Gold-catalyzed efficient synthesis of azepan-4-ones *via* a two-step [5 + 2] annulation†

Li Cui, Longwu Ye and Liming Zhang*

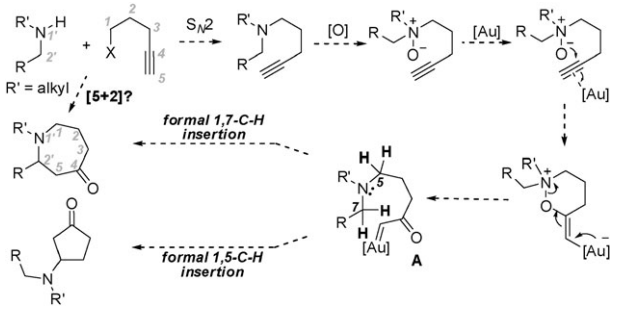
Received (in College Park, MD, USA) 20th January 2010, Accepted 18th February 2010
First published as an Advance Article on the web 30th March 2010
DOI: 10.1039/c001314e

A surprisingly efficient synthesis of azepan-4-ones *via* a two-step [5 + 2] annulation is developed. This reaction involves a key gold catalysis and shows generally high regioselectivities and good to excellent diastereoselectivities.

Azepane, a seven-membered *N*-heterocycle, is a building block frequently found in various natural products[1] including stenine,[1b] galanthamine,[1c] and croomine[1d] and a large array of compounds studied in medicinal chemistry.[2] Although functionalized azepanes can be prepared *via* various approaches,[3] methods based on synthetically flexible and versatile cycloaddition or annulation approaches are still much needed, and only a few examples[4] have been reported. Herein we report a gold-catalyzed efficient and flexible synthesis of azepan-4-ones *via* a two-step [5 + 2] annulation.

We previously reported a two-step synthesis of piperidin-4-ones in a two-step [4 + 2] manner.[5] It is speculated that a similar [5 + 2] sequence might be possible, which would afford synthetically versatile azepan-4-ones (Scheme 1).[6] This sequence might involve a gold carbene intermediate (*i.e.*, **A**) *via* a gold-catalyzed intramolecular alkyne oxidation and require favoring a challenging formal 1,7-C(sp^3)–H insertion by carbene **A**[7] over a seemingly more feasible formal 1,5-C(sp^3)–H insertion in the ring formation step.[8,9]

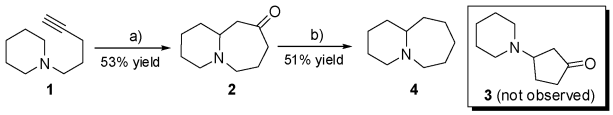
We tested the hypothesis, nevertheless, by subjecting *N*-(pent-4-yn-1-yl)piperidine (**1**) first to *m*-CPBA oxidation and then to $Ph_3PAuNTf_2$[10] catalysis without isolating the *N*-oxide intermediate (Scheme 2). The major product was isolated in 53% yield and, to our delight and surprise, assigned



Scheme 1 A two-step [5 + 2] annulation toward the synthesis of azepan-4-ones?.

Department of Chemistry and Biochemistry, University of California, CA 93106, Santa Barbara. E-mail: zhang@chem.ucsb.edu; Fax: (+01) (805) 893-4120

† Electronic supplementary information (ESI) available: Experimental procedure, ^1H and ^{13}C NMR spectra, and the X-ray structure of compound **6a**. CCDC 762367. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c001314e



Reaction conditions: a) 1. *m*-CPBA (1.0 equiv), 4 Å MS, 0 °C, 1 h; 2. $Ph_3PAuNTf_2$ (5 mol %), 10 h
b) 1. $(CH_2SH)_2$, BF_3•Et_2O; 2. Raney Ni

Scheme 2 Initial studies.

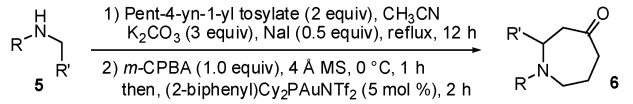
as bicyclic azepan-4-one **2** instead of cyclopentanone **3**. This structural assignment was initially supported by the lack of symmetry in the ^{13}C NMR spectrum of deoxygenated **2** (*i.e.*, compound **4**) and later corroborated by X-ray crystallography (*vide infra*). No cyclopentanone **3** or its dehydroamination product, cyclopentenone, was observed. Different gold(I) catalysts as well as $AuCl_3$ and $PtCl_2$ were screened, and (2-biphenyl)$Cy_2PAuNTf_2$[11] was found to be the most efficient, furnishing **2** in 79% isolated yield. Of note, Tf_2NH did not catalyze this reaction.

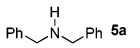
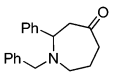
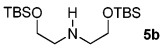
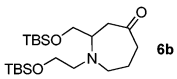
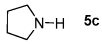
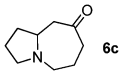
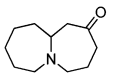
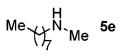
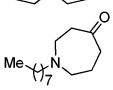
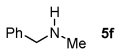
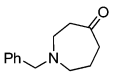
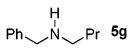
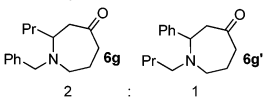
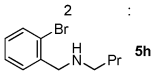
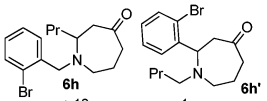
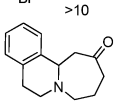
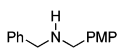
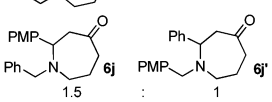
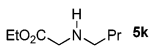
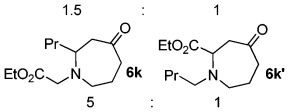
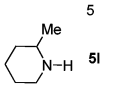
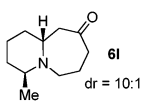
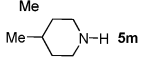
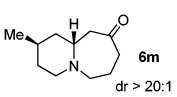
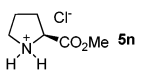
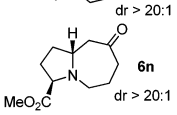
The scope of this surprising chemistry was studied in a two-step sequence: (1) alkylation with *in-situ* generated 5-iodopent-1-yne in refluxing MeCN for 12 h using K_2CO_3 as base; (2) *m*-CPBA (1 equiv.) oxidation followed by (2-biphenyl)$Cy_2PAuNTf_2$ (5 mol%) catalysis at 0 °C. As shown in Table 1, the alkylation step was expectedly efficient and, to our delight, the one-pot oxidation/gold catalysis was in general efficient as well; together, these two steps constituted an efficient synthesis of azepan-4-ones *via* [5 + 2] annulation. For symmetric secondary amines (entries 1–4), the two-step sequence tolerated phenyl (entry 1) or TBSO (entry 2) groups and allowed the formation of bicyclic azepan-4-ones fused with either a pyrrolidine (entry 3) or another azepane ring (entry 4) in good yields.

Fortuitously, **6a** was crystalline, and its azepane skeleton was confirmed by X-ray crystallography (Fig. 1).

For non-symmetric secondary amines, this chemistry was sensitive to steric difference and in most cases good to excellent regioselectivities were observed. For example, a Me group participated in the ring formation highly selectively over a primary alkyl (entry 5) or a benzyl (entry 6) group, yielding only one azepan-4-one product in each case. Comparing an *n*-butyl and a benzyl group was rather revealing. As shown in entry 7, the former was surprisingly favored over the latter albeit to a small extent, which, however, could be rationalized by the fact that phenyl is bigger than *n*-propyl. A further example substantiated this rationale: with a bulkier 2-bromophenyl group, the selectivity was increased to >10 : 1 (entry 8). Notably, the 2-bromobenzyl group is a removable group and can be employed in radical translocation reactions.[12] While clearly sterics outplayed electronics in determining regioselectivity, under similar steric environment, however,

Table 1 Synthesis of azepan-4-ones *via* a two-step, 5 + 2 annulation process: scope study



Entry[a]	Substrate	Product[b]	Yield (%) 1st step	Yield (%) 2nd step
1	 **5a**	 **6a**	99	87
2	 **5b**	 **6b**	98	51[c]
3	 **5c**	 **6c**	88	80
4	 **5d**	 **6d**	83	89
5	 **5e**	 **6e**	78	69
6	 **5f**	 **6f**	85	85
7	 **5g**	 **6g** : **6g'** 2 : 1	93	
73[d,e]	8	 **5h**		
		 **6h** : **6h'** >10 : 1	91	71[c]
9	 **5i**	 **6i**	80	70
10	 **5j** PMP = *p*-MeOPh	 **6j** : **6j'** 1.5 : 1	99	63[f]
11	 **5k**	 **6k** : **6k'** 5 : 1	90	
93[d,g]	12	 **5l**		
	 **6l** dr = 10:1	87	74	
13	 **5m**	 **6m** dr > 20:1	84	76[h]
14	 **5n**	 **6n** dr > 20:1	90	71[d]

[a] The reaction concentration was 1 M for the first step and 0.05 M for the second step. [b] Regioselectivity, if not indicated, is >20 : 1. [c] Reaction time: 8 h. [d] $Et_3PAuNTf_2$ (5 mol%) was used instead. [e] Reaction time: 6 h. [f] An inseparable mixture. [g] A ratio of 1.2/1 was observed using (2-biphenyl)$Cy_2PAuNTf_2$ as catalyst. [h] Reaction time: 3.5 h.

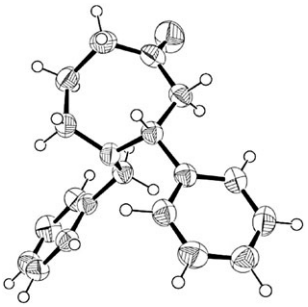
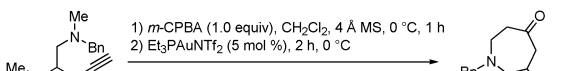
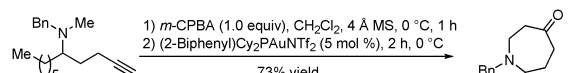


Fig. 1 ORTEP drawing of compound **6a**.

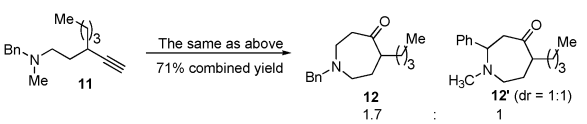
electronic difference could provide significant regioselectivity. For example, 1,2,3,4-tetrahydroisoquinoline underwent exclusive formal insertion into its benzylic C–H bond, yielding tricyclic azepan-4-one **6i** in 70% yield (entry 9). While no significant selectivity between PMB (*p*-MeOBn) and Bn was observed (entry 10), the low selectivity in the case of **5k** (**6k**/**6k′** = 1.2/1) was surprising and in contrast to what was previously observed in the synthesis of piperidin-4-ones (exclusive insertion into the butyl group).[5a] The selectivity was improved to 5/1 using $Et_3PAuNTf_2$ as catalyst (entry 11). The sensitivity of this chemistry to sterics was further evident as the gold catalysis in the case of sterically demanding *N*-butyl-3-pentanamine proceeded sluggishly and no azepan-4-one product was isolated. In contrast, 2-methylpiperidine reacted smoothly to yield bicyclic azepan-4-one **6l** in 74% yield (entry 12). Although the NH group of 2-methylpiperidine is similarly flanked by a secondary and a primary carbon centers, the ring structure likely alleviated steric hindrance for the gold catalysis. Importantly, this reaction showed good diastereoselectivity and excellent regioselectivity. Even better diastereoselectivities were observed in the cases of 4-methylpiperidine (entry 13) and methyl prolinate hydrochloride (entry 14). While (2-biphenyl)-$Cy_2PAuNTf_2$ was generally the catalyst to use, in some cases (entries 7, 11 and 14), $Et_3PAuNTf_2$ gave better results. Substitutions on the pent-4-ynyl chain were readily tolerated at the 1, 2 and 3 positions (eqn (1)–(3)), leading to azepan-4-ones with substitutions at the 5, 6 and 7 positions in fairly good yields. Notably, decreased regioselectivity was observed with substrate **11**, indicating the subtlety of regiochemistry control.



(1)



(2)



(3)

We have discovered a gold-catalyzed efficient synthesis of azepan-4-ones *via* a two-step [5 + 2] annulation. This reaction

is sensitive to steric differences and can in general be highly regioselective. Good to excellent diastereoselectivities can be achieved. This chemistry opens an easy, flexible, and efficient route to access various azepane derivatives. The detailed mechanism of this surprising reaction is currently probed and the results will be reported in due course.

We gratefully thank Sloan Fellowship, NIH (R01 GM084254) and UCSB for generous financial support and Dr Guang Wu for help with X-ray crystallography.

Notes and references

1 For a review, see: (*a*) D. O'Hagan, *Nat. Prod. Rep.*, 1997, **14**, 637; (*b*) S. Ueo, H. Irie and H. Harada, *Chem. Pharm. Bull.*, 1967, **15**, 768–770; (*c*) W. C. Wildman, *Alkaloids*, 1968, **11**, 348, and references cited therein; (*d*) T. Noro, S. Fukushima, A. Ueno, T. Miyase, Y. Iitaka and Y. Saiki, *Chem. Pharm. Bull.*, 1979, **27**, 1495–1497.

2 A simple SciFinder search for azepane-containing compounds studied for biological activities retrieved more than 25000 hits.

3 For selected examples or reviews, see: (*a*) E. J. Kantorowski and M. J. Kurth, *Tetrahedron*, 2000, **56**, 4317–4353; (*b*) K. Maruyama and Y. Kubo, *Chem. Lett.*, 1978, 769–772; (*c*) J. Diamond, W. F. Bruce and F. T. Tyson, *J. Med. Chem.*, 1964, **7**, 57–60; (*d*) I. Ryu, H. Miyazato, H. Kuriyama, K. Matsu, M. Tojino, T. Fukuyama, S. Minakata and M. Komatsu, *J. Am. Chem. Soc.*, 2003, **125**, 5632–5633; (*e*) J. Aubé, P. M. Burgett and Y. Wang, *Tetrahedron Lett.*, 1988, **29**, 151–154; (*f*) C. Brocke, M. A. Brimble, D. S. H. Lin and M. D. McLeod, *Synlett*, 2004, 2359–2363.

4 For selected examples, see: (*a*) P. A. Wender, T. M. Pedersen and M. J. C. Scanio, *J. Am. Chem. Soc.*, 2002, **124**, 15154–15155; (*b*) B. M. Trost and C. M. Marrs, *J. Am. Chem. Soc.*, 1993, **115**, 6636–6645; (*c*) N. D. Shapiro and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 9244–9245.

5 (*a*) L. Cui, Y. Peng and L. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 8394–8395. For an application in natural product synthesis, see: (*b*) L. Cui and L. Zhang, *Sci. China B: Chem.*, 2010, **53**, 113–118.

6 This is characteristically different from our early work on tetrahydrobenzazepin-4-one synthesis (L. Cui, G. Zhang, Y. Peng and L. Zhang, *Org. Lett.*, 2009, **11**, 1225–1228), where the cyclization step proceeded most likely *via* an electrophilic aromatic substitution.

7 This formal insertion could mechanistically require a rare 1,7-hydride migration over an aliphatic carbon chain; for an example, see: (*a*) K. Nishide, Y. Shigeta, K. Obata and M. Node, *J. Am. Chem. Soc.*, 1996, **118**, 13103–13104; (*b*) M. Node, K. Nishide, Y. Shigeta, H. Shiraki and K. Obata, *J. Am. Chem. Soc.*, 2000, **122**, 1927–1936. For 1,7-hydrogen migrations in highly conjugated systems, see: (*c*) C. W. Spangler, B. Keys and D. C. Bookbinder, *J. Chem. Soc., Perkin Trans. 2*, 1979, 810–813; (*d*) R.-L. Chen and R. S. H. Liu, *Tetrahedron*, 1996, **52**, 7809–7816; for a radical case, see: (*e*) A. L. J. Beckwith and D. R. Boate, *J. Chem. Soc., Chem. Commun.*, 1985, 797–798.

8 For examples of hydride migration in gold catalysis, see: (*a*) S. Bhunia and R.-S. Liu, *J. Am. Chem. Soc.*, 2008, **130**, 16488–16489; (*b*) V. K.-Y. Lo, M.-K. Wong and C.-M. Che, *Org. Lett.*, 2008, **10**, 517–519; (*c*) E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2009, **48**, 6152–6155; (*d*) J. Barluenga, A. Fernandez, F. Rodriguez and F. J. Fananas, *Chem.–Eur. J.*, 2009, **15**, 8121–8123; (*e*) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.*, 2008, **47**, 5224–5228.

9 For examples of hydrogens α to a heteroatom migrating as a hydride, see: (*a*) S. J. Pastine, K. M. McQuaid and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 12180–12181; (*b*) P. Mátyus, O. Elias, P. Tapolcsanyi, A. Polonka-Balint and B. Halasz-Dajka, *Synthesis*, 2006, 2625–2639; (*c*) S. Murarka, I. Deb, C. Zhang and D. Seidel, *J. Am. Chem. Soc.*, 2009, **131**, 13226.

10 N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.*, 2005, **7**, 4133–4136.

11 L. Cui, G. Zhang and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3884–3887.

12 K. Takasu, H. Ohsato and M. Ihara, *Org. Lett.*, 2003, **5**, 3017–3020.