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A Two-Step, Formal [4 + 2] Approach toward Piperidin-4-ones via Au Catalysis

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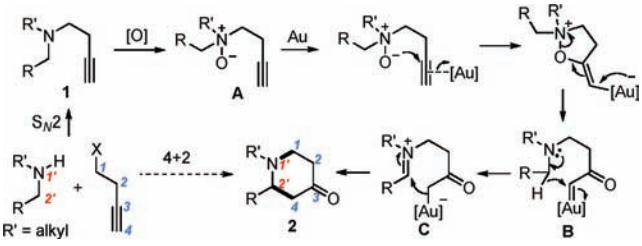
The piperidine ring is an essential building block in many bioactive alkaloids, and modular constructions of functionalized piperidines such as piperidin-4-ones can serve as powerful tools in alkaloid synthesis.

In our ongoing program of expanding gold catalysis[1] into N-heterocycle synthesis, we have developed an efficient, two-step synthesis of piperidin-4-ones in a formal [4 + 2] manner from secondary amines. Herein, we disclose the details of this chemistry, including its regioselectivity and diastereoselectivity as well as its application in a highly diastereoselective synthesis of (±)-cermizine C.[2]

We have previously reported that in situ-generated tertiary aniline *N*-oxides can oxidize tethered terminal C—C triple bonds in the presence of $Ph_3PAuNTf_2$, generating α-oxo gold carbene intermediates and subsequently affording tetrahydrobenzazepinones.[3,4] We anticipated that tertiary aliphatic amine *N*-oxide **A**, readily generated from tertiary amine **1** substituted with a 3-butynyl group, might undergo similar gold-catalyzed intramolecular alkyne oxidation, leading to α-oxo gold carbene **B** (Scheme 1); furthermore, we reasoned that the amine α-hydrogens in **B** could migrate to the gold carbene in the form of hydride,[5] leading to intermediate **C** containing both an electrophilic iminium and a nucleophilic gold enolate. Notably, intramolecular hydride migrations from arylacetals to gold carbenes have been proposed in a novel study by Bhunia and Liu.[6] Cyclization of **C** would afford piperidin-4-one **2**. As tertiary amine **1** can be prepared readily from a secondary amine and 3-butynyl halide/tosylate, the overall transformation would constitute a facile two-step, formal [4 + 2] synthesis of synthetically versatile piperidin-4-ones.

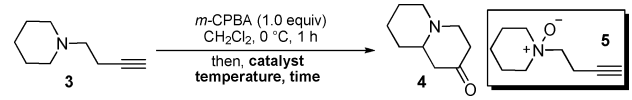
Scheme 1. Design of a Two-Step, Formal [4 + 2] Approach to the Synthesis of Piperidin-4-ones



We started with *N*-(3-butynyl)piperidine (**3**). One-pot sequential *m*-CPBA oxidation and gold-catalysis with $Ph_3PAuNTf_2$ at 0 °C indeed led to an excellent yield of bicyclic piperidin-4-one **4** (Table 1, entry 1). Running the reaction at −20 °C (entry 2) did not improve the yield, and screening of other gold(I) and other metal catalysts as well as $HNTf_2$ (1 equiv) did not lead to improved results (entries 3−9). Notably, removal of H_2O from commercial *m*-CPBA using 4 Å molecular sieve (MS) resulted in an improved yield (entry 10), and $Et_3PAuNTf_2$ worked equally well (entry 11).

We then probed the scope of this reaction using the optimized conditions with the goal of clearly defining its regioselectivity and stereoselectivity. To improve the overall efficiency of this two-step procedure, the intermediate 3-butynylamines were isolated as crude residues and used directly without column purification. As shown in Table 2, this procedure worked delightfully well with a range of secondary amines, and the overall yields of this formal [4 + 2] reaction ranged from 54 to 79%. The regioselectivity of the gold catalysis was studied in entries 1−7. It was apparent that the less-substituted alkyl groups in amine **6** were preferentially involved in the ring formation (entries 1−2) with serviceable selectivities. Electronic factors also affected the selectivity, and cation-stabilizing substituents at the amine α-carbon expectedly facilitated regioselective ring formation, albeit to a moderate extent [e.g., phenyl (entry 4)]. The enhanced selectivity in the case of 1,2,3,4-tetrahydroisoquinonine (entry 5) is notable. Interestingly, when two aryl groups were compared, a MeO group at the para position did not impart detectable selectivity (entry 6). An ester group essentially prohibited the participation of its α-hydrogens (entry 7). This facile formation of piperidin-4-ones is rather diastereoselective. Thus, when 2-methylpiperidine was used, the diastereomer with an axial methyl group (i.e., **7h**) was formed with 7:1 selectivity (entry 8); in the case of 4-methylpiperidine, only **7i** was observed (entry 9). For L-proline methyl ester hydrochloride (i.e., **6j**), 6:1 diastereoselectivity was achieved at −78 °C.[7] In addition, this chemistry allowed ready preparation of five- and seven-membered ring-fused piperidin-4-ones (entries 12 and 13), and functional groups such as TBSO (entry 14), ester (entries 7 and 10), and aryl (entries 3−6, 11) were readily tolerated.

Table 1. Reaction Optimization



entry[a]	catalyst (5 mol %)	*T* (°C)	time (h)	yield (%)[b]
1	$Ph_3PAuNTf_2$	0	1	87
2	$Ph_3PAuNTf_2$	−20	8	80
3	dichloro(2-picolinato)gold(III)	0	1	52
4	(2-biphenyl)$Cy_2PAuNTf_2$	0	1	65
5	$(4\text{-}CF_3Ph)_3PAuNTf_2$	0	1	54
6	$Ph_3PAuCl/AgSbF_6$	0	1	72
7	$AgBF_4$	0	1	0[c]
8	$PtCl_2$	0 to rt	12	0[c]
9	$HNTf_2$ (1 equiv)	0 to rt	12	0[d]
10[e]	**$Ph_3PAuNTf_2$**	**0**	**1**	**94 (85[f])**
11[e]	$Et_3PAuNTf_2$	0	1	93

[a] The reaction concentration was 0.05 M. [b] Estimated by ^1H NMR using diethyl phthalate as an internal reference. [c] With no **5** left. [d] With 94% of **5** left. [e] Using 4 Å MS (5 × weight of *m*-CPBA). [f] Isolated yield.

The diastereoselectivity of this chemistry was further probed using substrates with substituted 3-butynyl groups. While substitutions at the propargylic and homopropargylic positions were well tolerated (eqs 1 and 2), a high diastereoselectivity was observed with a propargylic *n*-propyl group (eq 2).

Besides the anticipated hydride migration mechanism shown in Scheme 1,[8] an alternative direct C−H insertion by the gold carbene in **B** could readily explain the reaction outcomes as well. To shed light on the reaction mechanism, we performed the reaction shown in eq 3 without using 4 Å

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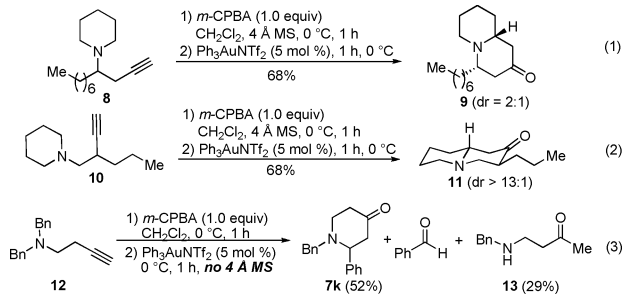
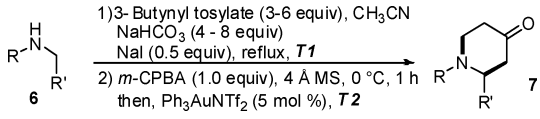
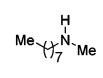
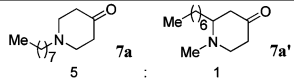
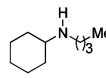
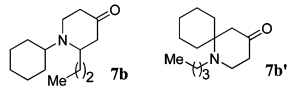
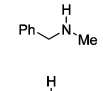
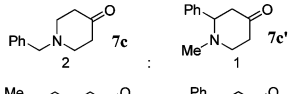
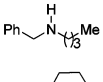
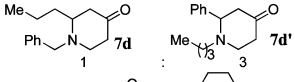
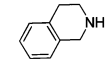
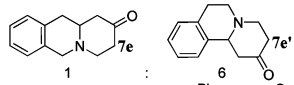
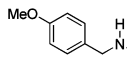
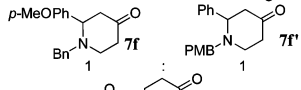
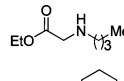
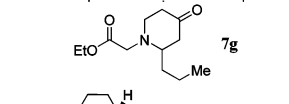
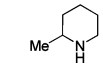
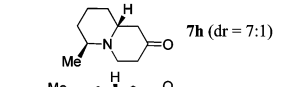
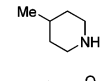
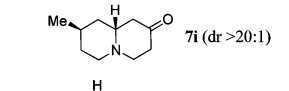
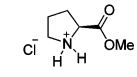
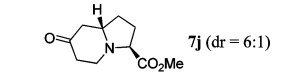
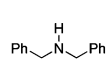
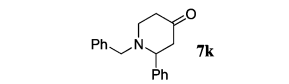
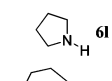
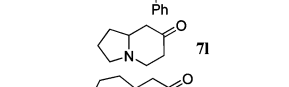
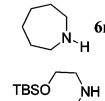
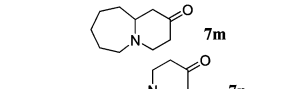
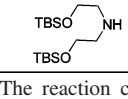
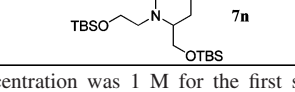


MS. If the hydride migration mechanism is operating, H_2O from commercial *m*-CPBA would hydrolyze the iminium intermediate of type **C** to give detectable side products. Indeed, benzaldehyde was observed, and amino ketone **13** was formed in 29% yield. This result argues against the direct C−H insertion mechanism and in addition suggests that the gold enolate in intermediate **C** cyclizes at a moderate rate.

Table 2. Two-step, Formal [4 + 2] Formation of Piperidin-4-ones: Scope Study



entry[a]	substrate	product	T1/T2	yield[b]
1	 **6a**	 **7a** : **7a'** = 5 : 1	20 h /1 h	70%
2	 **6b**	 **7b** : **7b'** = 5 : 1	24 h /7 h	54%[c,d]
3	 **6c**	 **7c** : **7c'** = 2 : 1	30 h /1 h	79%
4	 **6d**	 **7d** : **7d'** = 1 : 3	36 h /1 h	67%
5	 **6e**	 **7e** : **7e'** = 1 : 6	24 h /1 h	67%
6	 **6f**	 **7f** : **7f'** = 1 : 1	24 h /1 h	69%
7	 **6g**	 **7g**	24 h /1 h	66%
8	 **6h**	 **7h** (dr = 7:1)	24 h /12 h	74%[c,d,e]
9	 **6i**	 **7i** (dr >20:1)	12 h /1 h	68%
10	 **6j**	 **7j** (dr = 6:1)	5 h /12 h	65%[f]
11	 **6k**	 **7k**	36 h /1 h	64%
12	 **6l**	 **7l**	12 h /1 h	59%
13	 **6m**	 **7m**	8 h /1 h	61%
14	 **6n**	 **7n**	24 h /1 h	75%

[a] The reaction concentration was 1 M for the first step and 0.05 M for the second step. [b] Overall yield for two steps. [c] Cs_2CO_3 as the base and $Et_3PAuNTf_2$ as the catalyst were used instead. [d] Gold catalysis temperature: −20 °C. [e] DMF was used as the solvent for alkylation. [f] Gold catalysis temperature: −78 °C.

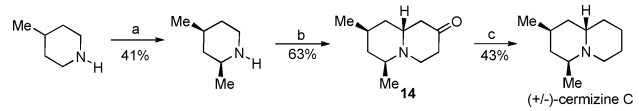


Figure 1. Diastereoselective synthesis of (±)-cermizine C. Reagents and conditions: (a) (i) $(Boc)_2O$, THF/H_2O, NaOH (1 N); (ii) $RuO_2 \cdot xH_2O$ (20 mol %), $NaIO_4$ (5 equiv), EtOAc/H_2O; (iii) MeMgBr; (iv) CF_3CO_2H, then NaOH; (v) $Pd(OH)_2/C$, H_2 (45 psi). (b) (i) 3-Butynyl tosylate, NaI, Cs_2CO_3, CH_3CN, reflux; (ii) *m*-CPBA (1 equiv), 0 °C, 1 h, then $Ph_3PAuNTf_2$ (5 mol %), 0 °C, 1 h. (c) (i) $(CH_2SH)_2$, $BF_3 \cdot Et_2O$; (ii) Raney Ni, MeOH, reflux.

This expedient two-step construction of piperidin-4-ones is a powerful method in total synthesis of alkaloids. Figure 1 outlines a highly diastereoselective synthesis[9] of (±)-cermizine C. Hence, *cis*-2,4-dimethylpiperidine,[10] prepared from 4-methylpiperidine in five steps, was readily converted into quinolizidinone **14** following this two-step sequence with the desired stereochemistry (dr > 50:1) and in a 63% overall yield; subsequent routine deoxygenation afforded the natural product as a racemic mixture.

In summary, we have developed an efficient, formal [4 + 2] synthesis of synthetically valuable piperidin-4-ones in two steps without the purification of tertiary amine intermediates. The reaction is selective toward less-hindered alkyl substituents and shows moderate to excellent diastereoselectivities. Comparing with related Rh-catalyzed C−H insertions,[11] this gold catalysis achieves formal insertions into C−H bonds without using hazardous diazo starting materials and moreover is compatible with basic amines, which usually coordinate and poison Rh catalysts.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected reviews on gold catalysis, 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) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (g) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (h) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (i) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.
(2) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. i. *Tetrahedron* **2004**, *60*, 7015.
(3) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225.
(4) For other studies involving gold-catalyzed intramolecular oxidation of alkynes, see: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (b) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156. (c) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040.
(5) For a gold catalysis with a proposed long-range hydride migration, see: (a) Lo, V. K. Y.; Wong, M. K.; Che, C. M. *Org. Lett.* **2008**, *10*, 517. For examples of hydrogens α to a heteroatom migrating as hydrides, see: (b) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (c) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625.
(6) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488.
(7) The presence of two epimeric isomers was established by NaOMe-promoted interconversion. The ratio changed from the original 6:1 to 1:1.8.
(8) It has been suggested that a gold carbene is less a carbene and more a gold-substituted cation. See: Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510.
(9) Snider, B. B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039.
(10) Dwyer, M. P.; Lamar, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 8965.
(11) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Taber, D. F. In *Carbon-Carbon σ-Bond Formation*; Pattenden, G., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, pp 1045−1062. (c) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

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