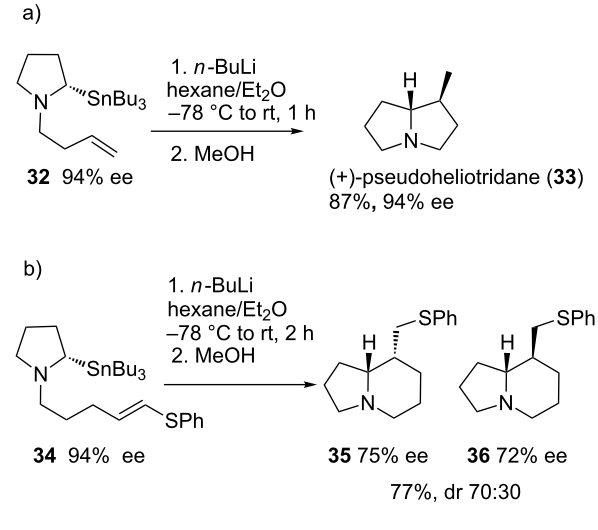
Scheme 10: Carbolithiation of 5-alkenylcarbamates.

and enantiomeric ratios, in moderate yield. (Scheme 11) [42]. The resulting benzyllithium can also be trapped with electrophiles, though the stereoselectivity in this fourth center is not so high, and depends largely on the electrophile.



Scheme 11: Carbolithiation of cinnamylpiperidines.

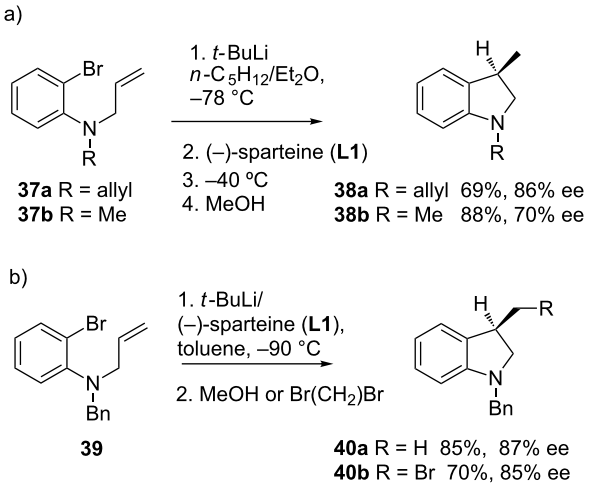
However, in these examples, the chiral ligand induces the enantioselective deprotonation to generate a nonracemic organolithium, which adds diastereoselectively to the carbon–carbon double bond. In this context, configurationally stable secondary α-amino alkyllithiums have also been obtained by tin–lithium exchange (Scheme 12). Addition to the double bond with complete retention of configuration affords a new organolithium, which can be reacted with electrophiles to afford pyrrolizidines with no loss of optical purity. Scheme 12a shows the application to the synthesis of the pyrrolizidine alkaloid (+)-pseudoheliotridane (**33**) [43]. The reaction can be extended to the formation of six-membered rings, though the slow cyclization rate results in racemization. The use of a phenylthio-substituted alkene favors the cyclization, and the faster reaction rate results in an improved optical purity of the indolizidines **35** and **36**, though with moderate diastereo- and enantioselectivity. The addition of TMEDA increases the rate of racemization, resulting in an inversion of diastereoselectivity to obtain **36**, albeit in racemic form [44].



Scheme 12: Carbolithiation of alkenylpyrrolidines.

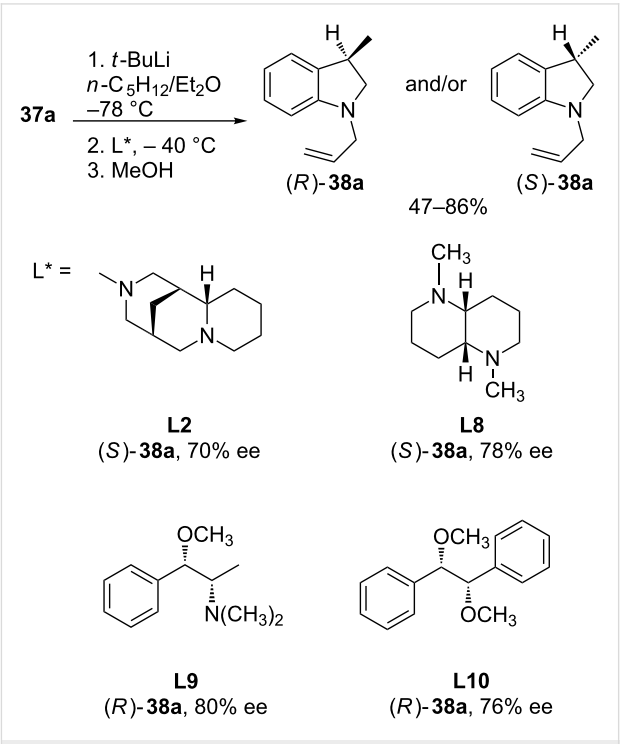
The enantioselective cycloisomerization of achiral organolithiums in the presence of a chiral ligand has been reported with aryllithium reagents, which can be efficiently prepared by halogen–lithium exchange. Hence, the enantioselective intramolecular carbolithiation of *N*-allyl-2-bromoanilines by using *tert*-butyllithium in the presence of (−)-sparteine (**L1**) for the synthesis of 3-substituted indolines, was reported simultaneously by Bailey [45] and Groth [46]. Thus, (*R*)-(−)-1-allyl-3-methylindoline (**38a**) was obtained in high yield and ee by reaction of *N*,*N*-diallyl-2-bromoaniline (**37a**) with *t*-BuLi in

n-pentane/diethyl ether in the presence of (−)-sparteine (**L1**) (Scheme 13a). The choice of solvent has an important effect on the enantioselectivity, favoring the coordination of the ligand with lithium. While solvent systems composed of hydrocarbon/diethyl ether are effective, the use of THF resulted in almost complete loss of enantioselectivity. The cyclization of amine **37b** under identical conditions was less enantioselective than the analogous diallyl substrate **37a** (70% versus 86%) [45]. On the other hand, *N*-allyl-*N*-benzyl-2-bromoaniline (**39**) also undergoes enantioselective intramolecular carbolithiation with *t*-BuLi/(−)-sparteine (**L1**) in toluene as solvent (Scheme 13b) [46].



Scheme 13: Enantioselective carbolithiation of *N*-allyl-2-bromoanilines.

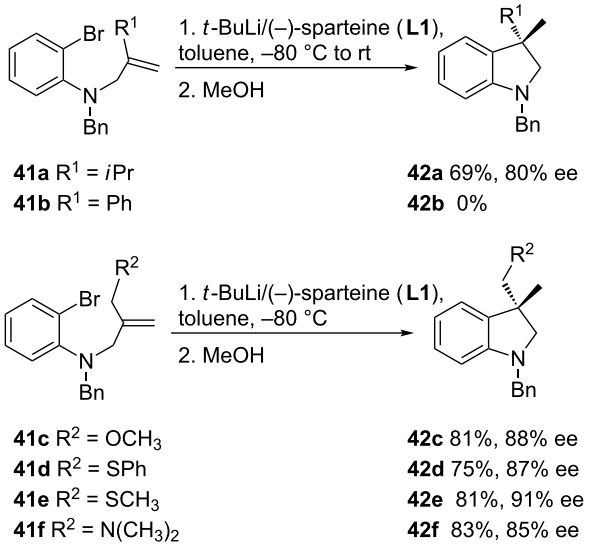
The ability of a large and chemically diverse set of thirty chiral ligands to effect the asymmetric intramolecular carbolithiation of *N*,*N*-diallyl-2-bromoaniline (**37a**) has been investigated in an attempt to elucidate the structural motifs required to provide high enantiofacial selectivity in the ring closure [47]. Although none of the ligands examined affords 1-allyl-3-methylindoline (**38a**) in significantly higher enantiomeric excess than previously observed with (−)-sparteine (**L1**), several ligands available in either enantiomeric form match its utility in this chemistry (Scheme 14). Among ethers and aminoethers, ligands (1*S*,2*S*)-*N*,*O*-dimethylpseudoephedrine (**L9**) and (1*S*,2*S*)-1,2-dimethoxy-1,2-diphenylethane (**L10**) are particularly effective surrogates for sparteine, affording 3-methylindoline (*R*)-**38a** in good yield and high enantiomeric excess (Scheme 14). With regard to chiral diamine ligands, enantiomeric excess is only maintained by using *cis*-1,5-diazadecalin **L8**, leading to the indoline of opposite configuration. Unfortunately, this diamine is not commercially available, and its synthesis requires resolution. More recently, O'Brien [48] has reported that (+)-sparteine surrogate **L2** gave a similar degree of enantioselectivity and indoline (*S*)-**38a** of 85:15 er (84% yield) was produced (Scheme 14).



Scheme 14: Effect of the ligand in the carbolithiation reaction.

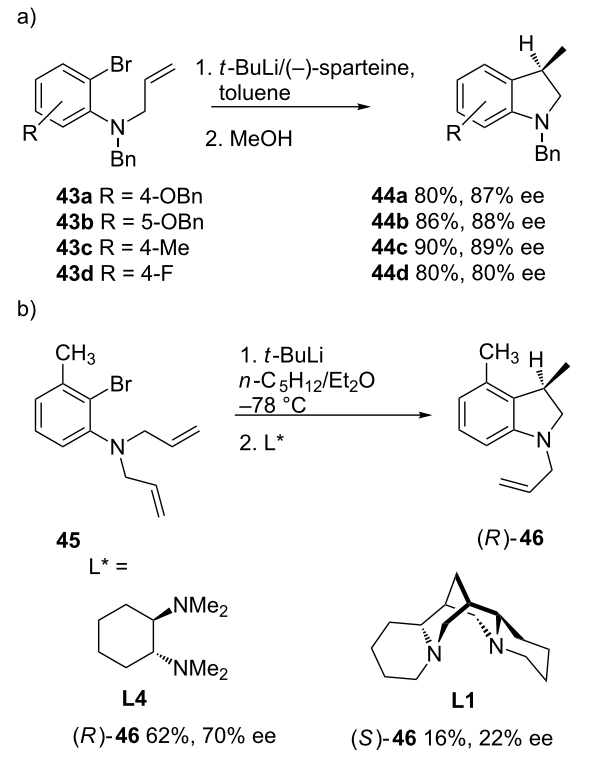
Substituted alkenes may also be used in these reactions, and 3,3-disubstituted indolines **42** are obtained in moderate to high enantiomeric excesses, depending on the nature of the substituent on the alkene (Scheme 15) [49]. The steric demand of an isopropyl group increases the enantioselectivity in the cyclization of **42a** (Scheme 15), though the reaction fails with a phenyl substituent (**42b**). A chelating donor substituent in the allylic moiety may assist the carbolithiation reaction. The best results regarding both chemical yields and enantioselectivity are obtained when R^1 = OMe, SPh, SMe, and NMe_2, at −80 °C in toluene as solvent.

The influence of the substitution pattern in the aromatic ring on both the yield and the enantioselectivity is not clearly established. The introduction of electron-deficient substituents may require higher temperatures for the reaction to proceed to completion but maintain good enantioselection (Scheme 16a) [46]. On the other hand, a seemingly minor variation in substrate structure may have a pronounced effect on the ability of a given ligand to facilitate cyclization. Thus, the presence of a substituent in the position *ortho* to the lithium atom leads to lower yields and the opposite enantiomer (*S*)-3-methylindoline (*S*)-**46** with low enantiomeric excess (22% ee) when (−)-



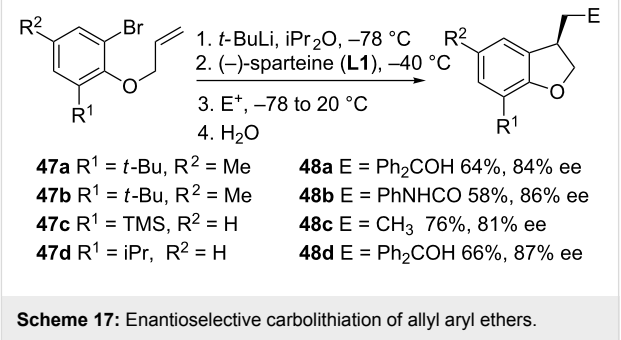
Scheme 15: Effect of the alkene substitution in the carbolithiation reaction.

sparteine (**L1**) is used (Scheme 16b). However, in this case, the (1*R*,2*R*)-*N*,*N*,*N*',*N*'-tetramethylcyclohexane-1,2-diamine (**L4**) proves to be a more efficient ligand for lithium, leading to (*R*)-3-methylindoline (*R*)-**46** in 70% ee [47].



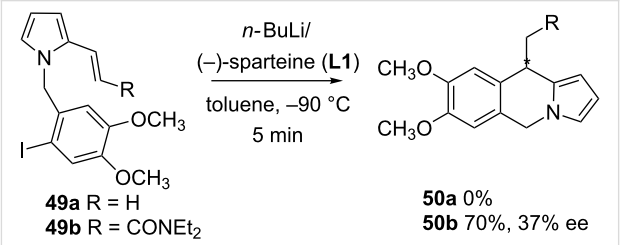
Scheme 16: Effect of the ring substitution in the carbolithiation reaction.

This type of intramolecular carbolithiation is also useful for the synthesis of fused furan systems. Thus, enantiomerically enriched 2,3-dihydrobenzofurans **48** are obtained in moderate to good yields and high enantiomeric purity by using (−)-sparteine (**L1**) as chiral ligand, and diisopropyl ether as solvent (Scheme 17). The resulting organolithium can be trapped with several external electrophiles [50]. The presence of a substituent at the 6-position of the aromatic ring ($R^1 \neq H$) is necessary to obtain the benzofurans **48**. Otherwise, the aryllithium intermediate undergoes a tandem carbolithiation–γ-elimination leading to enantioenriched 2-cyclopropylphenols [51].



Scheme 17: Enantioselective carbolithiation of allyl aryl ethers.

As shown, these enantioselective intramolecular cyclizations are mostly employed for the formation of five-membered rings. The 6-*exo* cyclization of an aryllithium intermediate is also possible, but generally the alkene has to be substituted with a stabilizing group for the resulting organolithium to favor the cyclization, as has been shown before for alkyllithium derivatives (Scheme 12b) [44]. This type of reaction has been used, for instance, for the diastereoselective synthesis of enantiomerically pure isoquinoline rings [34,37], but just a few examples of the enantioselective variant have been reported so far. Thus, as shown on Scheme 18, the cyclization of the aryllithium generated from **49a** does not occur on the unsubstituted alkene, whereas the introduction of an amide group favors a fast cyclization at low temperature, and pyrroloisoquinoline **50b** is isolated in good yield. However, this higher reactivity results in a low enantioselection when (−)-sparteine (**L1**) is used as chiral ligand, under various reaction conditions [34].



Scheme 18: Formation of six-membered rings: pyrroloisoquinolines.

Similarly, the intramolecular carbolithiation of *N*-alkenyl substituted *o*-iodoanilines **51** affords enantiomerically enriched 2,4-disubstituted tetrahydroquinolines **52** and **53** by using (−)-sparteine (**L1**) as chiral ligand [52]. An amide group is also required to favor the cyclization, and also has an important effect in both the diastereoselectivity and the enantioselectivity. As shown on Scheme 19, the best results in terms of enantioselectivity were obtained by using Weinreb amide **51c**, though with moderate diastereoselectivity.

Conclusion

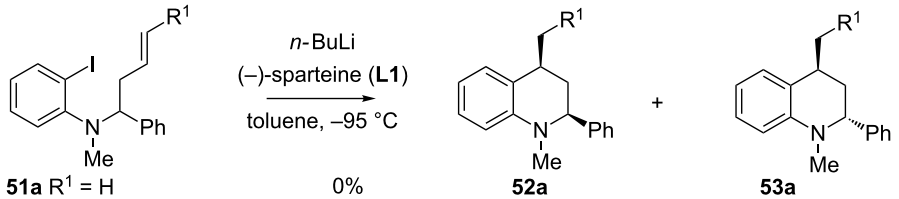
As has been shown through these examples, the enantioselective carbolithiation reaction is an attractive approach for the construction of carbon–carbon bonds. However, the applicability of this method is not yet general. Among the different types of ligands used, chiral bidentate diamines, and especially (−)-sparteine, are the most generally employed. However, the structural requirements of the chiral ligand required to provide high enantiofacial selectivity for a broader range of substrates are still unclear. The intermolecular reactions usually take advantage of chelation and stabilizing effects on the resulting organolithium to obtain high enantioselectivity and avoid polymerization. Enantiomerically enriched five-membered rings can be prepared through intramolecular carbolithiation reactions of unsaturated aryllithiums in the presence of chiral ligands. The application to the formation of six-membered or larger cycles with the same degree of stereo- and regiochemical efficiency has not been fully developed. On the other hand, the high reactivity of the organolithiums requires the use of stoichiometric amounts of the chiral ligand.

Acknowledgements

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51a R^1 = H	0%	**52a**	**53a**
51b R^1 = $CONEt_2$	63%, dr 27:73	**52b** 17% ee	**53b** 33% ee
51c R^1 = CONMeOMe	48%, dr 33:67	**52c** 92% ee	**53c** 94% ee

Scheme 19: Formation of six-membered rings: tetrahydroquinolines.

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Regio- and stereoselective carbometallation reactions of *N*-alkynylamides and sulfonamides

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Full Research Paper

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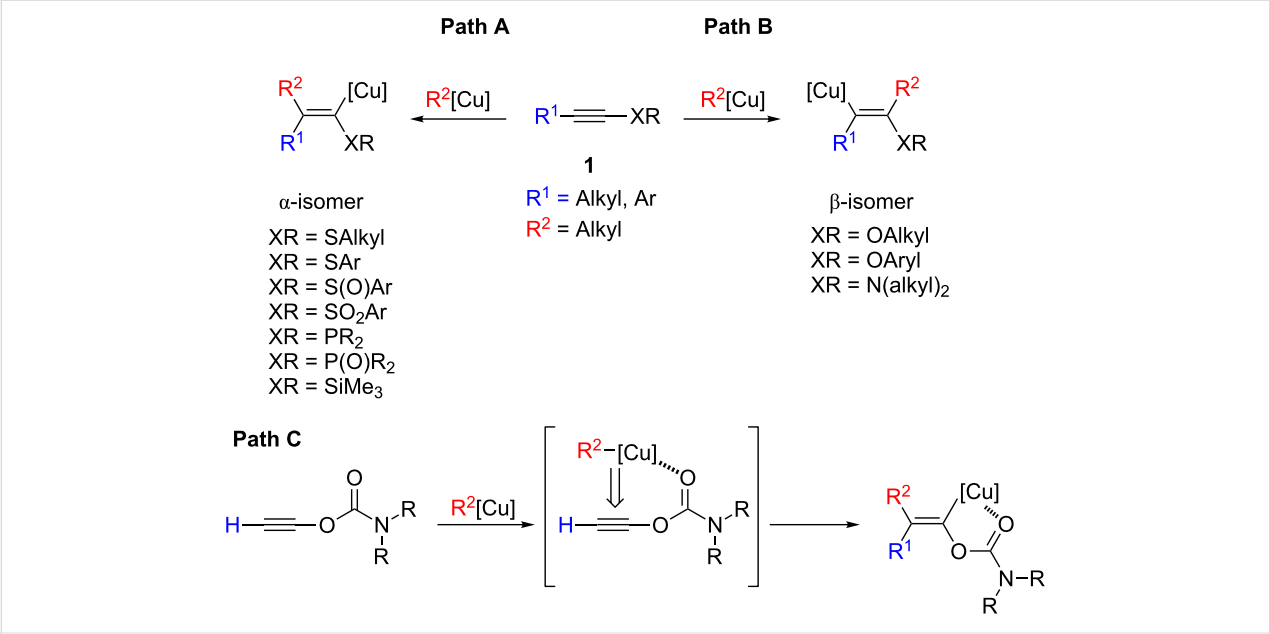
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Abstract

The carbocupration reactions of heterosubstituted alkynes allow the regio- and stereoselective formation of vinyl organometallic species. *N*-Alkynylamides (ynamides) are particularly useful substrates for the highly regioselective carbocupration reaction, as they lead to the stereodefined formation of vinylcopper species geminated to the amide moiety. The latter species are involved in numerous synthetically useful transformations leading to valuable building blocks in organic synthesis. Here we describe in full the results of our studies related to the carbometallation reactions of *N*-alkynylamides.

Introduction

Due to a strong differentiation of electron density on the two sp-hybridized carbon atoms, *N*-alkynylamides (ynamides) have become attractive substrates involved in many synthetically useful transformations [1-4]. The remarkable renaissance of *N*-substituted alkynes in synthesis is primarily due to the combination of the easy and straightforward access to these compounds with their notable stability [5-7]. A rather large variety of synthetic approaches have been therefore developed in the last decade that allow ynamides to be of easy access to the whole synthetic community [8-14]. Similarly, enamides are another important class of substrates involved in numerous applications in organic synthesis [5,15]. As one of the most straightforward and well-developed methods to generate polysubstituted alkenes is the carbometallation reaction of alkynes [16-18], ynamide should be a suitable substrate for the regio- and stereoselective synthesis of enamide through carbometallation reaction [19-22]. Although the stereoselectivity of the carbocupration is usually controlled through a *syn*-addition of the organocopper reagent on the triple bond [23], the regioselectivity is dependent on the nature of the α-substituent on the alkyne **1**. The presence of a donor substituent (XR = OR, NR_2, **Path B**, Scheme 1) leads generally to the β-isomer in which the copper atom adds to the carbon β of the heteroatom [16,17], whereas an acceptor substituent (XR = SR, SOR, SO_2R, $SiMe_3$, PR_2, $P(O)R_2$, **Path A**, Scheme 1) would preferably give the α-isomer [16,17] (copper geminated to the heteroatom,



Scheme 1: Possible regioisomers obtained in the carbocupration reaction of α-heterosubstituted acetylenes **1**.

Scheme 1). Although *N*-substituted alkynes are known to give the β-isomer, we thought that a precomplexation of the organometallic species (i.e., copper) with a polar functional group in the vicinity of the reactive center should be able to reverse the regioselectivity of the carbometallation, as we have shown for the carbocupration of ethynyl carbamate (XR = $OCONR_2$, **Path C**, Scheme 1) [24].

Herein we describe our results for the regio- and stereoselective carbometallation reaction of *N*-alkynylsulfonyl amides and various *N*-alkynylcarbamates [25].

Results and Discussion

Carbocupration of sulfonyl-substituted ynamides

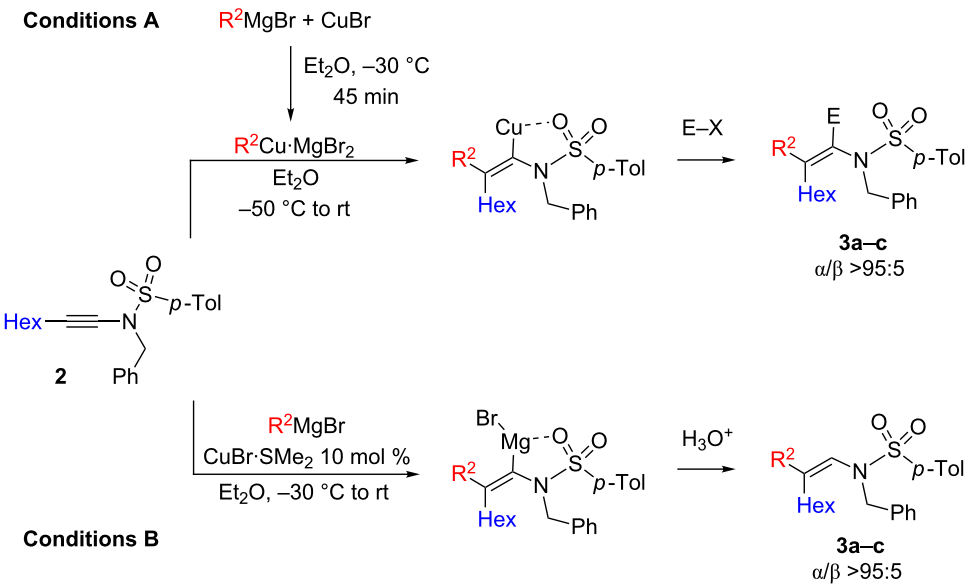
Our initial experiments were directed towards the carbometallation reaction of *N*-alkynylsulfonylamides, as the coordination of the organometallic species by the sulfonyl group should control the regioselectivity of the carbometallation reaction in favor of the α-isomer. When **2** was added to an organocopper (easily prepared by the addition of one equivalent of R^2MgBr to one equivalent of CuBr in Et_2O at −50 °C), the carbometalated products **3** were obtained in good isolated yields after hydrolysis (Scheme 2, conditions A and Table 1, entries 1–3). Some of these results were published as a preliminary note in [25].

The reaction proceeds smoothly for classical primary alkylcopper species (Table 1, entry 1), but for groups that are known to be sluggish in carbocupration reaction, such as the introduction of a Me group (Table 1, entry 2), yield is significantly lower. The presence of the vinylcopper was proved by the reaction with allyl bromide as a classical electrophile used in organocopper chemistry to give **3c** (Table 1, entry 3). Although *N*-heterosubstituted alkynes were used in all cases, the α-isomer is regioselectively obtained, as confirmed by ^1H NMR analysis of the crude reaction mixture after hydrolysis, through an intramolecular chelation between the *N*-sulfonamide moiety and the organocopper species. To improve the chemical yield of this transformation, we considered the copper-catalyzed carbomagnesiation reaction. However, such catalytic reaction requires a transmetallation reaction of the intermediate vinylcopper into vinylmagnesium halide, and due to the intramolecular chelation, it is usually performed at higher temperature. Thus, a thermally more stable organocopper species [formed from copper(I) bromide–dimethylsulfide complex ($CuBr{\cdot}Me_2S$)], was used for this copper-catalyzed carbomagnesiation reaction. We were pleased to see that the reaction is very efficient for the addition of

Table 1: Carbometallation reactions of the *N*-alkynylsulfonamide **2**.

Entry	Conditions[a]	R^2	E–X	Product	Yield (%)[b]
1	A	*n*-Bu	H_3O^+	**3a**	93
2	A	Me	H_3O^+	**3b**	30
3	A	*n*-Bu	AllylBr	**3c**	50
4	B	*n*-Bu	H_3O^+	**3a**	90
5	B	Me	H_3O^+	**3b**	70

[a]Conditions A: 2.0 equiv of R^2Cu (prepared from an equimolar amount of R^2MgBr and CuBr at −50 °C to rt in Et_2O. Conditions B: 2.0 equiv of R^2MgBr with 10 mol % of $CuBr{\cdot}Me_2S$ in Et_2O from −30 °C to rt. [b]Yields of isolated product after flash column chromatography (based on **2**).

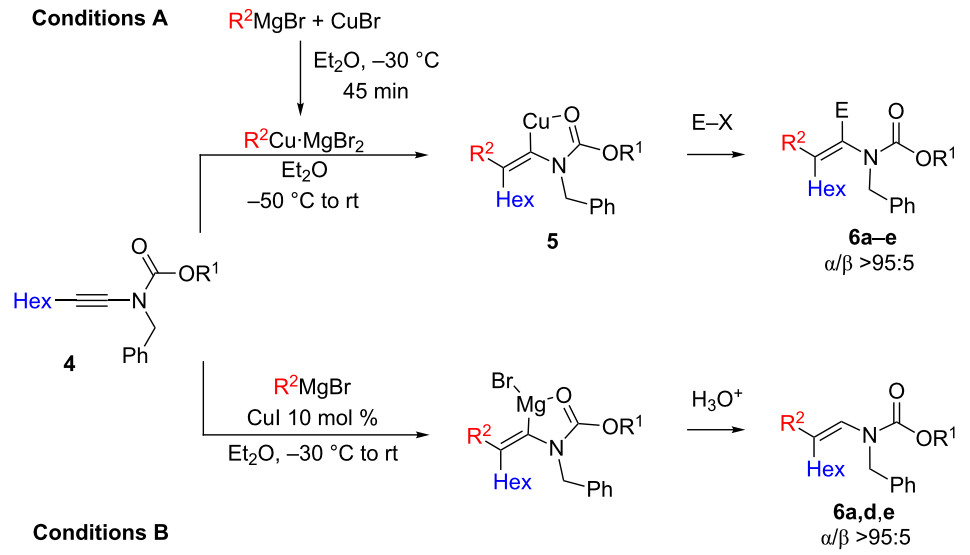


Scheme 2: Regioselective carbometallation of *N*-alkynylsulfonamide **2**.

BuMgBr, as **3a** was obtained in 90% yield as a unique α-isomer. More importantly, the copper-catalyzed methylmagnesiation now proceeded in good yield to lead to the carbometalated product **3b** in 70% yield after hydrolysis (Table 1, entry 5) [25,26].

Carbocupration reaction of acyclic *N*-alkynylcarbamates

As the carbocupration of an *N*-alkynylsulfonamide could be easily achieved, we were interested to see whether such a carbocupration reaction could be extended to ynamide **4** bearing an acyclic carbamate moiety. We were pleased to find that this reaction could also be performed on *N*-alkynylcarbamate **4** with primary and secondary alkylcopper species (still obtained in diethyl ether from 1.0 equiv of a Grignard reagent and 1.0 equiv of CuBr, conditions A) to give the corresponding vinylcopper intermediate **5**. Simple hydrolysis led to the enamide **6a**,**c** in good isolated yields after purification by column chromatography (Scheme 3 and Table 2, entries 1 and 3). The vinylcopper species could also be successfully trapped at low temperature with allylbromide to give the functionalized adduct **6b** (Scheme 3, Table 2, entry 2) [25]. The addition of the Me and Ph groups proceeds more easily on the *N*-alkynylamide **4** than *N*-alkynylsulfonamide **2** as yields could reach 68 and 84%, res-



Scheme 3: Regioselective carbometallation of ynamide **4**.

Table 2: Carbometallation reactions of alkynylcarbamates **4**.

Entry	Conditions[a]	R^1	R^2	E–X	Product	Yield (%)[b]
1	A	Et	*n*-Bu	H_3O^+	**6a**	72
2	A	Me	*n*-Bu	Allyl–Br	**6b**	55
3	A	Me	*c*-C_6H_{11}	H_3O^+	**6c**	50
4	A[c]	Et	Me	H_3O^+	**6d**	68
5	A[c]	Et	Ph	H_3O^+	**6e**	84
6	A[c]	Et	*n*-Bu	H_3O^+	**6a**	94
7	B	Et	*n*-Bu	H_3O^+	**6a**	81
8	B	Me	Me	H_3O^+	**6d**	60
9	B	Et	Ph	H_3O^+	**6e**	90
10	B	Me	*c*-C_6H_{11}	H_3O^+	**6c**	81

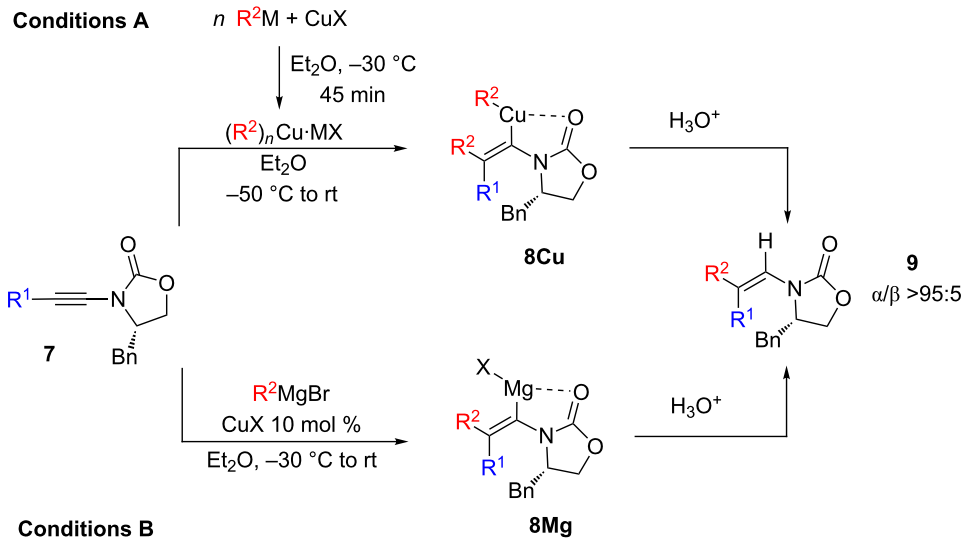
[a]Conditions A: 2.0 equiv of R^2Cu (prepared from equimolar amount of R^2MgBr and CuBr at −50 °C to rt in Et_2O. Conditions B: 2.0 equiv R^2MgBr with 10 mol % of CuI in Et_2O from −30 °C to rt. [b]Yields of isolated product after flash column chromatography (based on **4**). [c]CuBr·Me_2S complex was used as a copper source.

pectively (Table 2, entries 8 and 9). Yield could be further improved when CuBr·Me_2S was used as the copper source (Table 2, compare entries 1 and 6) [25]. In all cases, the expected α-isomer of **6** was exclusively formed and the regiochemistry was determined by NOE (nuclear Overhauser effect) between the methyl substituent and the corresponding vinylic proton (E = H, Table 2, entry 4). However, such selectivity can only be achieved in nonpolar solvent, such as Et_2O, since the same reaction performed in THF leads mainly to the formation of the β-isomer in a α/β ratio of 18:82.

When *N*-alkynylamide **4** was treated under our copper-catalyzed carbomagnesiation conditions (conditions B), enamides **6** were similarly obtained as a pure α-isomer. Although this transformation requires higher temperature, yields are usually better than in reactions with the preformed organocopper species (Table 2, entries 7–10) [25].

Carbocupration of cyclic *N*-alkynylcarbamate (chiral oxazolidinone moiety)

Recently, our group was particularly interested in the carbometallation reaction of ynamides bearing chiral cyclic carbamates **7**, particularly the Evans's oxazolidinone [27], as vinylmetal species could subsequently react with a large variety of electrophiles leading to diastereomerically enriched functionalized adducts [28-30]. Thus, the carbometallation reaction of *N*-alkynylamide **7** was performed with several organometallic species as described in Scheme 4 and Table 3.



Scheme 4: Regioselective carbometallation of cyclic *N*-alkynylcarbamate **7**.

Table 3: Carbometallation reactions of cyclic *N*-alkynylcarbamates **7** (Scheme 4).

Entry	Conditions[a]	R^1	R^2	M	CuX	α/β	Product	Yield (%)[b]
1	A	Hex (**7a**)	Me	MgBr	CuI	>95:5	**9a**	75
2	B	Bu (**7b**)	Me	Li	CuI	>95:5	**9b**	59
3	B	Bu (**7b**)	Me	Li	CuBr	>95:5	**9b**	69
4	B	Bu (**7b**)	Me	Li	CuCN	90:10	**9b**	80
5	B	Bu (**7b**)	Me	Li	CuBr·Me_2S	>95:5	**9b**	80
6	C	Bu (**7b**)	Me	MgBr	CuI	>95:5	**9b**	86
7	B	$(iPr)_3SiO(CH_2)_2$ (**7c**)	Me	Li	CuBr·Me_2S	>95:5	**9c**	51
8	B	$Ad^1CO_2(CH_2)_3$ (**7d**)	Me	Li	CuBr·Me_2S	80:20	**9d**	90
9	B	Ph (**7e**)	Me	Li	CuBr·Me_2S	90:10	**9e**	50
10	B	*p*-FC_6H_4 (**7f**)	Me	Li	CuBr·Me_2S	>95:5	**9f**	71
11	B	*p*-$MeOC_6H_4$ (**7g**)	Me	Li	CuBr·Me_2S	>95:5	**9g**	60

[a]Conditions A: 2.0 equiv of R^2Cu (prepared from an equimolar amount of R^2MgBr and CuBr at −50 °C to rt in Et_2O. Conditions B: 2.4 equiv MeLi, 1.2 equiv CuX, Et_2O, −30 to −20 °C, 2 h. Conditions C: 1.2 equiv MeMgBr with 10 mol % of CuI in Et_2O from −20 to 0 °C. [b]Yields of isolated product after flash column chromatography (based on **7**).

Our initial attempt was performed with organocopper species prepared from alkylmagnesium halide and CuBr (1:1 ratio) and ynamide **7a** (R^1 = Hex), which cleanly led to the enamide **9a** in very good isolated yield for the addition of MeCu, and with excellent regioselectivities (α/β > 95:5, Table 3, entry 1). For subsequent reaction of **8Cu**, we were also interested in evaluating the regioselectivity of the carbometallation reaction of an organocuprate, and we were pleased to see that the same α-regioisomer was obtained. However, yields are lower with CuI and CuBr (Table 3, entries 2 and 3) than that with a more soluble complex CuBr·Me_2S (Table 3, entry 5). However, when CuCN was employed, only an α/β ratio of 9:1 was obtained, probably due to the decreased chelating effect of the resulting mixed organometallic species (Table 3, entry 4). When the copper-catalyzed carbomagnesiation reaction was performed (Table 3, entry 6), results were very similar to those from the addition of copper or cuprate reagents (Table 3, entries 1 and 5, respectively).

Thus, the best compromise we found for the regioselective addition of a methyl group on ynamides **7a** and **7b** was through the addition of a cuprate $Me_2CuLi·Me_2S$ prepared from the addition of methyllithium (2 equiv) to Me_2S·CuBr (1 equiv). These experimental conditions were used for the stereo- and regioselective carbocupration of several functionalized ynamides **7c**–**g**. With a TIPS-protected alcohol **7c** (Table 3, entry 7), the carbocupration gave only the α-regioisomer, albeit in moderate yield. On the other hand, in the presence of the 1-adamantylester substituted substrate **7d**, the two α/β-isomers were formed in a 8:2 ratio (Table 3, entry 8). This loss of selectivity may be explained either by a competitive chelation of the carbonyl group of the ester functionality or the presence of THF (ca. 20 vol %) as a co-solvent used to dissolve the starting ynamide **7d**. When the reaction was performed with aryl-substituted ynamides (**7e**–**g**), THF had to be added as a co-solvent to improve the solubility of the starting materials as well, which may affect the resulting selectivity. Indeed, in the case of phenylsubstituted ynamine **7e**, a 1:1 mixture of Et_2O and THF was used to avoid precipitation of the starting material, which led to a 9:1 ratio in favor of the α-isomer (Table 3, entry 9). However, for substrates bearing *p*-fluoro and *p*-methoxyphenyl substituents (**7f** and **7g** respectively), only around 8 vol % of THF was necessary to add to the reaction mixture to obtain a homogeneous solution. In such circumstances, the α-adduct was detected as the sole product of the carbocupration (Table 1, entries 10 and 11) as confirmed by NMR spectroscopy and X-ray crystallographic analysis of the major isomer of **9f** (Figure 1).

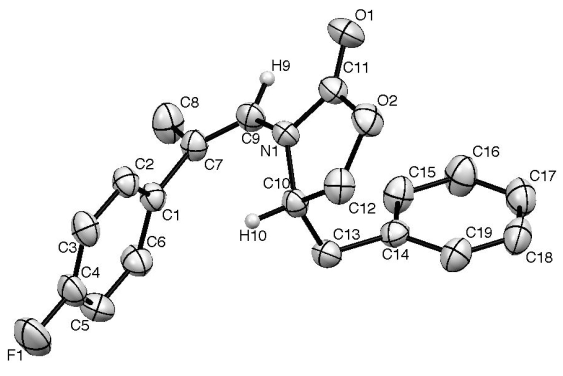


Figure 1: Molecular structure of **9f** (hydrogen atoms except of H9 and H10 are omitted for clarity).

In the past few years we have witnessed the renaissance of the selective functionalization of heterosubstituted alkynes. From the pioneering work of Alexakis, Cahiez and Normant, which led to a myriad of beautiful selective transformations of alkynes, the carbocupration reaction is again at the center of interest but this time for the regioselective addition of organocopper derivatives to various ynamide species. Particularly interesting is the carbocupration of *N*-alkynyl carbamates **7**, bearing Evans's oxazolidinone chiral auxiliary, which leads to the formation of a single regioisomer of vinylcopper **8** that may be used for the preparation of functionalized adducts in acyclic systems [28-30]. Solvent plays a detrimental role in the regioselectivity of the reaction, and only Et_2O leads to the α-isomer, due to a precomplexation of the organocopper with the carbamate moiety.

Supporting Information

Supporting Information File 1

Full experimental procedures and detailed analytical data for the synthesis of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-57-S1.pdf]

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Intramolecular carbolithiation cascades as a route to a highly strained carbocyclic framework: competition between 5-*exo*-*trig* ring closure and proton transfer

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carbolithiation cascade; carbometallation; intramolecular carbolithiation; intermolecular proton transfer; lithium–halogen exchange; strained hydrocarbons

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Abstract

The preparation of fairly strained carbocyclic ring systems by intramolecular 5-*exo*-*trig* ring closure has been well documented, and the absence of proton transfers that would compromise such cyclizations is a hallmark of this chemistry. In an effort to explore the limitations of this approach to more highly strained systems, the preparation of a stellane (tricyclo[3.3.0.0^{3,7}]octane) framework by an intramolecular carbolithiation cascade involving three coupled 5-*exo*-*trig* cyclizations of the vinyllithium derived from 2-bromo-4-vinyl-1,6-heptadiene by lithium–bromine exchange was investigated. The cascade does not afford the stellane; rather, the cascade is terminated after two cyclizations by a proton transfer that occurs by an intermolecular process catalyzed by trace amounts of *endo*-5-methyl-2-methylenebicyclo[2.2.1]heptane present in reaction mixtures as a consequence of inadvertent quenching of an intermediate alkyllithium during prolonged reaction times at room temperature.

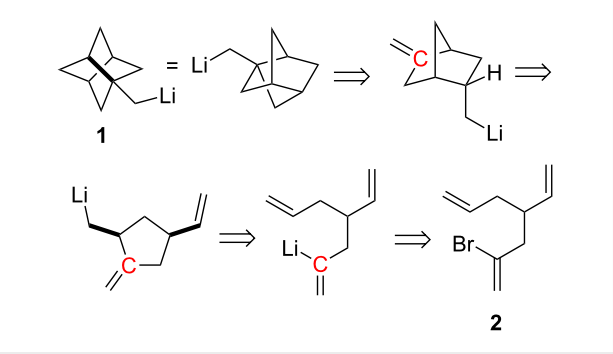
Introduction

The first publication describing an intramolecular carbolithiation appeared in 1968: Drozd and co-workers reported that 5-hexenyllithium, prepared in Et_2O by treatment of 6-bromo-1-hexene with lithium metal, cyclized at 0 °C to give (cyclopentylmethyl)lithium [1,2]. This observation was confirmed and extended in a seminal 1972 communication by John Oliver's group [3] in which it was presciently noted that, "this reaction appears to provide an interesting … procedure for formation of five-membered ring systems which is potentially significant for synthetic purposes" [3]. Indeed, the facile cyclization of olefinic and acetylenic organolithiums has proven to be a regiospecific and highly stereoselective route [4] to a variety of functionalized carbocyclic [5-7] and heterocyclic systems [8,9].

The bonding changes that accompany cyclization of an unsaturated organolithium indicate that the process should be energetically favorable since a σ-bond (bond energy ca. 88 kcal/mol) is generated at the expense of a π-bond (bond energy ca. 60 kcal/mol). As a consequence, strained carbocyclic systems may be constructed by operationally irreversible [10] intramolecular carbolithiations [11-15]. At the outset of our foray into this area several decades ago [16], we were initially surprised to find that the cyclization of olefinic alkyllithiums was not compromised by proton transfers that would afford the more stable allyllithium isomers. A subsequent study of the behavior of 5-hexenylalkalis demonstrated that cyclization is unique to the lithium species: the Na, K, Rb, and Cs analogues of 5-hexenyllithium rearrange rapidly by [1,4]-proton transfer to afford the allylic species [17]. In fact, the absence of proton transfers that would compromise 5-*exo* cyclization of 5-hexenyllithiums is a hallmark of this chemistry. Intrigued by these observations, we were prompted to investigate the possibility of constructing a highly strained system by an intramolecular carbolithiation cascade involving three coupled 5-*exo*-*trig* cyclizations.

Although many strained molecules could have been selected for this exploration, the stellane framework (tricyclo[3.3.0.0^{3,7}]octane [18,19]), **1**, with its mesmerizing symmetry, was chosen as the synthetic target. The retrosynthesis is depicted in Scheme 1; the stereochemical outcome anticipated for each of the ring closures finds ample literature precedent [4]. It may be noted that the nucleophilic carbon of the vinyllithium that initiates the first cyclization becomes the electrophilic carbon that terminates the cascade to give **1**.

As demonstrated by the results presented below, this cascade does not afford **1**. Rather, the cascade is terminated after two cyclizations by a proton transfer that occurs through an intermolecular process.

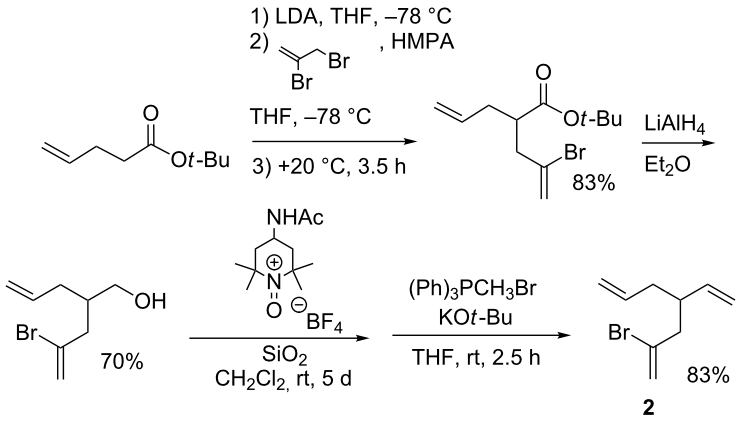


Scheme 1: Retrosynthetic plan.

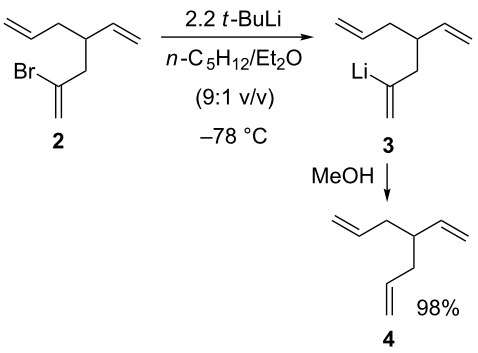
Results and Discussion

The 2-bromo-4-vinyl-1,6-heptadiene (**2**), required for the lithium–halogen exchange step that initiates the cascade, was prepared as illustrated in Scheme 2 (for details, see Supporting Information File 1). Vinyllithium **3** was cleanly generated in virtually quantitative yield at –78 °C by addition of 2.2 molar equiv of *tert*-butyllithium (*t*-BuLi) in pentane to a 0.1 M solution of **2** in *n*-pentane/diethyl ether (9:1 v/v). As would be expected, vinyllithium **3** is stable at low temperature and, as depicted in Scheme 3, quenching of a typical reaction mixture at –78 °C with oxygen-free MeOH affords 4-vinyl-1,6-heptadiene (**4**) in 98% isolated yield. Quenching with MeOD afforded an authentic sample of **4** deuterated at the C(2) position (^{2}H NMR: δ 5.84–5.75 (m, 1D)); the lack of a molecular ion in the GC–MS of triene **4** precluded accurate determination of the deuterium content.

Addition at –78 °C of dry, oxygen-free *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) to solutions of **3** in *n*-C_5H_{12}/Et_2O (9:1 v/v) and subsequent warming of the reaction mixtures for various times at several different temperatures initiated the cascades. The results of these experiments are summarized in



Scheme 2: Preparation of **2**.

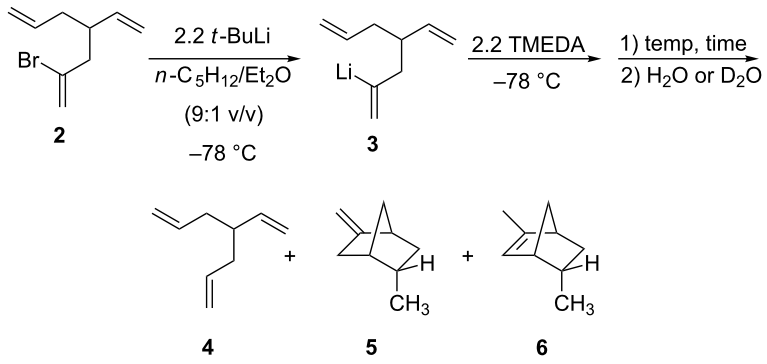


Scheme 3: Generation of **3** by lithium–bromine exchange.

Scheme 4 and Table 1. Crude product mixtures were analyzed by capillary GC and by GC–MS affording baseline separation of the three products (**4**–**6**), illustrated in Scheme 4, which accounted for essentially the total material balance. The structures of the bicyclic products, **5** and **6**, were established as detailed in the Experimental Section (see Supporting Information File 1 for details) by NMR and GC–MS: an authentic sample of **5** was prepared as illustrated below and **6** is a known compound [20]. It is noteworthy that no 1-methylstellane was detected as a product from any of the reactions.

Stirring a reaction mixture for 1 h at room temperature demonstrated that the first cyclization was not complete, as 23% of the quenched vinyllithium (**4**) remained (Table 1, entry 1). Warming reaction mixtures at room temperature for 3 h decreased the proportion of **4** (~6%); however, the yield of the norbornene product, **6**, increased from 12% after 1 h to ~30% (Table 1, entries 2 and 3). Longer reaction times at both −40 °C and +24 °C were probed to access the effect of temperature on the product distribution. Holding a reaction mixture at room temperature for 20.5 h did not favorably change the product distribution (Table 1, entry 5), while keeping a reaction at −40 °C for 20.5 h limited the amount of **6** while increasing the proportion of **5** (Table 1, entry 4). In an attempt to drive a final cyclization to give 1-methylstellane, a sample was kept at −40 °C for 8 h before being warmed to +40 °C for 3 h; the product distribution from this experiment (Table 1, entry 6) was similar to that obtained when the reaction mixture was stirred for 3 h at room temperature.

In an effort to follow the progress of the reaction, product formation was monitored by removing aliquots from a reaction mixture held at room temperature and, following quenching with a mixture of diethyl ether and water, analysis of the product mixtures by capillary GC. The graph depicted in Figure 1



Scheme 4: Cascade products.

Table 1: Intramolecular cascade results (Scheme 4).

entry	time, h	temp, °C	quench	products, % yield[a] (% d_1)[b] 4	5	6
1	1	−78 to +24	D_2O	22.8	65.2 (62)	12.0 (75)
2	3	−78 to +24	H_2O	4.8	63.4	31.8
3	3	−78 to +24	D_2O	5.8	64.0 (90)	30.2 (99)
4	20.5	−78 to −40	MeOD	7.6	79.2 (94)	13.2 (84)
5	20.5	−78 to +24	D_2O	3.2	55.0 (94)	41.8 (92)
6	8; 3	−78 to −40, +40	D_2O	1.5	60.0 (98)	38.5 (94)

[a]Yields were determined by capillary GC. [b]Percent (d_1) deuterium incorporation determined by GC–MS.

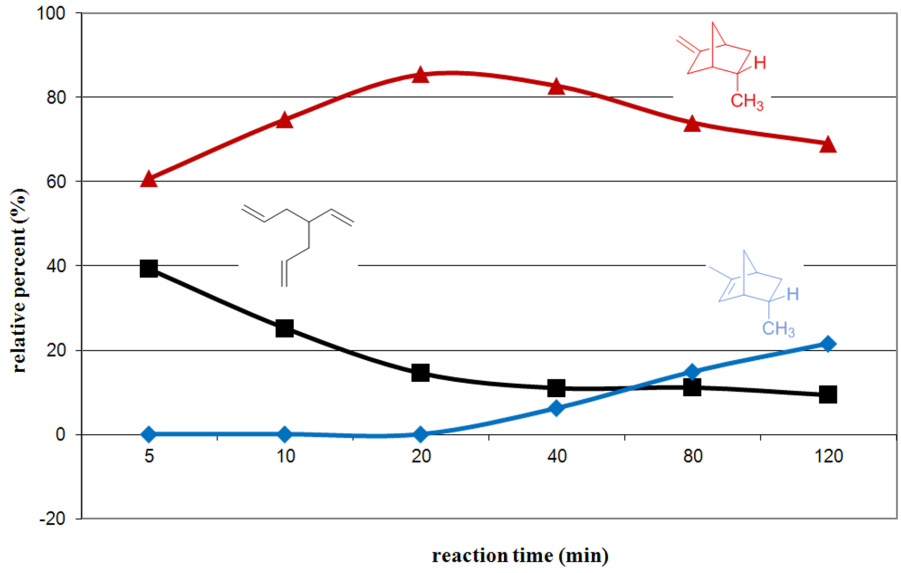
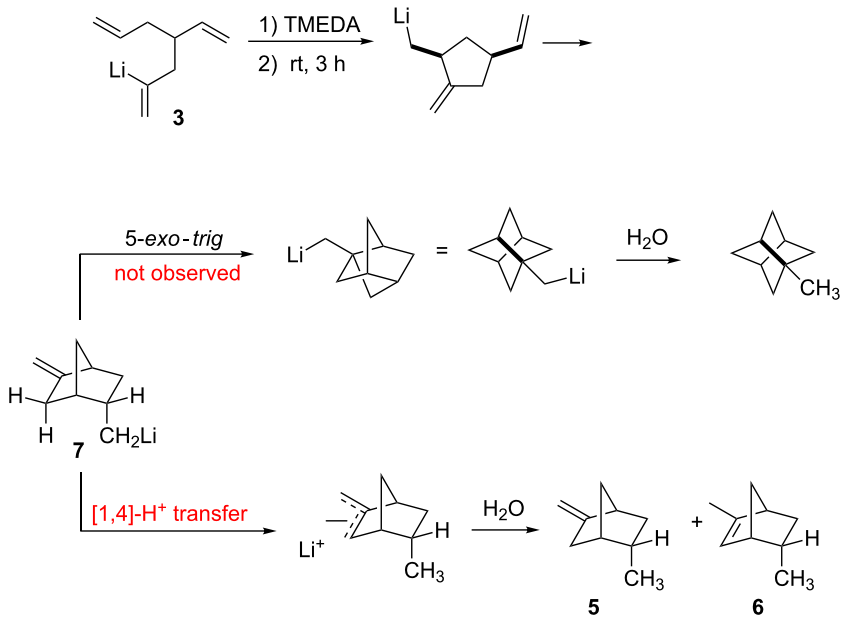


Figure 1: Reaction progress of the attempted triple-cyclization cascade.

illustrates that the first cyclization is essentially completed after about 30 min at room temperature. Longer reaction time results in the formation of **5** and **6**; there was no evidence for the presence of 1-methylstellane. Indeed, the product distribution observed after 2 h at room temperature is similar to those observed after 3 h or 20.5 h at this temperature. Apparently, the cascade, involving two sequential cyclizations, is complete after ~2 h.

It would seem that a final cyclization to give 1-methylstellane is foiled by a formal [1,4]-proton transfer as depicted in Scheme 5. Cyclization of **3** quickly generates the monocyclic product and a second cyclization gives the *endo*-5-methyl-2-methylene organolithium **7** in nearly 90% yield. However, a proton transfer to give the more stable allylic anion apparently foils the final ring closure. Quenching of the reaction mixture then affords **5** and **6** in an approximate ratio of 2:1. In this connec-



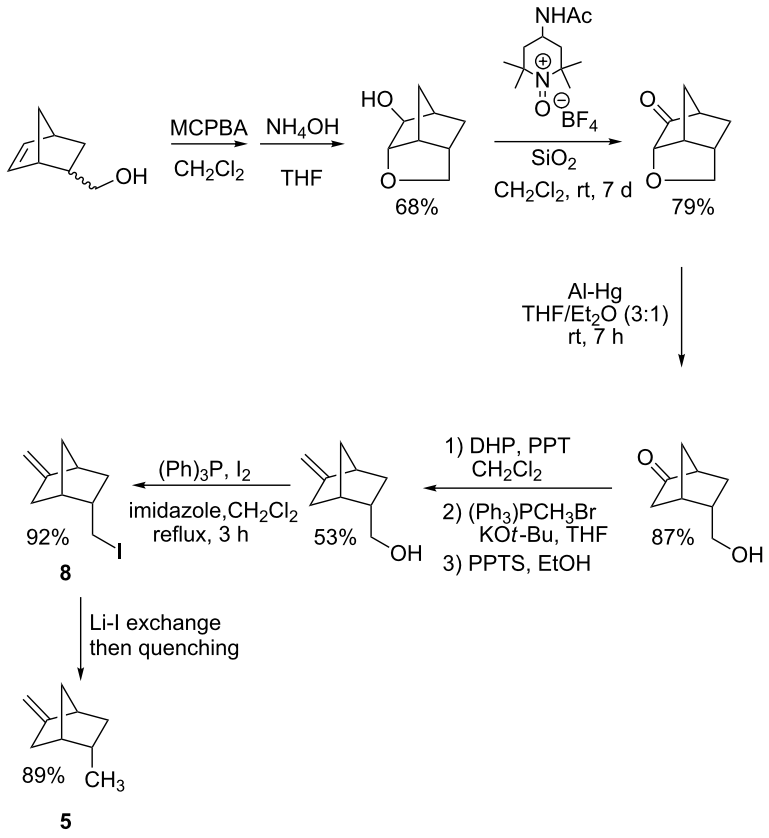
Scheme 5: Proton transfer that foils final cyclization.

tion, it should be noted that a 2-methylene-substituted bicyclo[2.2.1]heptane, such as product **5**, is known to be more stable than the isomeric norbornene, such as **6** [21]. Clearly, the energy required for the final 5-*exo*-*trig* cyclization to give the stellane framework is far greater than that required for the formal [1,4]-proton transfer that terminates the cascade.

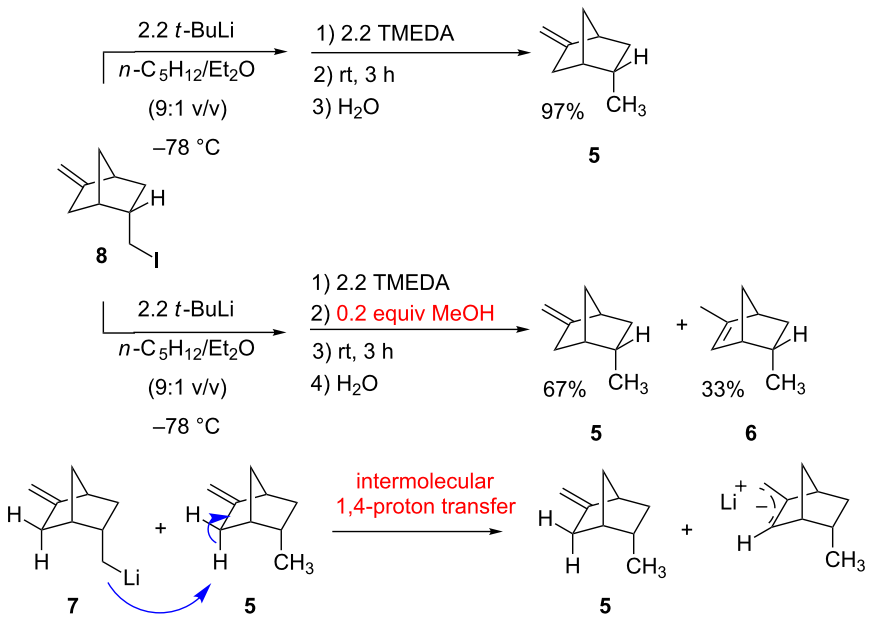
In an effort to further elucidate the nature of the proton transfer that terminates the cascade, *endo*-5-iodomethyl-2-methylenebicyclo[2.2.1]heptane (**8**) was prepared as illustrated in Scheme 6 (for details, see Supporting Information File 1). Iodide **8** was converted to the corresponding alkyllithium by low temperature lithium–iodine exchange in *n*-C_5H_{12}/Et_2O (9:1 v/v) following our general protocol [22]. The exchange reaction is quite efficient as evidenced by the fact that quenching of a reaction mixture with MeOH affords an authentic sample of **5** in 89% isolated yield.

A series of experiments, involving warming solutions of alkyllithium **7** in scrupulously dry and oxygen-free pentane/Et_2O containing 2.2 molar equiv of TMEDA for 3 h at room temperature, gave no evidence of the expected [1,4]-proton transfer, nor was there any evidence of 1-methylstellane: as illustrated at the top of Scheme 7, the exclusive product from such reactions, following quenching with water, was **5** isolated in 97% yield; there was no trace of **6** in any of the samples (for details, see Supporting Information File 1, p. S15). The failure to observe any rearranged product when alkyllithium **7** was warmed at room temperature was cause for initial concern since the result seemed to indicate that the proton transfer depicted in Scheme 5 is not a viable process. However, upon further consideration, it became apparent that the absence of **6** as a product from these reactions was an indication that the proton transfer is not an intramolecular process.

The intermolecular nature of the proton transfer is strongly supported by the following observation (Scheme 7): proton transfer is only observed when a small amount of **5** is present in the reaction mixture. Thus, the addition of a small quantity (0.2 molar equiv) of oxygen-free MeOH at −78 °C to a solution of bicyclic alkyllithium **7** served to generate a correspondingly small quantity of alkene **5**. As depicted in Scheme 7, when such a reaction mixture is allowed to stand at room temperature for 3 h in the presence of TMEDA, both **5** and **6**, in a ratio of 2:1, were produced after quenching with water. It would seem, as illustrated in Scheme 7, that the proton transfer is an *intermole-*



Scheme 6: Preparation of iodide **7** and an authentic sample of **5**.



Scheme 7: Evidence for the intermolecular nature of the formal [1,4]-proton transfer.

cular process catalyzed by a small quantity of *endo*-5-methyl-2-methylenebicyclo[2.2.1]heptane (**5**) present in reaction mixtures as a consequence of inadvertent quenching of **7** by solvent or adventitious acid during prolonged reaction times at room temperature.

Conclusion

In retrospect, the failure to access the highly strained 1-methylstellane framework from an acyclic tri-olefinic vinyllithium (**3**) by sequential 5-*exo*-*trig* cyclizations is perhaps not surprising. The results of these studies do, however, serve to define a limit to the strain that may be accommodated by intramolecular carbolithiation. Moreover, it is significant that the penultimate olefinic alkyllithium **7** generated in the cascade appears to be resistant to rearrangement by proton transfer in the absence of a catalytic quantity of the hydrocarbon formed upon quenching of **7**. In short, 5-*exo*-*trig* carbolithiations are robust processes that are much more energetically favorable than are potential intramolecular proton transfers that would compromise such chemistry.

Supporting Information

Supporting Information File 1

Experimental details and procedures for the preparation of all previously unreported compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-59-S1.pdf]

Acknowledgements

We are grateful to Dr. Terry L. Rathman of Optima Chemical, Douglas, GA, for generous gifts of *t*-BuLi and *n*-BuLi. This work was supported by a grant from the Process Chemistry Division, H. Lundbeck A/S, Copenhagen, Denmark.

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Carbolithiation of *N*-alkenyl ureas and *N*-alkenyl carbamates

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Full Research Paper

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Abstract

N-Alkenyl ureas and *N*-alkenyl carbamates, like other *N*-acyl enamines, are typically nucleophilic at their β-carbon. However, by incorporating an α-aryl substituent, we show that they will also undergo attack at the β-carbon by organolithium nucleophiles, leading to the products of carbolithiation. The carbolithiation of *E* and *Z* *N*-alkenyl ureas is diastereospecific, and *N*-*tert*-butoxycarbonyl *N*-alkenyl carbamates give carbolithiation products that may be deprotected in situ to provide a new connective route to hindered amines.

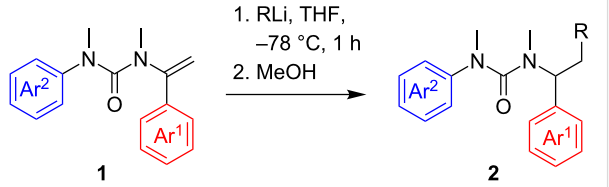
Introduction

Enamines and *N*-acyl enamines are in general nucleophiles, reacting with electrophiles at the carbon atom β to the nitrogen atom [1,2]. The resulting intermediate iminium or *N*-acyliminium ions are electrophilic, and may themselves trap a nucleophile at the position α to the nitrogen substituent. However, we [3,4] and others [5-7] have shown that this typical reactive polarity may be reversed when *N*-acylenamines (especially *N*-vinyl ureas [8]) meet organolithium nucleophiles. *N*-Carbamoyl enamines bearing α-aryl substituents (in other words, α-acylaminostyrenes), may undergo reaction as electrophiles, with the carbon atom β to nitrogen succumbing to attack by organolithium nucleophiles in an enamine carbolithiation reaction [9]. Similar reactivity is observed with related *O*-carbamoyl enols [10-12]. The organolithium resulting from the enamine carbolithiation is nucleophilic at the atom α to nitrogen, and such carbolithiations have been used to generate hindered organolithiums as intermediates for further rearrangement reactions [13], for example intramolecular acylation [6], arylation [3,4] or vinylation [4]. In this paper, we now report our studies on the scope of the carbolithiation–protonation of styrenes carrying α-acylamino substituents, namely *N*-alkenyl ureas and *N*-alkenyl carbamates.

Results and Discussion

Simple *N*-alkenyl ureas **1** were prepared by a reported method [2] entailing N-acylation of an acetophenimine with an iso-

cyanate, followed by N-alkylation of the resulting urea. When urea **1a** was treated with *t*-BuLi or *s*-BuLi in THF at −78 °C for one hour, followed by protonation, carbolithiated products **2a** and **2b** were isolated in good yield (Scheme 1 and Table 1, entries 1 and 2). Similar reactivity was observed between urea **1a** and less hindered organolithiums such as iPrLi or *n*-BuLi [3], but in THF even at −78 °C a rearrangement [14-18] of the intermediate benzyllithium reduces the yield of the simple carbolithiation product. However, by lowering the temperature to −85 °C rearrangement occured to only a limited extent, and the addition product **2c** was obtained in 53% yield (Table 1, entry 3). Rearrangement was also suppressed if the substituent Ar^2 was replaced by either a *p*-chlorophenyl or a *p*-methoxyphenyl ring, and even with *n*-BuLi the carbolithiation–protonation product may be obtained in moderate yield from **1b** and **1c** (Table 1, entries 4 and 5).



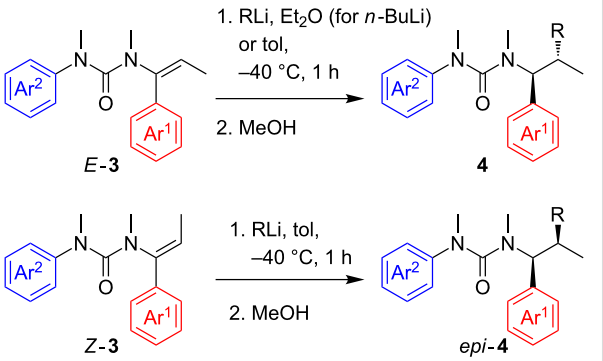
Scheme 1: Carbolithiation of ureas **1**.

Table 1: Organolithium addition to ureas **1**.

Entry	SM	Ar^1	Ar^2	R	**2**, yield (%)
1	**1a**	Ph	Ph	*t*-Bu	**2a**, 77[a]
2	**1a**	Ph	Ph	*s*-Bu	**2b**, 74[b]
3	**1a**	Ph	Ph	iPr	**2c**, 53[c]
4	**1b**	Ph	4-$MeOC_6H_4$	*n*-Bu	**2d**, 61
5	**1c**	Ph	4-ClC_6H_4	*n*-Bu	**2e**, 47

[a]Reported in ref [3]; [b]mixture of diastereoisomers; [c]reaction carried out at −85°C.

β-Substituted vinyl ureas **3** are available as either *E* or *Z* geometrical isomers according to the method of synthesis: N-acylation of a propiophenimine typically generates an *E*-alkenylurea, but deprotonation and reprotonation of the urea inverts its geometry to *Z* [2], probably via an intramolecularly chelated urea-substituted allyl anion [17]. Urea *E*-**3a** was treated with *n*-BuLi in Et_2O (the less-coordinating solvent suppresses rearrangement of the product [4]) at −40 °C: it underwent clean carbolithiation of the double bond, and on protonation urea **4a** was obtained as a single diastereomer in 85% yield (Scheme 2 and Table 2, entry 1). Other *E*-alkenyl ureas bearing a range of substituted aromatic rings *E*-**3b**–**f** were likewise treated with alkyllithium reagents *s*-BuLi, iPrLi and *t*-BuLi, this time in toluene. As before, a noncoordinating solvent was used to suppress rearrangement. In each case the addition product **4b**–**f** was obtained in good yield always as a single diastereomer (Table 2, entries 2–5 and 7). Styrenes with substituents on the aromatic ring underwent carbolithiation irrespective of the electronic character of the ring: with electron-rich or electron-poor aromatic rings Ar^1 carbolithiation was complete in one hour.



Scheme 2: Diastereospecific carbolithiation of ureas **3**.

Table 2: Organolithium additions to ureas **3**.

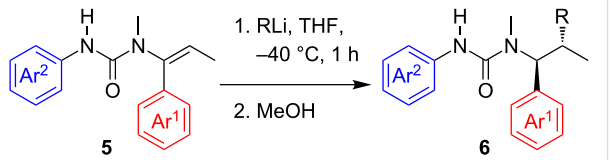
Entry	SM	Ar^1	Ar^2	R	**4**, yield (%)
1	*E*-**3a**	Ph	3-$MeOC_6H_4$	*n*-Bu	**4a**, 85
2	*E*-**3b**	4-F-C_6H_4	Ph	*s*-Bu	**4b**, 70[a]
3	*E*-**3c**	Ph	4-MeC_6H_4	iPr	**4c**, 78
4	*E*-**3d**	4-MeC_6H_4	Ph	*t*-Bu	**4d**, 63
5	*E*-**3e**	4-ClC_6H_4	Ph	iPr	**4e**, 81
6	*Z*-**3e**	4-ClC_6H_4	Ph	iPr	*epi*-**4e**, 80
7	*E*-**3f**	Ph	4-$MeOC_6H_4$	*n*-Bu	**4f**, 85
8	*E*-**3f**	Ph	4-$MeOC_6H_4$	iPr	**4g**, 85[b]
9	*Z*-**3f**	Ph	4-$MeOC_6H_4$	iPr	*epi*-**4g**, 85[b]
10	*E*-**3g**	4-ClC_6H_4	4-$MeOC_6H_4$	iPr	**4h**, 60

[a]2:1 mixture of diastereoisomers; [b]reaction reported in ref [3] but yield now improved.

When the reaction was performed using the *Z*-isomer of the starting materials, *Z*-**3e** and *Z*-**3f** (Scheme 2 and Table 2, entries 6 and 8), the other diastereomer of the product urea *epi*-**4** was obtained selectively: the carbolithiation–protonation is completely diastereospecific. Both geometrical isomers of **3** presented similar reactivity and the products **4** were obtained in similar yields under the same reaction conditions.

To avoid possible contamination of the carbolithiation products by compounds arising from tandem carbolithiation–rearrangement, we were also keen to explore the possibility of carbo-

lithiating vinyl ureas incapable of rearrangement, either because they lack the *N*'-aryl substituent or because the remote nitrogen is protected from attack by existing as an anion. Urea **5a**, which was available as an intermediate from the synthesis of **3a**, was treated with *n*-BuLi, using an additional equivalent of the organolithium to allow for deprotonation of the urea NH (Scheme 3) and in THF since a competing rearrangement is not a problem. Despite the carbolithiation now requiring an anion to act as an electrophile, the corresponding carbolithiated and protonated product **6a** was obtained as a single diastereoisomer in excellent yield without chromatography (Table 3, entry 1) after one hour in THF at −40 °C. With urea **5b** primary (*n*-BuLi), secondary (iPrLi) and also tertiary (*t*-BuLi) alkyllithium reagents were added successfully in excellent yields (Table 3, entries 2–4), and no chromatography was needed.



Scheme 3: Diastereospecific carbolithiation of ureas **5**.

Table 3: Carbolithiation of urea **5**.

Entry	SM	Ar^1	Ar^2	R	**6**, yield (%)
1	**5a**	Ph	4-$MeOC_6H_4$	*n*-Bu	**6a**, 80
2	**5b**	4-ClC_6H_4	4-$MeOC_6H_4$	*n*-Bu	**6b**, 87
3	**5b**	4-ClC_6H_4	4-$MeOC_6H_4$	iPr	**6c**, 98
4	**5b**	4-ClC_6H_4	4-$MeOC_6H_4$	*t*-Bu	**6d**, 98

The relative configuration of the carbolithiation products **6** was established by X-ray crystallography of urea **6c** (Figure 1). The stereochemical outcome of the reaction is consistent with *syn*-addition of the organolithium across the double bond (as is typical for carbolithiation [9,19]) followed by retentive protonation.

The relative configuration of the carbolithiation products **4** was likewise confirmed by methylation (NaH, MeI) of **6d** to provide a single diastereoisomer of urea **4g** in 60% yield, which was spectroscopically identical with the compound obtained by treating urea *E*-**3g** with iPrLi (Table 2, entry 9). Again, the stereochemical outcome is consistent with *syn*-carbolithiation followed by retentive protonation.

In principle, the urea products **2**, **4** and **6** could be solvolysed to liberate free amines, as has been demonstrated for related compounds [4,15,20]. However, we reasoned that the related *tert*-butyloxycarbonyl-substituted carbamates would give more readily manipulated carbamate products bearing a standard Boc protecting group, providing they too could be carbolithiated and trapped without rearrangement. Related carbamates are reactive towards carbolithiation–rearrangement reactions [6]. Thus, Boc-protected carbamates **9**–**11** were synthesised by acylation of the imines **7** and **8** with di-*tert*-butyl dicarbonate or with (−)-menthylchloroformate (Scheme 4). The *N*-alkenylcarbamates **10** and **11** were formed exclusively as their *E* isomers, and the X-ray crystal structure of *E*-**10** is shown in Figure 2.

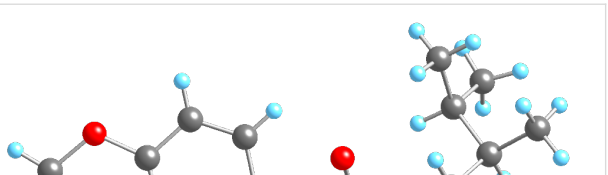
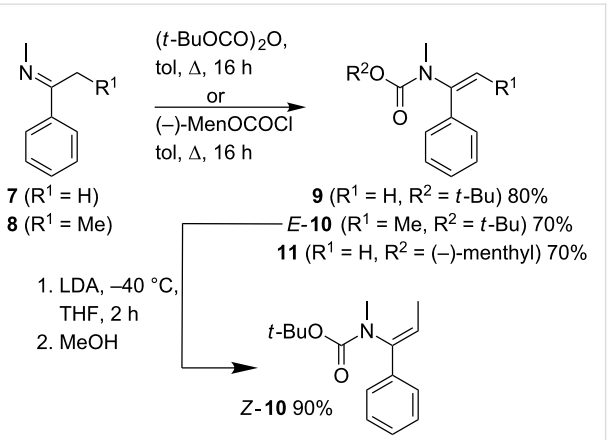


Figure 1: X-ray crystal structure of urea **6c**.



Scheme 4: Synthesis of *N*-alkenyl carbamates **9**–**11**.

Vinyl carbamate **9** was treated with primary, secondary or tertiary alkyllithium reagents at −78 °C in THF for one hour (Scheme 5), and after protonation the addition products **12a**–**c** were isolated in good yields (Table 4, entries 1–3) . Substituted carbamate **10** also reacted with primary, secondary or tertiary alkyllithium reagents under similar conditions, and in this case the carbamates were deprotected by treatment with CF_3CO_2H in a one-pot process, to provide the amines **13a**–**c** in good yields over the two steps (Table 4, entries 4–6). In every case, the amine **13** was obtained as a single diastereomer, which we

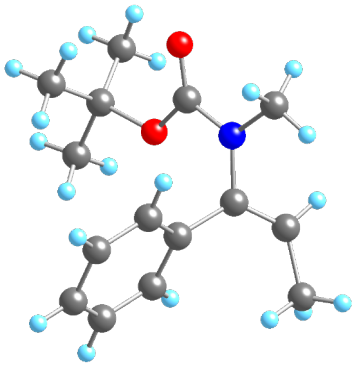
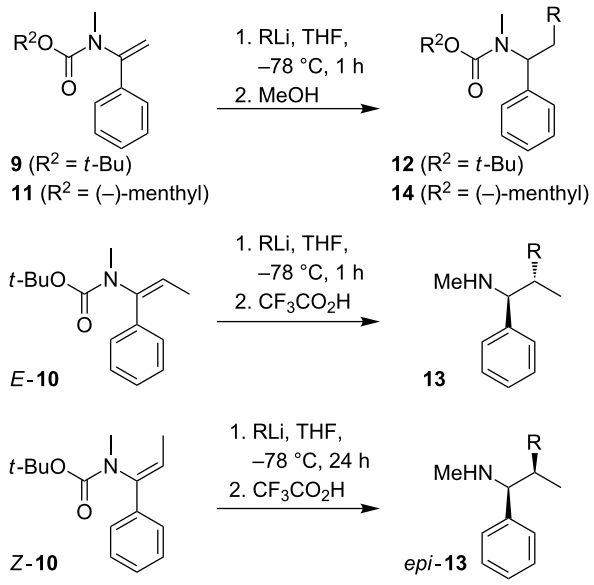


Figure 2: X-ray crystal structure of carbamate *E*-**10**.

assume, by analogy with the reactions of the equivalent ureas, to be that shown, arising from *syn*-carbolithiation and retentive protonation.



Scheme 5: Umpolung carbolithiation of carbamates **9** and **10**.

E-**10** was isomerised to *Z*-**10** by treatment with LDA and reprotonation (presumably, like the equivalent ureas [2,3], via an intramolecularly coordinated *Z*-allyllithium [21,22]), giving *Z*-**10** in excellent yield (Scheme 4). However, in contrast to *Z*-alkenyl ureas, *Z*-**10** was rather less reactive than its *E*-isomer. The carbolithiation with iPrLi (Scheme 5) was slower, and had to be performed for 24 hours instead of 1 hour. After deprotection with trifluoroacetic acid, the amine *epi*-**13b** was obtained in lower yield (50%) and as a 8:2 mixture of diastereomers (Table 4, entry 7). The loss of diastereospecificity may be explained by the long reaction time: we assume that *syn*-carbolithiation is followed by a partial epimerisation of the intermediate organolithium during the 24 h before the reaction is quenched.

Table 4: Organolithium addition to vinyl carbamates.

Entry	SM	R	Product, yield (%), (dr)
1	**9**	*n*-Bu	**12a**, 61
2	**9**	iPr	**12b**, 61
3	**9**	*t*-Bu	**12c**, 80
4	*E*-**10**	*n*-Bu	**13a**, 70 (>95:5)
5	*E*-**10**	iPr	**13b**, 80 (>95:5)
6	*E*-**10**	*t*-Bu	**13c**, 81 (>95:5)
7[a]	*Z*-**10**	iPr	*epi*-**13b**, 50 (80:20)
8	**11**	iPr	**14**, 60 (50:50)

[a]24 h reaction time.

Related vinylureas will undergo enantioselective carbolithiation in the presence of (−)-sparteine or a (+)-sparteine surrogate [4], but enantioselective carbolithiation of carbamate **9** in the presence of (−)-sparteine led to product with only 60:40 er. The use of a chiral auxiliary in the form of a (−)-menthylcarbamate (**11**) also failed to induce selectivity, reacting with iPrLi to yield a carbolithiated product **14** in 60% yield as a 50:50 mixture of diastereoisomers (Table 4, entry 8).

Conclusion

In conclusion, we have demonstrated that electron-rich double bonds of vinyl ureas and carbamates may undergo carbolithiation with primary, secondary and tertiary organolithium reagents. *N*-*tert*-butoxycarbonyl vinylcarbamates may be carbolithiated, protonated and deprotected in a one-pot synthesis of amines employing this unusual umpolung nucleophilic β-alkylation. With β-substituted vinylureas, the carbolithiation is diastereospecific, with (*E*) and (*Z*)-isomers of the ureas giving different diastereoisomers of the products; (*E*)-*N*-alkenylcarbamates react with complete diastereospecificity. The overall *syn*-relative configuration of the reaction products, which probably arises from *syn*-carbolithiation followed by retentive protonation, was confirmed by X-ray crystallography.

Experimental

1-(4-Methoxyphenyl)-1,3-dimethyl-3-[(1*R,2*R**)-2-methyl-1-phenylhexyl]urea (4f):** To a solution of urea **3f** (0.086 g, 0.28 mmol, 1 equiv) in dry toluene (0.1 M) cooled to −40 °C, *n*-BuLi (2 equiv) was added slowly. After 1 h at −40 °C, the reaction was quenched slowly with MeOH and a saturated aqueous solution of NH_4Cl. The resulting solution was extracted with EtOAc, dried with $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel (eluting with petroleum ether/EtOAc 9:1). The title compound **4f** (0.086g, 85%) was obtained as a colourless oil. R_f 0.5

(PE/EtOAc 8:2); IR (film) ν_{max} (cm^{-1}): 2957, 2931, 1651, 1644, 1510; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.17 (m, 5H, 5 × Ar*H*), 6.79 (dt, *J* = 8.8, 2.5 Hz, 2H, 2 × Ar*H*), 6.66 (dt, *J* = 8.8, 2.5 Hz, 2H, 2 × Ar*H*), 5.02 (d, *J* = 12.0 Hz, 1H, C*H*-N), 3.70 (s, 3H, O-CH_3), 3.05 (s, 3H, N-CH_3), 2.21 (s, 3H, N-CH_3), 2.04 (m, 1H, C*H*-CH_3), 1.20 (m, 6H, 3 × CH_2), 0.88 (t, *J* = 7.6 Hz, 3H, CH_3-CH_2), 0.70 (d, *J* = 6.4 Hz, 3H, CH_3-CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (C=O), 156.6 (C_{ar}-OCH_3), 140.1 (C_{ar}), 139.2 (C_{ar}), 128.6 (2 × CH_{ar}), 128.1 (2 × CH_{ar}), 127.1 (CH_{ar}), 126.1 (2 × CH_{ar}), 114.4 (2 × CH_{ar}), 64.3 (CH-N), 55.3 (O-CH_3), 41.0 (N-CH_3), 32.6 (*C*H-CH_3), 32.1 (*C*H_2-CH), 30.7 (N-CH_3), 29.2 (*C*H_2-CH_2-CH_3), 23.1 (*C*H_2-CH_3), 17.1 (*C*H_3-CH), 14.2 (*C*H_3-CH_2); HRMS–ES (*m*/*z*): $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_2$, 369.2537; found, 369.2536.

Supporting Information

Supporting Information File 1

Experimental procedures for the synthesis of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-70-S1.pdf]

Supporting Information File 2

cif file for **6c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-70-S2.txt]

Supporting Information File 3

cif file for *E*-**10**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-70-S3.txt]

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Intramolecular carbonickelation of alkenes

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Full Research Paper

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Abstract

The efficiency of the intramolecular carbonickelation of substituted allylic ethers and amines has been studied to evaluate the influence of the groups borne by the double bond on this cyclization. The results show that when this reaction takes place, it affords only the 5-*exo*-*trig* cyclization products, viz. dihydrobenzofurans or indoles. Depending on the tethered heteroatom (O or N), the outcome of the cyclization differs. While allylic ethers are relatively poor substrates that undergo a side elimination and need an intracyclic double bond to proceed, allylic amines react well and afford indoline and indole derivatives. Finally, the synthesis of the trinuclear ACE core of a morphine-like skeleton was achieved by using $NiBr_2$bipy catalysis.

Introduction

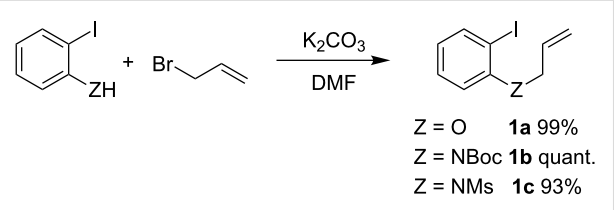
Carbometalation is a reaction involving the addition of an organometallic species to a nonactivated alkene or alkyne to form a new carbon–carbon bond and generate a new organometallic entity, which may subsequently undergo synthetic transformations [1,2]. Even though these reactions have been known for over 85 years [3], they have emerged as practical organometallic tools only during the past forty years, in particular through the development of palladium chemistry [4]. The catalytic cycle starts with the oxidative addition of Pd(0) to generate a σ-arylpalladium(II), then a rapid insertion of a double or triple bond takes place [5]. This method was particularly applied in the "Mizoroki–Heck reaction" [6] for the synthesis of pharmaceutical and agrochemical intermediates using nonactivated olefins with high regio- and stereoselectivity [7]. Besides the typical intermolecular version, some intramolecular variants were developed leading to useful heterocycles [8-10]. Even if palladium is very efficient, nickel appears to be among the most promising metallic substitutes [11]. However, the tedious preparation of Ni(0) complexes such as $Ni(cod)_2$ explains that nickel chemistry is hardly perceived as a realistic alternative to palladium, except in electrochemical processes [12,13]. Nevertheless, some nickel-catalyzed Heck vinylations have been recently reported on activated olefins [14,15]. Some years ago, we showed that the in situ generation of Ni(0)

complexes in the presence of both the aromatic halide and the electrophile [16] represents an interesting alternative to electrochemical processes. The main advantages of the method are the use of an easily prepared Ni(II)bipy complex in combination with manganese dust as a reducing agent, which is not air sensitive, is compatible with fragile functions, and can be used in a catalytic amount. We showed that this nickel catalysis applies to cross-coupling reactions, efficiently leading to a variety of functionalized 2-arylpyridines [17]. More recently, this nickel-catalyzed reaction provided a convenient and mild method for a one-pot synthesis of substituted benzofurans, chromans and indoles by carbonickelation of alkynes [18]. We finally decided to extend the scope of this heterocyclization reaction to various nonactivated olefins in a nickel-catalyzed intramolecular base-free Heck-type coupling.

Results and Discussion

Scope of the reaction

We applied the Nickel-catalyzed intramolecular base-free Heck-type coupling to two model substrates, assumed to provide either a benzofuran or an indole core. Our first study involved the cyclization of allyl moieties such as allyl ether **1a** or *N*-allyl protected anilines **1b–c**, easily prepared by quantitative allylation of *o*-iodophenol and o-iodoanilines using allyl bromide in DMF (Scheme 1).

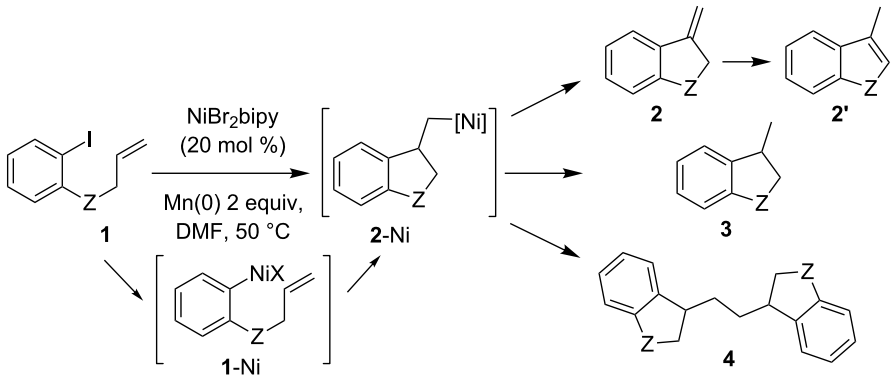


Scheme 1: Synthesis of substrates **1a–c**.

Following the protocol optimized for the carbonickelation of triple bonds [19], we exposed **1a–c** to a mixture containing 0.2 equiv of $NiBr_2$bipy and 2 equiv of finely grown manganese in DMF containing trace amounts of trifluoroacetic acid at 50 °C (Table 1). Disappointingly, using **1a** the major new product recovered was the dimer **4a**, obtained with trace amounts of several other byproducts (Table 1, entry 1). The formation of this symmetrical dimer suggests that: (i) the oxidative addition of Ni(0) into the carbon–iodine bond leads to **1a**-Ni, which triggers a 5-*exo*-*trig* carbonickelation on the terminal olefin; (ii) the resulting **2a**-Ni does not undergo the expected Ni–H elimination but probably evolves by disproportionation [20] leading to $alkyl_2Ni$ and $NiBr_2$bipy [21,22]. The subsequent reductive elimination of $alkyl_2Ni$ would explain the formation of the dimer **4a**.

In contrast, the carbonickelation of **1b** led to an equimolar mixture of the expected 3-methylindole **2b'** (3-methyleneindoline **2b** rearranging into 3-methylindol **2b'**, probably during work-up) and 3-methylindoline **3b** in an overall good 60% isolated yield (Table 1, entry 2). The formation of **3** is probably due to the sluggishness of the NiH elimination, which allows for the

Table 1: Carbonickelation of compound **1a–c**.

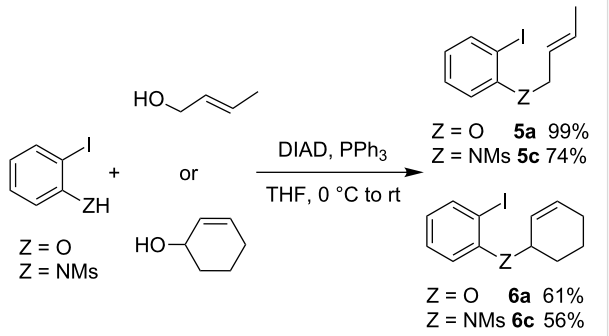


entry	ArI	Z	ratio **2**/**2'**/**3**/**4**[a]
1	**1a**	O	ε/ε/ε/100 (26%[b])
2	**1b**	N-Boc	0/50/50/0 (60%)
3	**1c**	N-Ms	61/26/13/0 (60%[c])
4[d]	**1c**	N-Ms	40/22/38/0 (69%[c])

[a]Determined by NMR, isolated yield between brackets; [b]trace amounts of **2a**, **2a'** and **3a** were identified as well as several other byproducts; [c]NMR yield with respect to an internal standard, based on initial aryl iodide **1c**; [d]reaction run with 1 equiv of $NiBr_2$bipy.

competitive protonation of the fragile intermediate alkylnickel **2**-Ni. While the Pd-catalyzed reductive Heck reaction promoted by a hydride generated in situ is well known [23,24], the nickel-catalyzed process is likely to occur through a radical hydrogen transfer from the DMF [20,25]. The *N*-allylaniline **1c** gives the same good yield added to an attractive (**2c** + **2c'**)/**3c** ratio of 87/13 (Table 1, entry 3). Formation of the 3-methylindoline **3** is therefore disfavored when a mesyl protecting group is used instead of a carbamate. When this reaction is run with stoichiometric amounts of nickel, the reductive pathway affording indoline **3c** is slightly increased, and a (**2c** + **2c'**)/**3c** ratio of 62/38 is observed (Table 1, entry 4).

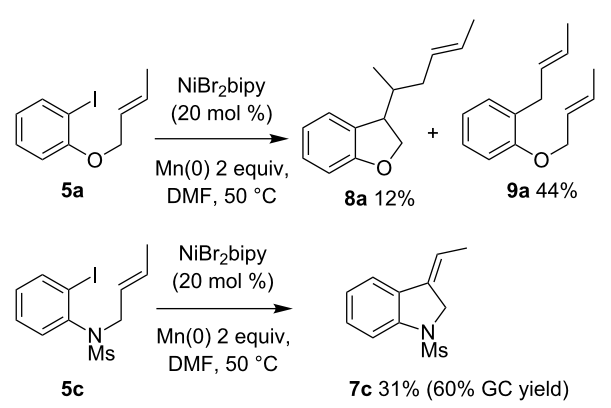
In conclusion to the first part of this study, the formation and cyclization of arylnickel intermediates **1**-Ni is observed in all cases. Afterward, the stability of the *exo*-methylene-nickel **2**-Ni seems to govern the formation of the cyclized product. Particularly, the dimerization of **2**-Ni threatens the synthetic utility of this reaction, as observed in the case of **1a**. In an effort to escape this pathway, we tried to stabilize **2**-Ni by using allyl moieties that would provide secondary alkylnickel intermediates. Crotyl and cyclohexenyl ethers and amines were thus employed instead of the allyl. Compounds **5** and **6** were easily prepared by a Mitsunobu condensation involving 2-iodophenol or 2-iodo-*N*-mesylaniline and crotyl alcohol or cyclohex-2-enol (Scheme 2). An *N*-mesyl derivative was retained, with a lesser amount of indoline **3** being obtained above when this protecting group was employed.



Scheme 2: Synthesis of substrates **5a**, **5c**, **6a** and **6c**.

The carbonickelation protocol was applied to the cyclization of crotyl derivatives **5** (Scheme 3).

When applied to ether **5a**, as expected, the substitution of the allyl moiety at the terminal position by a methyl tends to disfavor the dimerization of the alkylnickel intermediate, and type-**4** dimers are no longer observed. However, the expected cyclized compound **7a** is obtained only in trace amounts, with



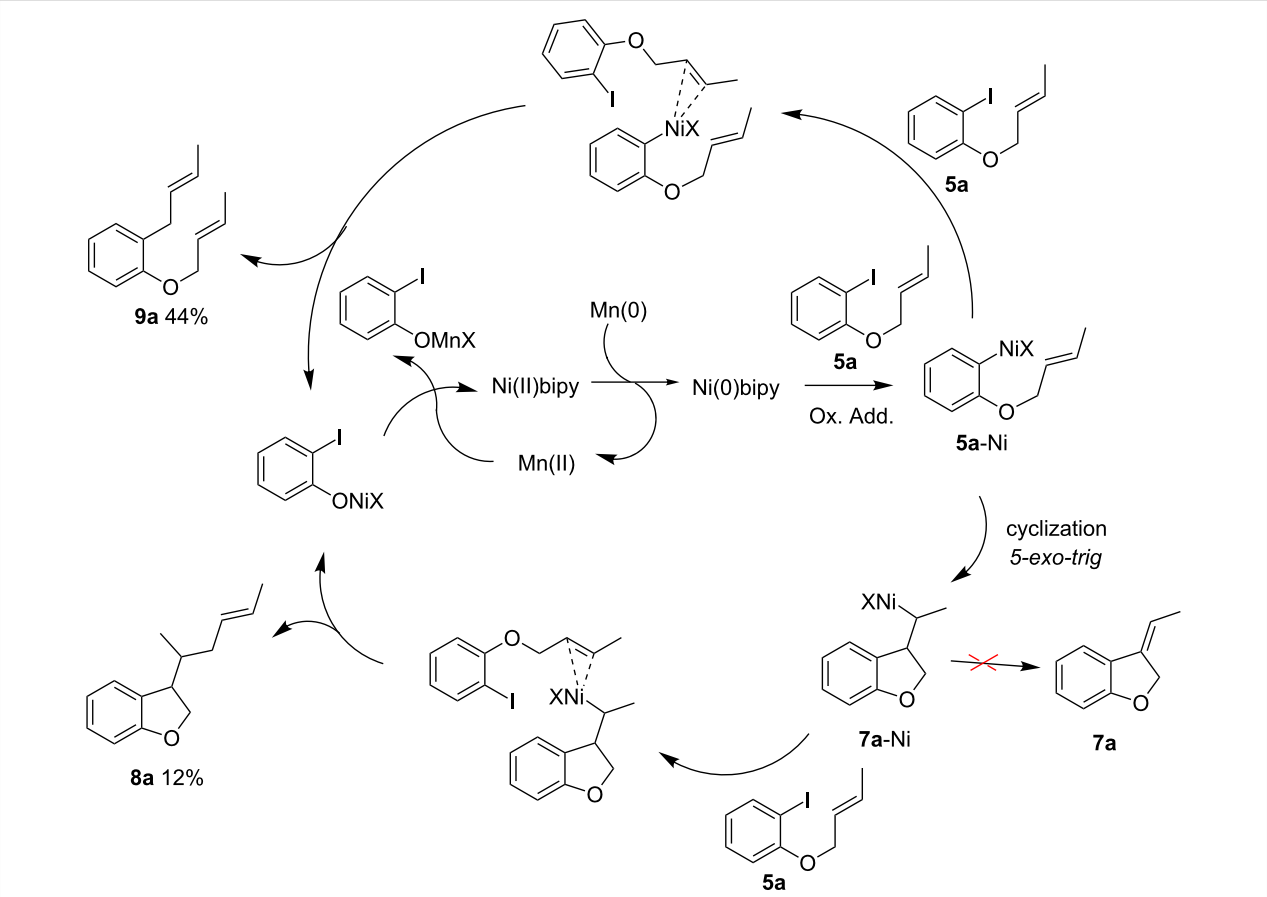
Scheme 3: Cyclization of substrate **5a** and **5c**.

the major products isolated being compounds **8a** and **9a**. Formation of these unexpected products could result from the consecutive intermolecular reactions between **5a** and the alkylnickel **7a**-Ni or the arylnickel **5a**-Ni, respectively (Scheme 4). This reactivity is not unexpected: allyl ethers are known to be good allylating agents in the presence of nickel-bipyridine complexes [26,27]. In addition, the electroreductive allylation of aromatic or heteroaromatic halide and allylic acetate [28,29] was successfully carried out using nickel-bipyridine complexes as catalysts in DMF. More recently, Weix noted that the same reaction could be achieved under chemical conditions, always using bi-(or ter-)pyridine nickel catalysts [30]. These data explain the formation of **9a**. Finally, the **8a**/**9a** ratio suggests that **5a**-Ni can undergo two competitive pathways: the 5-*exo*-*trig* cyclization leading to **7a**-Ni, and the aromatic allylation affording **9a**. Based on the figures we conclude that **5a**-Ni reacts more rapidly with the allyl derivative than it cyclizes.

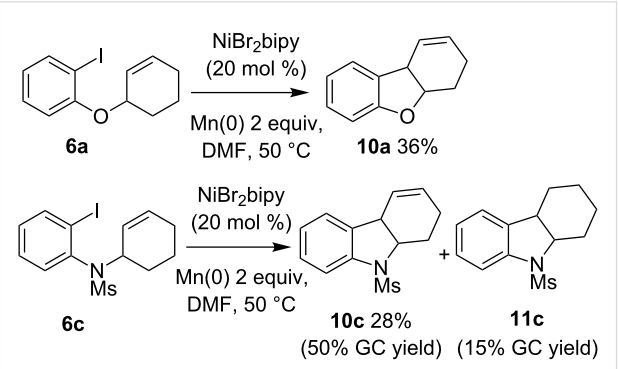
Under the same conditions, *N*-mesylaniline **5c** is more efficient (Scheme 3), and the expected cyclized product **7c** is obtained as the major product (60% GC yield, 31% isolated yield due to the instability of the exocyclic double bond during the purification) [31].

In the cyclohexenyl series, we were pleased to observe that ether **6a** affords only the benzofuran **10a**, but the conversion is limited (30% of the starting material **6a** is recovered) and the yield modest (36% isolated, 51% based on recovered material, Scheme 5).

Interestingly, the intracyclic character of the double bond in **6** appears to influence the relative kinetics of the competing reactions in favor of both the carbonickelation and the β-elimination (thus the Heck-type coupling) over the formation of a π-allyl complex that would afford allylation products such as **8** or **9**. In the aniline series, the indole **10c** (50% GC yield, 28%



Scheme 4: Proposed mechanism involving π-allylnickel formation.

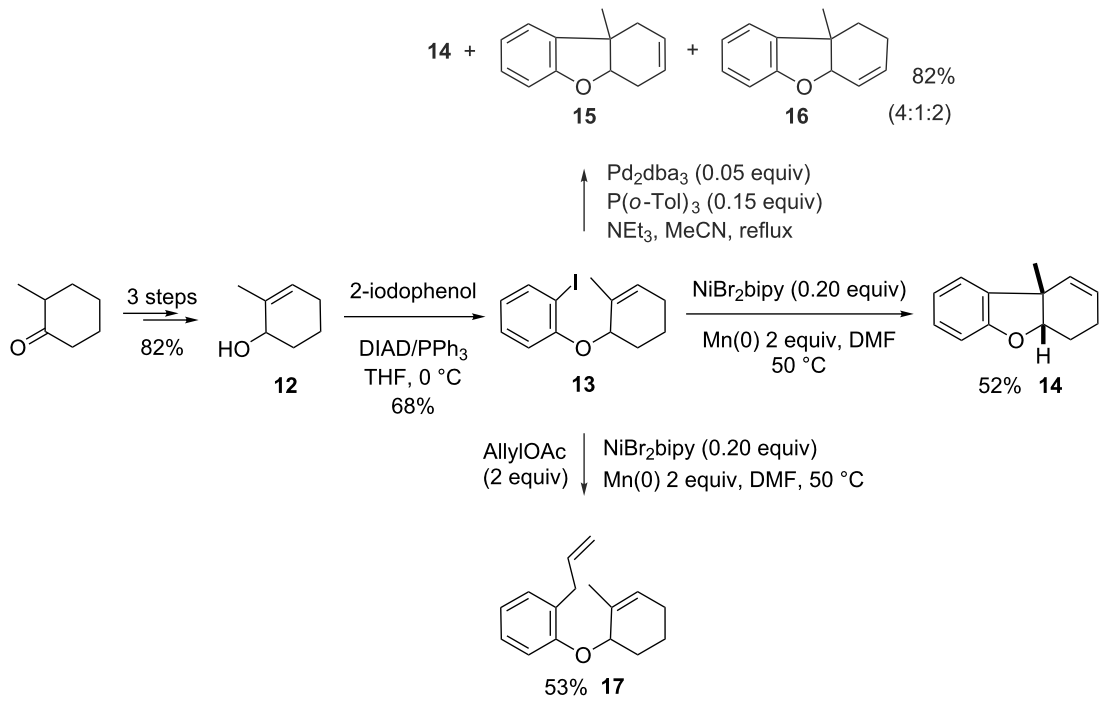


Scheme 5: Cyclization of substrate **6a** and **6c**.

isolated yield) is obtained together with the indoline **11c**, in an indol/indoline **10c**/**11c** ratio of 80/20.

Creation of an all-carbon quaternary center at a ring junction

The success of the above experiments prompted us to conduct this reaction with trisubstituted olefins, in an effort to construct tricyclic skeletons with an all-carbon quaternary center at a ring junction. This pattern is found in important natural products such as morphine whose ACE ring system exhibits a tetrahydrodibenzofuran motif with an angular ethylamino chain on C13. We thought that the nickel-catalyzed intramolecular carbometalation reaction could help to tackle the problem of the central ring (E) closure. To validate this hypothesis, we retained substrate **13** as a simplified working model. If ether **13** is little functionalized, it bears the methylvinyl moiety that is essential to the construction of the quaternary ring junction. Substrate **13** was prepared by a simple Mitsunobu condensation between 2-methylcyclohex-2-enol (**12**), a known compound prepared in three steps from commercially available 2-methylcyclohexanone and 2-iodophenol (Scheme 6). The carbonickelation protocol applied to **13** led in one hour to the expected (and sole) tricyclic product **14** in 52% isolated yield, resulting from a nickel-catalyzed intramolecular base-free Heck-type coupling and exhibiting an all-carbon quaternary center at a cis-ring junction (as established by NOESY experiments). This result, added to that obtained above with aryl ether **6a**, underlines that the endocyclic character of the unsaturation is essential to favor the Heck coupling. The carbonickelation process leads to a secondary alkylnickel intermediate, which is sufficiently stabilized to



Scheme 6: Synthesis and carbometalations of **13**.

avoid the side reactions observed above. Actually, the carbonickelation remains the rate-determining step as suggested by an experiment in which allyl acetate was mixed with **13** before the addition of the catalyst (Barbier conditions). In this case, the only product was the allylated aryl derivative **17**, recovered in comparable yields, suggesting that in the presence of a good allyl donor, the σ-arylnickel undergoes an intermolecular allylation quicker than the intramolecular carbonickelation.

From a synthetic point of view, it is interesting to note that **14** was obtained as only one isomer, the double bond remaining at the location imposed by the nickel hydride elimination. In order to compare the Ni-catalyzed version to the Pd(0) one, the same reaction was run following the protocol recently described by Fukuyama [32] in the key-step of his total synthesis of morphine. Under these conditions, the cyclization took place in an excellent 82% yield after 3.5 h, but a mixture of the three regioisomers **14**–**16** was recovered (Scheme 6). By contrast, under Larock's conditions [33] [$Pd(OAc)_2$ (5 mol %), Na_2CO_3, DMF, 80 °C], an even higher yield (90% after 2 days) was returned but consisted of a 1:1:1 mixture of the same three products **14**–**16**. Replacing sodium carbonate by silver carbonate avoids these post-cyclization isomerizations [34,35], but the yield (52% after 16 h) was not higher than with nickel. Thus, this study suggests that a Heck-coupling reaction relying on a carbonickelation step can be considered as a useful tool in the total synthesis.

Conclusion

In this work, we have shown that the $NiBr_2$bipy complex can be used to catalyze an intramolecular Heck-type reaction in the absence of any additional base. This glove-box-free procedure occurs using 20% of $NiBr_2$bipy and does not require the handling of air- or moisture-sensitive reagents. Thus, this single process gives access to a simplified model of the trinuclear ACE core of morphine. Beyond the appeal of the possible replacement of expensive palladium by cheap nickel, the absence of post-coupling isomerization of the double bond seems particularly worthy of note.

Experimental

General procedure for the intramolecular carbonickelation of alkenes

To a solution of aryliodide (0.5–1 mmol, 1 equiv) in anhydrous DMF (5 mL) under argon atmosphere at 50 °C is added manganese (2 equiv) followed by $NiBr_2$bipy (0.2 equiv) then rapidly TFA (20 μL). The medium is vigorously stirred at 50 °C, and disappearance of the starting material is monitored by gas chromatography. The mixture is hydrolyzed with water (10 mL), diluted with Et_2O (10 mL), and then filtered through celite. The aqueous layer is extracted with Et_2O (2 × 10 mL), and then the combined organic layers are washed with water (3 × 10 mL) and brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude is purified by flash chromatography.

cis-9b-methyl-3,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan (**14**)

The compound **14** is obtained by using ether **13** (314 mg, 1 mmol), $NiBr_2$bipy (75 mg, 0.2 mmol), and manganese powder (110 mg, 2 mmol) in anhydrous DMF (5 mL) following the carbonickelation procedure. The pure **14** (97 mg, 0.52 mmol, 52%) is isolated from the crude by flash chromatography on silica (2% of Et_2O in *n*-pentane) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) 1.41 (s, 3H), 1.78–2.03 (m, 2H), 2.18–2.31 (m, 2H), 4.62 (t, *J* = 3.6 Hz, 1H), 5.51–5.56 (m, 1H), 5.68–5.75 (m, 1H), 6.79 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.87 (td, *J* = 7.2, 0.9 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.12 (td, *J* = 6.6, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 19.4, 23.3, 25.1, 44.4, 87.8, 110.0, 120.7, 122.9, 125.5, 128.1, 132.1, 135.8, 158.9; NMR 2D NOESY: correlation between 1.41 (s, 3H) and 4.62 (t, *J* = 3.6 Hz, 1H); IR (neat): 3018, 2956, 1595, 1474, 1232, 1039 cm^{-1}; MS (CI) *m*/*z*: 186 (M^+), 171 (M − Me, base), 143, 128; HRMS (EI): calcd for (M^+) $C_{13}H_{14}O$: 186.1045; found: 186.1049.

Supporting Information

Supporting Information File 1

Experimental procedures and compound characterization.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-81-S1.pdf]

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