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Formal Alkyne Aza-Prins Cyclization: Gold(I)-Catalyzed Cycloisomerization of Mixed N,O-Acetals Generated from Homopropargylic Amines to Highly Substituted Piperidines

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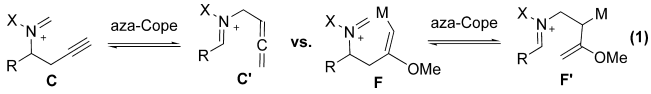
Highly substituted piperidines are found in numerous bioactive alkaloid natural products and pharmaceuticals.[1] Thus, considerable attention has been paid to the synthesis of this moiety.[2] We envisioned that cycloisomerization of mixed N,O-acetal **A** generated from homoproparygylic amines to 4-methoxy-1,2,3,6-tetrahydro-pyridine **B** (Scheme 1) would be highly useful in accessing piperidine frameworks, because the enol ether could be easily transformed into other functional groups.

Based on the well-established chemistry of iminium ions, we initially considered using an oxophilic metal-catalyzed method depicted in pathway 1.[3] In this scenario, the key step involves the endocyclization of iminium ion **C** onto alkynes (alkyne aza-Prins reaction).[4] Apparently simple reactions of this type have been surprisingly rare, due to the slow cyclization of **C** to form unstable vinyl cation **D** and the rapidly competing aza-Cope rearrangement of **C** (eq 1).[5] In fact, this type of alkyne aza-Prins reaction reported in the literature has been limited to the 4-amino-1-butyne substrates possessing no branch alkyl groups.[6,7]



In view of the above-mentioned inherent problems associated with the classical alkyne aza-Prins reactions, we envisioned an alternative pathway promoted by the addition of the methoxy group onto the metal-activated alkynes (pathway 2).[8,9] Even though generation of iminium ion **F** via this pathway is unprecedented, we were highly encouraged by alkoxycyclization-induced generation of an oxacarbenium ion reported by Zhang.[10] Moreover, the methoxy group should accelerate cyclization of **F** (Scheme 1) to form relatively stable carbocation **G**. Thus, we anticipated that potential limitations derived from aza-Cope rearrangement of **F** could be minimized in this pathway (eq 1).[11]

To test the viability of this catalytic cycle, we examined easily accessible mixed N,O-acetal **1a** possessing an electron-withdrawing tosyl group. Based on our previous experience in the related area,[9b] we explored various cationic gold(I) complexes. While using 2 mol % of **4a** showed poor conversion (~10%), switching to a more electrophilic complex **4b** (2 mol %) quickly completed the reaction to generate the methoxypyridine **2a** in 86% yield (Table 1, entry 1) with no hydrolysis of the starting material.[12a] In this case, formation of the piperidin-4-one **3a** (~10% yield) was noted, which arose from the hydration of **2a**. After extensive efforts to minimize this undesired hydration, we discovered that the addition of 1.6 mol % (0.8 equiv to Au) of 2,6-di-*tert*-butylpyridine (2,6-DBP) improved the yield to 96%

Scheme 1. Two Pathways for the Cycloisomerization of A

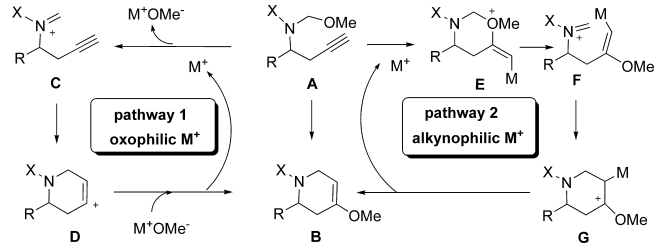
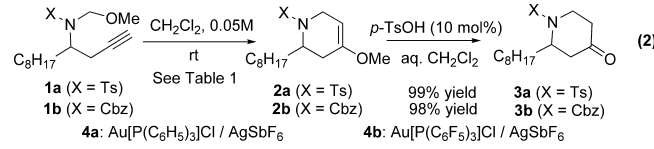


Table 1. Optimization of the Reaction Condition

entry	substrate	catalyst (mol %)	additive (mol %)	time (min)	product	yield[a]
1	**1a**	**4b** (2)	–	10	**2a**	86[b]
2	**1a**	**4b** (2)	2,6-DBP (1.6)	10	**2a**	96 (95[c])
3	**1b**	**4b** (2)	–	10	**2b**	55[d]
4	**1b**	**4b** (2)	2,6-DBP (1.6)	10	**2b**	91 (89[c])

[a] Isolated yield. [b] Ketone **3a** was obtained in 10% yield. [c] Isolated yield of the ketone after hydration. [d] Ketone **3b** was obtained in 35% yield.

with little effect on the catalytic efficiency (entry 2).[12b,c] The synthetic utility of **2a** was easily demonstrated by the conversion into **3a** in 99% yield under acidic conditions. Interestingly, even the cbz-derived mixed acetal **1b** was successfully engaged in the reaction to give the mixture of cycloisomerization product **2b** and the ketone **3b** in comparable 90% combined yield.[12d,e] Again, addition of 2,6-DBP suppressed the hydration, improving the yield of **2b** to 91%. The unstable methoxytetrahydro-pyridine **2b** was then converted into piperidin-4-one **3b** in 98% yield.[12f]



With the optimized conditions in hand, we explored the scope of the gold(I)-catalyzed cycloisomerization using mixed acetals generated from tosyl- or cbz-protected homopropargylic amines (Table 2).[13] Moreover, all cycloisomerization products except for entry 3 were converted into the corresponding piperidin-4-ones for characterization.[14] Remarkable chemoselectivity was noted. For example, a potentially competing Friedel–Craft reaction of the acyliminium ion generated from substrate **5** was not observed (entry 1). The reaction was also compatible with terminal olefin (entry 2), and even with the acid-labile cyclic acetal group (entry 3). Next, we explored the effect of alkyl substitution on the cycloisomerization. Elimination (entry 4) or addition (entry 5) of an akyl group at the homopropargylic position

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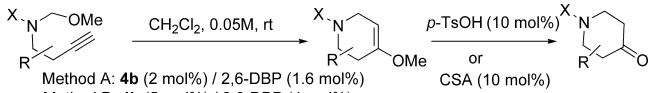
Table 2. Scope of the Gold(I)-Catalyzed Reaction



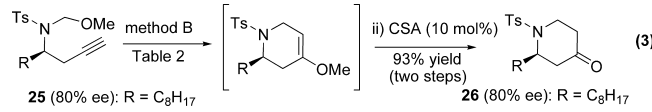
Entry	Substrate[a]	Product	Method	Yield(%)
1	**5**:R_1 =CH_2CH_2Ph	**6**	A (10min)	87[b](92[c])
2	**7**:R_1 =$(CH_2)_7CH{=}CH_2$	**8**	A (10min)	80[b](87[c])
3	**9**	**10**	A (10min)	--- (96[c])
4	**11**: R_2 = H	**12**	B (10min)	87[b](94[c])
5[e]	**13**: R_2 = -$(CH_2)_5$-	**14**	B (40min)	71[b](76[c])
6	**15**	**16**	A (10min)	88[b](93[c])
7	**17**: n = 1	**18**	B (10min)	83[b](91[c])
8[e]	**19**: n = 2	**20**	B (2 h)	63[b](---[d])
9	**21**: n = 3	**22**	B (10min)	82[b](90[c])
10	**23**	**24**	A (10min)	82 [b](84[c])

[a] Racemic substrates. [b] Two-step yield. [c] Isolated yield of the cycloisomerization product. [d] Not measured. [e] 2,6-DBP was not used.

slowed the reaction, requiring 5 mol % catalyst loading for complete conversion. In the latter case, hydration was not observed even when the reaction was performed without 2,6-DBP. Although alkyl substitution at the propargylic position in an acyclic substrate had little effect (entry 6), similar substitution in cyclic substrates possessing a *cis*-relationship of the alkyne and amine group slowed the reaction (entries 7−9). While the cycloisomerization of the cyclopentane substrate **17** (entry 7) and cycloheptane substrate **21** (entry 9) was quickly completed at rt with 5 mol % catalyst loading, the reaction of cyclohexane substrate **19** was much slower. In this case, hydration of the cycloisomerization product was observed. Thus, the cycloisomerization was performed without 2,6-DBP. The crude mixture was then treated with *p*-TsOH to give the piperidin-4-one **20** in 63% yield. Interestingly, *trans*-isomer **23** was more reactive than the *cis*-isomer **19**, providing the cycloisomerization product in 84% yield in the presence of 2 mol % catalyst.

Notably, no epimerization was observed in the reaction of the substrates possessing alkyl groups at the propargylic position.[14] This result indeed supports our hypothesis that the cyclization of the intermediate F is significantly faster than the competing aza-Cope rearrangement (eq 1). This rationale is further strengthened by the reaction of enantioenriched substrate **25**,[13] which produced **26** in 93% yield (two steps) with no loss of ee (eq 3).[15] Furthermore, this example firmly establishes the utility of the proposed reaction in the synthesis of optically active piperidin-4-ones.

In summary, we have developed a gold(I)-catalyzed formal alkyne aza-Prins reaction of mixed N,O-acetals derived from homopropargylic



(3)

amines. This new gold(I)-catalyzed reaction successfully circumvents a long-standing problem of the classical aza-Prins reaction and, thus, opens up a new way to access piperidine alkaloids. Extrapolation of the reaction to the stereoselective synthesis of 2,6-disubstituted piperidines and tetrahydropyrans, as well as the application to the total synthesis of bioactive natural products, is in progress.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139, and references cited therein.
(2) (a) Celestini, P.; Danieli, B.; Lesma, G.; Sacchetti, A.; Silvani, A.; Passarella, D.; Virdis, A. *Org. Lett.* **2002**, *4*, 1367, and references cited therein. (b) For a recent gold(I)-catalyzed approach to piperidin-4-ones, see: Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394.
(3) For reviews on the aza-Prins reactions, see:(a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, O., Heathcock, C. H., Eds.; Pergamon: New York, 1991: Vol. 2, p 1047.
(4) (a) For a recent discussion on the 2-aza Cope rearrangement of iminium ions, see:Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913, and references cited therein. (b) Similar problems have been noted in the aza-Prins cyclization, see: Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235.
(5) Unlike the endo-cyclization, the exo-cyclization of iminium ion derived from 5-amino-1-pentynes to access piperidine alkaloids is well-known, see: Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210, and references cited therein.
(6) (a) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877. (b) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612. (c) Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143. (d) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009**, *11*, 357.
(7) Our attempts for the cycloisomerization of the **1a** using various oxophilic Lewis/Brønsted acids also failed to give **2a** or the ketone **3a**.
(8) For selected reviews on the alkynophilic metal-catalyzed reactions, see:(a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (g) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (h) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.
(9) For selected examples of catalytic reactions initiated by alkoxycyclization onto alkynes, see:(a) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (b) Bae, H. J.; Baskar, B.; An, S. E.; Cheong, J. Y.; Thangadurai, D. T.; Hwang, I.-C.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2263. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (e) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432. (f) Hashmi, A. S. K.; Bührle, M.; Salathé, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059.
(10) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598.
(11) For related discussion in silicon-directed aza-Prins reaction, see: Castro, P.; Overman, L. E.; Zhang, X.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5243. (b) For an example of Prins reaction in the gold(I)-catalyzed reaction, see: Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452.
(12) (a) The catalysts **4a** and **4b** were generated *in situ* from $AuPR_3Cl$ and $AgSbF_6$. (b) Using molecular sieves to remove water significantly lowered the yield. (c) Employing more than 0.8 equiv of 2,6-DBP to the Au complex significantly slowed the reaction. (d) Changing the counteranions ($AgBF_4$, AgOTf) led to poorer conversion. (e) Using $AgSbF_6$ or HF showed no cycloisomerization. (f) One-pot reaction of substrate **1b** (2 mol % catalyst **4a**, then 10 mol % *p*-TsOH) led to the formation of ketone **3b** in slightly lower 85% yield.
(13) For the detailed procedure for the synthesis of all substrates including enantioenriched compound **25**, see the Supporting Information.
(14) Formation of single compound for the cycloisomerization was unambiguously confirmed by the ^1H NMR spectrum.
(15) At this stage, however, an alternative explanation involving sigmatropic rearrangement of F and the subsequent stereospecific cyclization of F′ (see eq 1) cannot be completely ruled out.

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