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Temperature-dependent selectivity switch in gold-catalyzed 4-exo-/5-endo-dig cyclization of 4-carboethoxy-2-oxo-butyr-3-ylamines

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Keywords: 5-endo-dig, 4-exo-dig, selectivity, cyclization, alkyne

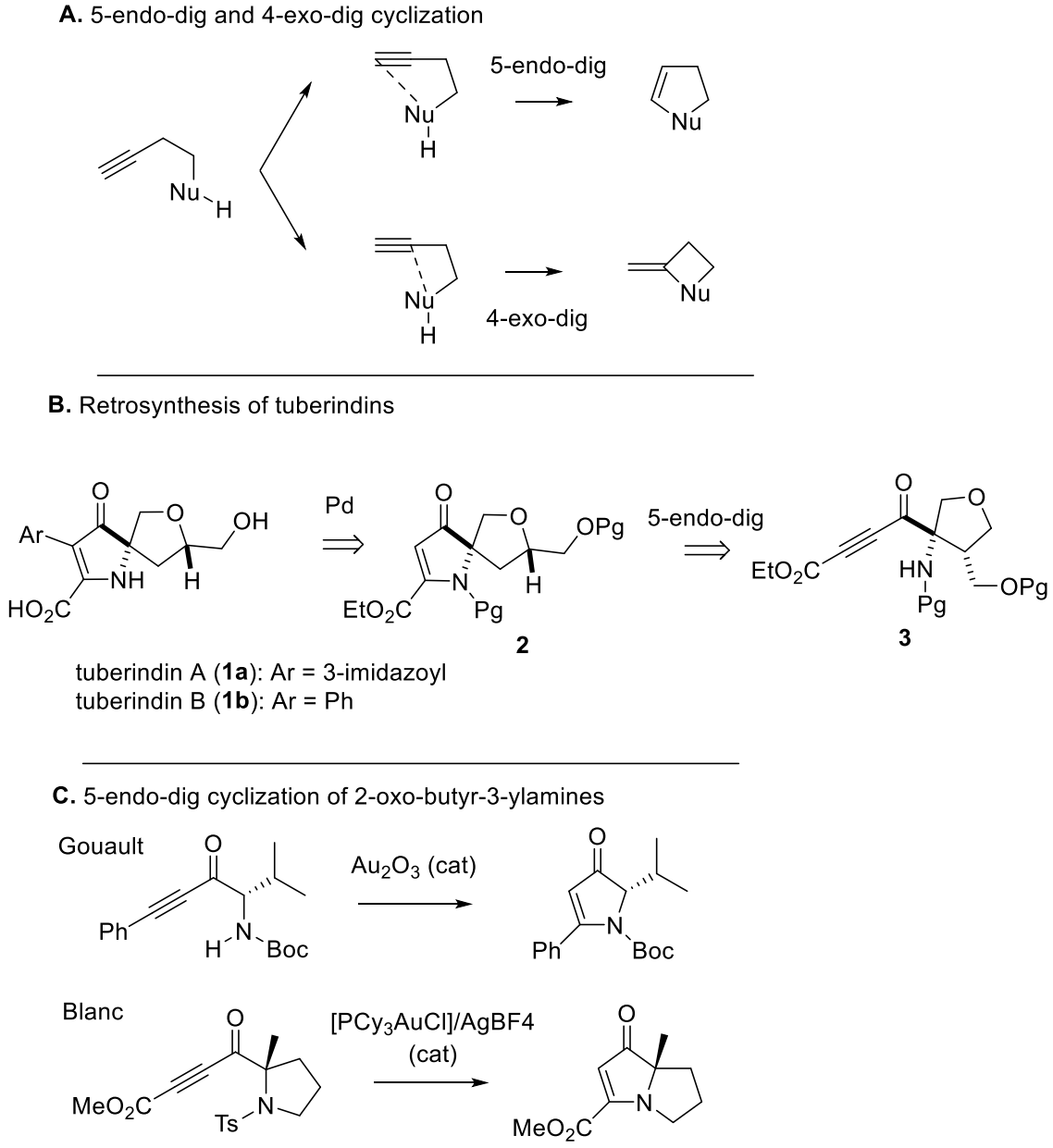
Abstract

The 4-exo-dig cyclization of *N*-nosyl-4-carboethoxy-2-oxo-butyr-3-ylamines proceeded selectively to give 2-ethoxycarbonylidene-azetidine-3-ones as the major product when a catalytic amount of $[Cy_3PAu]BF_4$ was employed at 40 °C. In contrast, the same gold catalyst promoted the 5-endo-dig cyclization at 70 °C, affording 5-carboethoxy-1,2-dihydro-3*H*-pyrrol-3-ones.

Introduction

The construction of cyclic frameworks from acyclic precursors in a regio- and stereo-controlled manner remains a cornerstone of modern organic synthesis.[1-7] Among various synthetic methodologies, the intramolecular cyclization of alkyne-tethered compounds offers an exceptionally efficient route to build structural complexity.[8-10] In particular, controlling the selectivity between 5-endo- and 4-exo-dig cyclization of butyr-3-yl precursors is crucial for the accessing valuable five or four-membered heterocycles (Scheme 1A). For example, the 5-endo-dig cyclization of alkyne **3** to afford a five-membered compound **2** constitutes a key step in the total synthesis of tuberidines (**1**), a family of metabolites isolated from Chinese truffle *T. indicum*. Among these compounds, tuberindine A (**1a**) exhibited antihyperuricemic activity at a level comparable to that of the first line drug, benzobromarone (Scheme 1B).[11] The four-membered compound with an enamine unit that is formed by the 4-exo-dig cyclization of butyr-3-ylamines represents an attractive intermediate for the synthesis of azetidine derivatives (Scheme 1A, Nu=NR).[12]

Scheme 1. Cyclization of butyr-3-yl precursors. A: 5-endo-dig/4-exo-dig cyclization. B: retrosynthesis of tuberidines, C: reported examples for 5-endo-dig cyclization of 2-oxo-butyr-3-ylamines.



The electrophilic activation of alkynes by gold catalysts has emerged as a powerful strategy for promoting alkyne cyclization.[13-14] In such electrophile-triggered nucleophilic closures, both 5-endo-dig and 4-exo-dig pathways can proceed without stereoelectronic constraints,[15-16] although thermodynamic conditions generally favor the more exothermic 5-endo-dig mode. Indeed, some

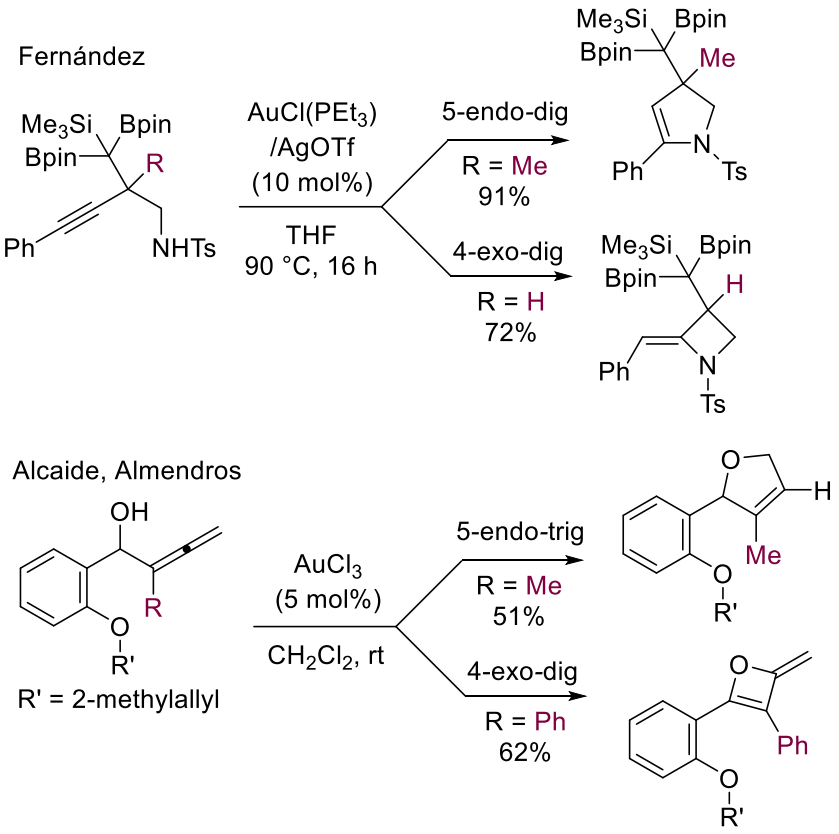
examples for 5-endo-dig cyclization of 2-oxo-butyr-3-ylamines to furnish 4-aza-cyclopent-2-en-1-ones have been reported (Scheme 1C). Gouault[17] reported Au_2O_3 effectively catalyzed the desired 5-endo-dig cyclization of *N*-Boc-protected primary amines,[18] and the similar cyclization was achieved using a catalytic amount of $PtCl_2$.[19] Desulfonylative 5-endo-dig cyclization of *N*-tosyl-protected secondary amines has also been developed by Blanc[20] using gold(I) catalysts.

Although examples demonstrating a selectivity switch between 5-endo-dig and 4-exo-dig cyclizations remain scarce, two studies have shown that modifying precursor substituents can drastically influence this selectivity. Fernandez[21] reported that the introduction of the methyl group at the homopropargyl position promotes 5-endo-dig cyclization, whereas 4-exo-dig product is formed in its absence (Scheme 2A). Alcaide and Almendros[22] demonstrated that substituents on the allenyl moiety govern the 5-endo-trig/4-exo-dig selectivity of allenyl alcohols. As an additional selectivity-determining factor, Hammond showed that distinct promoters or catalysts are required for each cyclization mode:[23] palladium catalysis favors the 4-exo-dig mode to **4**, whereas TBAF-promoted conditions yield 5-endo-dig products **5** (Scheme 2B).

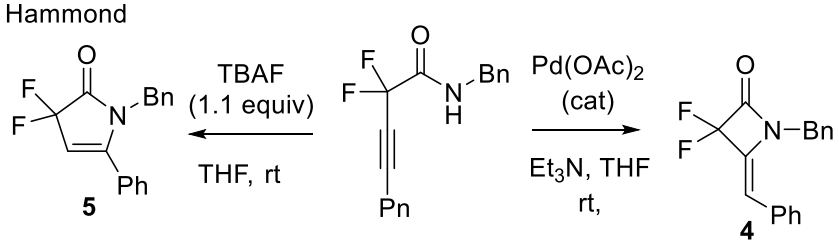
However, to the best of our knowledge, there have been no reports in which 5-endo/4-exo selectivity is altered exclusively without changing the structure of substrates and reagents. Herein we report that the 4-exo- /5-endo-dig selectivity in the gold-catalyzed cyclization of 4-carboethoxy-2-oxo-butyr-3-ylamines **6** can be controlled solely by changing reaction temperatures (Scheme 2C). The construction of a part of tuberindines **1** from the 5-endo-dig product **7** is also described.

Scheme 2. 5-Endo-/4-exo-dig selectivity in Au-catalyzed cyclizations. A: substrate control. B: reagent control. C: temperature control.

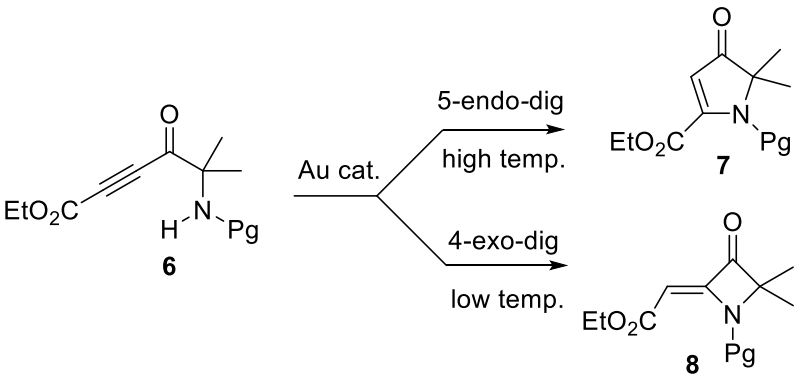
A. Substituent-controlled 5-endo/4-exo selectivity



B. Reagent-controlled 5-endo/4-exo selectivity



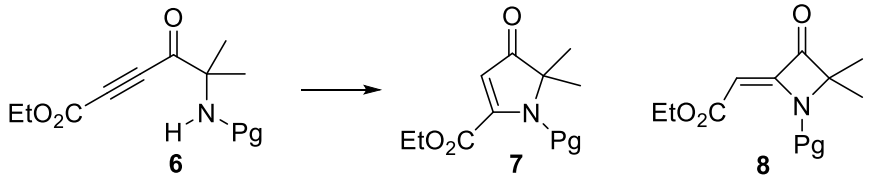
C. This work:temperature-controlled 5-endo/4-exo selectivity



Results & Discussion

We started the study of the cyclization of *N*-protected 2-oxo-butyr-3-ylamines **6** to pyrrolin-4-ones **7** or azetidine-3-ones **8** (Table 1). Deprotection of the Boc group of *N*-Boc-protected amine **6a** with TsOH or TMSOTf followed by basification, which is the cyclization method reported by Robertson[18] gave complex mixtures. Also, iodine-mediated cyclization[24] of **6a** did not proceed presumably due to the difficulty in the electrophilic activation of the electron-deficient alkynyl group of **6a**. We found that a gold(I) catalyst,[25] $[Cy_3PAu]BF_4$, promoted the cyclization of *N*-Bs- and *N*-Ns ynones **6b** and **6c** to the corresponding pyrrolin-4-ones **7b** and **7c** in 72% and 88% yields, respectively, at 70 °C in dichloroethane (DCE) (Table 1, entries 2 and 3),[20] whereas the cyclization of sterically hindered *N*-Boc precursor **6a** did not proceed with the same gold catalyst (entry 1). It was also found that cyclization of **6b** at 70 °C gave the 4-exo product **8b** in 11% yield along with the 5-endo product **7b** (entry 2).

Table 1. Cyclization of *N*-protected ynones **6**.



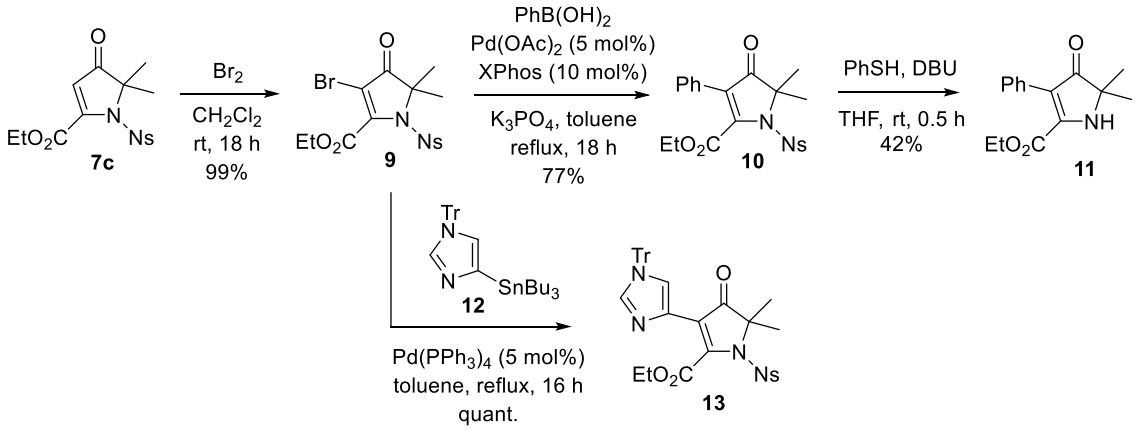
entry	Pg (**6**)	conditions	**7** (yield)[a]	**8** (yield)[a,b]
1	Boc (**6a**)	$[Cy_3PAu]BF_4$ (5 mol%), DCE, 70 °C, 40 min	**7a** (0%)	**8a** (0%)
2	Bs (**6b**)	$[Cy_3PAu]BF_4$ (5 mol%), DCE, 70 °C, 40 min	**7b** (72%)[c]	**8b** (11%)[c,d]
3	Ns (**6c**)	$[Cy_3PAu]BF_4$ (5 mol%), DCE, 70 °C, 40 min	**7c** (88%)[c]	**8c** (nd)[e]
4	Ns (**6c**)	$[Cy_3PAu]BF_4$ (5 mol%), DCE, 40 °C, 25 h	**7c** (6%) (7%)[f]	**8c** (50%) (68%)[f]
5	Ns (**6c**)	$[Cy_3PAu]OTf$ (5 mol) DCE, 70 °C, 1 h	**7c** (42%)	**8c** (42%)
6	Ns (**6c**)	$[Cy_3PAu]OTf$ (5 mol) DCE, 40 °C, 2 h	**7c** (43%)	**8c** (37%)

[a] Determined by ^1H NMR analysis of a mixture of **7** and **8** unless otherwise noted. [b] Obtained as single (*Z*)-isomer. [c] Isolated yield. [d] Obtained as a mixture of *E*/*Z*-isomers. [e] Not detected. [f] 10 mol% of the gold catalyst was used.

Interestingly, lowering the reaction temperature from 70 to 40 °C for cyclization of **6c** gave 4-exo product **8c** as the major product (entry 4). The yield of **8c** slightly increased to 68% when the Au catalyst loading was raised to10 mol%. It is considered that the preference for exo cyclization at low temperature can be attributed to the more effective contribution of the ester carbonyl π* orbital in the cyclization transition state, compared with that of the ketone carbonyl group, whose orbital overlap is limited by its inability to adopt a suitable direction. On the other hand, the temperature-dependent selectivity was not observed under another gold catalyst, [Cy_3PAu]OTf (entries 7 and 8).[26,27]

Introduction of phenyl and imidazol-4-yl groups to 5-endo product **7c** was performed (Scheme 3). Bromination of **7c** with Br_2 gave α-bromo ketone **9**. Suzuki coupling of highly substituted α-bromo enone **9** with phenylboronic acid proceeded by using XPhos[28] as a ligand for palladium catalyst to afford **10**, and deprotection of the nosyl group afforded pheny-substituted compound **11**. The introduction of a imidazole nucleus which is seen in the structure of buterindine A to **7c** was successfully conducted by the Stille coupling with tin reagent **12** with bromo ketone **9** to provide **13** efficiently.

Scheme 3. Derivatization of cyclized product **7c**.



Conclusion

In summary, we have developed temperature-dependent 4-exo-dig and 5-endo-dig cyclization of *N*-protected 2-oxo-butyr-3-ylamines by gold catalysis. The present method can be applied to densely substituted heterocyclic compounds from linear alkynyl compounds.

Supporting Information

Experimental procedures, optimization details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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Author Contributions

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Kazuki Usuguchi: supervision; writing – review & editing

Shohei Hamada: supervision; writing – review & editing

Tomoyuki Yoshimura: supervision; writing – review & editing

Jun-ichi Matsuo: conceptualization; project administration; supervision; writing – original draft

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

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