Published in final edited form as:

Angew Chem Int Ed Engl. 2011 March 28; 50(14): 3236–3239. doi:10.1002/anie.201007624.

A Flexible and Stereoselective Synthesis of Azetidin-3-Ones through Gold-Catalyzed Intermolecular Oxidation of Alkynes

Dr. Longwu Ye, Weimin He, and Prof. Dr Liming Zhang*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California (USA)

Small ring made easy and chiral

Chiral azetidin-3-ones could be easily prepared from chiral *N*-propargylsulfonamides, which in turn are readily accessible in excellent e.e. via chiral sulfonamide chemistry. Using *t*-butanesulfonyl as the protecting group avoids unnecessary deprotection and reprotection and allows its removal from the azetidine ring under acidic conditions.

Keywords

azetidine; cyclization; gold; stereoselectivity; carbene

Azetidine is a strained 4-membered nitrogen heterocycle and can be found in various natural products^[1] and compounds of biological importance. While β -lactams, i.e., azetidin-2-ones, are a rich source of antibiotics,^[2] their structural isomer, azetidin-3-ones, with the carbonyl group one-carbon removed from the nitrogen atom, have not been found in nature but could serve as versatile substrates for the synthesis of functionalized azetidines.^[3]

The synthesis of azetidin-3-ones^[3] has been mainly realized via acid-promoted or metal-catalyzed decomposition of α -amino- α' -diazo ketones^[4] and 4-*exo-tet* cyclizations of α -amino ketones. The diazo ketone approach is the most reliable in terms of substrate scopes, but it often suffers from competitive reactions and low yields;^[4b, 5] moreover, diazo compounds are toxic and potentially explosive.^[6] For the synthesis of chiral azetidin-3-ones,^[7] natural amino acids serve as a convenient and cheap chiral pool, which however at the same time poses limits on substrate scope and configuration. Herein, we report a straightforward, flexible and general sequence for efficient synthesis of chiral azetidin-3-ones with typically >98% e.e. that bypasses toxic diazo intermediates.

Early in 2010 we showed for the first time^[8] that reactive α -oxo gold carbenes^[9] could be readily accessed via simple intermolecular oxidation^[10] of terminal alkynes,^[11] therefore allowing substitution of toxic α -diazo ketones with benign and readily available alkynes (Scheme 1). This approach was later applied to the preparation of oxetan-3-ones from easily available propargyl alcohols.^[12] A further application of this chemistry calls for an intramolecular N-H insertion by an α -oxo gold carbene using protected propargylamines as substrates (Scheme 1).

To implement this design, we anticipated that the key is to find a suitable electron-withdrawing protecting group for the basic amino group, which might deactivate cationic

*Fax: (+1) 805-893-4120, zhang@chem.ucsb.edu, Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

gold catalysts. While an acyl group is in general not suitable due to a competitive carbonyl 5-*exo-dig* cyclization,^[13] the use of tosyl (toluenesulfonyl) group would encounter difficulty in its later removal, which is typically accomplished under harsh basic/reductive conditions.^[14] We decided to use *t*-butanesulfonyl (Bus)^[15] as the protecting group for two reasons: a) it can be removed under acidic conditions; b) it can be prepared from *t*-butanesulfinyl via simple *m*-CPBA oxidation. Of importance, *t*-butanesulfinamides are easily formed in chiral forms using Ellman's chemistry.^[16] As shown in Scheme 2, this protecting group strategy would allow us to access various *N*-*t*-butanesulfonylpropargylamines (i.e., **2**) with high e.e conveniently from chiral sulfinamides **1** without additional protection and deprotection steps, and eventually a range of chiral azetidin-3-ones could be obtained (Scheme 2).

We set out to screen different conditions for the key gold-catalyzed oxidative cyclization of *t*-butanesulfonylpropargylamines. Using racemic sulfonylpropargylamine **2a** as the substrate, some of the results are listed in Table 1. As it soon became obvious, the sulfonylpropargylamine behaved very differently from its alcohol counterpart, and azetidin-3-one **3a** was formed in only 28% yield along with a significant amount of mesylate **4a** using the optimized conditions for propargylic alcohol substrates (entry 1).^[12] Interestingly, no Wolff rearrangement product^[5a, 17] was observed. Varying the *N*-oxides (entries 2–6), however, revealed that bulky and electron-deficient 2,6-dibromopyridine *N*-oxide (**5e**) was the best (entry 5). Using this optimal oxidant, various gold catalysts were screened (entries 5, 7–11). Those with 2-biphenylphosphine ligands generally performed better (entries 9–11); moreover, a close comparison of the three 2-biphenylphosphine ligands revealed that the reaction was slightly more efficient with a bulkier biphenyl group (comparing entry 9 and entry 10) but less so if the cyclohexyl groups were replaced with bigger *t*-butyl groups (comparing entries 10 and 11). With this trend in mind, we decided to test dicyclohexylphosphine ligands containing even bulkier biphenyl moieties, and BrettPhos, a functionalized XPhos with MeO groups at the 3 and 6 positions developed by Buchwald,^[18] became an apparent choice. BrettPhosAuNTf₂ was easily prepared following a typical preparative procedure for cationic gold(I) complexes,^[19] and its structure was secured by single crystal X-ray diffraction studies.^[20] To our delight, this new cationic gold(I) complex offered a significant improvement (entry 12). Inspired by our recent work without using acid additives,^[11] the reaction was attempted without MsOH. Pleasingly, azetidin-3-one **2** was formed in an 85% (82% isolated) yield, and the reaction rate did not decrease to a significant extent (entry 13). Somewhat surprisingly, dichloro(2-picolinato)gold(III) could also catalyze this reaction with an acceptable efficiency albeit the need of MsOH (entry 14). PtCl₂, however, did not promote this chemistry (entry 15).

With the optimal reaction conditions secured, the reaction scope was then studied. Throughout this work, (*R*)-*t*-butanesulfinamide was used as the chiral auxiliary. As shown in Table 2, chiral *N*-propargylsulfinamides were prepared in excellent diastereoselectivities following Lin's procedure,^[21] and the configuration of the propargyl center is assigned accordingly. The oxidation of the sulfinamide using *m*-CPBA and subsequent gold-catalyzed oxidative cyclization were performed without column purification of the sulfonylpropargylamine intermediate, and the two-step overall yields are shown. Azetidin-3-ones with different substituents at the 2 position were prepared in mostly good yields. One exception is a *t*-butyl group, where <35% yield was observed by ¹H NMR presumably due to steric hindrance; in contrast, a cyclohexyl group was readily allowed (entry 3). A range of functional groups are tolerated, including a remote C-C double bond (entry 4), a halogen (entry 5), and an azido group (entry 6). In the case of a phenyl group (entry 9), sulfinamide **1i** was not stable upon desilylation using TBAF; instead, *m*-CPBA oxidation was done before desilylation. Pleasingly, the resulting sulfonylpropargylamine (i.e., **2i**) was stable and underwent the gold-catalyzed oxidative cyclization easily, and afforded azetidinone **3i** in 72% yield (entry 9). Notably, due to the absence of any acid additive, acid-labile protecting groups such as Boc (entry 7) and

MOM (entry 8) were not affected during the reaction. In addition, a silyl protecting group such as TBDPS was tolerated (entry 10). In all the entries, the azetidin-4-ones were isolated with excellent e.e., determined by chiral HPLC^[22] using racemic products as references, and essentially no epimerization was detected. The product configurations were assumed based on the reaction mechanism involving gold carbene N-H insertions.

Interestingly, when furan-containing sulfonamide **2k** was subjected to the gold catalysis, the desired azetidin-3-one was not observed. Instead, conjugated imine **7** was isolated as a yellow solid in 77% yield, and its structure was elucidated by X-ray diffraction studies (Scheme 3). This transformation can be rationalized by invoking a ring opening of the azetidine intermediate **A**, facilitated by the electron-rich furan ring, followed by π orbital reorganization.

(1)

(2)

This chemistry can also be extended to the synthesis of 2,2-disubstituted azetidin-3-ones with serviceable yields (Eq. 1), and 8-ethylquinoline *N*-oxide (**6**) was a better oxidant. Notably, **3n** was formed with 81% e.e. from the corresponding sulfinamide (dr: 91:9),^[23] Moreover, the parent *N*-*t*-butanesulfinylazetidin-3-one **3o** was readily prepared using Et₃PAuNTf₂ as the catalyst (Eq. 2).

Lately, heterospiro[3.3] heptanes have been proposed as building blocks in medicinal chemistry.^[24] This chemistry, in combination with our previous oxetan-3-one chemistry,^[12] provided a facile synthesis of oxazaspiro[3.3] heptanone **3p**. The sequence starting from cheap propargyl alcohol is outlined in Scheme 4, and the azetidine ring formation was achieved in a respectful 61% yield. This dual application of the α -oxo gold carbene chemistry highlights the synthetic utility of the gold-catalyzed alkyne oxidation strategy.

(3)

Although linear *N*-propargylcarboxamides are not suitable substrates due to competitive 5-exo-dig cyclization by its acyl group,^[13] lactams such as **1q** and **1r** with the acyl group tied back by the ring structure can avoid this issue. Indeed, these substrates underwent smooth oxidative cyclization, leading to strained bicyclic lactams **3q** and **3r** in fairly good yields and good enantiomeric excesses (Eq. 3).

Removal of the Bus group was then examined using **3a** as the exemplary substrate (Scheme 5). Direct deprotection under acidic conditions resulted in a complex mixture, which may be contributed to the reaction of the carbonyl group with the newly revealed amine moiety. Consequently, the ketone moiety was reduced with NaBH₄. The resulting diastereomeric diols were separated, and the *trans* stereochemistry of the major isomer (i.e., **8b**) was confirmed by X-ray diffraction studies. To our delight, the Bus group in **8b** was smoothly removed under acidic conditions.^[15] To facilitate its isolation, the free amine was capped with a Boc group.

In summary, a practical and flexible synthesis of chiral azetidin-3-ones has been developed. The key reaction is a gold-catalyzed oxidative cyclization of chiral *N*-propargylsulfonamides. Mechanistically, reactive α -oxogold carbenes are generated as intermediates via intermolecular alkyne oxidation and subsequently undergo intramolecular N-H insertion. The use of *t*-butanesulfonyl as the protecting group takes advantage of the chiral *t*-butanesulfinimine chemistry and avoids additional unnecessary deprotection and protection reactions. Moreover, the Bus group can be easily removed from the azetidine ring under acidic conditions. The extension of this chemistry using other sulfonyl protecting groups will soon be examined.

Experimental Section

General procedure for the gold-catalyzed oxidative cyclization

N-oxide **5e** (0.36 mmol) and BrettPhosAuNTf₂ (15.3 mg, 0.015 mmol) were added to a solution of the sulfonamide, generated as a crude residue via *m*-CPBA oxidation of sulfonamide **1**, in DCE (6 mL) at room temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was treated with 1 N HCl (15 mL) and extracted with DCM (2 $\times$ 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (eluent: hexanes/ethyl acetate) to afford desired azetidin-3-one **3**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank NIGMS (R01 GM084254) and UCSB for generous financial support and Dr. Guang Wu for helping with X-ray crystallography.

References

1. a) Budesínský M, Budzikiewicz H, Procházka Z, Ripberger H, Römer A, Scholz G, Schreiber K. *Phytochem.* 1980; 19:2295. b) Kobayashi, Ji; Cheng, JF.; Ishibashi, M.; Walchli, MR.; Yamamura, S.; Ohizumi, Y. *J Chem Soc, Perkin Trans 1.* 1991:1135. c) Ahmad Y, Le Quesne PW, Neuss N. *J Chem Soc D: Chem Commun.* 1970:538. d) Hayashi H, Asabu Y, Murao S, Arai M. *Biosci Biotech Biochem.* 1995; 59:246.
2. Hubschwerlen C. *Compr Med Chem II.* 2006; 7:479.
3. Dejaegher Y, Kuz'menok NM, Zvonok AM, De Kimpe N. *Chem Rev.* 2002; 102:29. [PubMed: 11782128]
4. a) Burtoloso ACB, Correia CRD. *Tetrahedron Lett.* 2004; 45:3355. b) Burtoloso ACB, Correia CRD. *Synlett.* 2005; 2005:1559.
5. a) Wang J, Hou Y. *J Chem Soc, Perkin Trans 1.* 1998:1919. b) Pusino A, Saba A, Desole G, Rosnati V. *Gazz Chim Ital.* 1985; 115:33.
6. Doyle, MP.; McKervey, MA.; Ye, T. *Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides.* Wiley; New York: 1998.
7. a) Burtoloso ACB, Correia CRD. *Tetrahedron.* 2008; 64:9928. b) Lall MS, Ramtohl YK, James MNG, Vederas JC. *J Org Chem.* 2002; 67:1536. [PubMed: 11871884] c) Hanessian S, Fu JM. *Can J Chem.* 2001; 79:1812.
8. Ye L, Cui L, Zhang G, Zhang L. *J Am Chem Soc.* 2010; 132:3258. [PubMed: 20166668]
9. a) Li G, Zhang L. *Angew Chem, Int Ed.* 2007; 46:5156. b) Shapiro ND, Toste FD. *J Am Chem Soc.* 2007; 129:4160. [PubMed: 17371031] c) Bhunia S, Liu RS. *J Am Chem Soc.* 2008; 130:16488. [PubMed: 19554723] d) Li CW, Lin GY, Liu RS. *Chem Eur J.* 2010; 16:5803. e) Yeom HS, Lee JE, Shin S. *Angew Chem, Int Ed.* 2008; 47:7040.
10. a) Cuenca AB, Montserrai S, Hossain KM, Mancha G, Lledos A, Medio-Simon M, Ujaque G, Asensio G. *Org Lett.* 2009; 11:4906. [PubMed: 19785397] b) Li CW, Pati K, Lin GY, Sohel SMA, Hung HH, Liu RS. *Angew Chem, Int Ed.* 2010; 49:9891. c) Davies PW, Cremonesi A, Martin N. *Chem Commun.* 2011; 47:379.
11. Lu B, Li C, Zhang L. *J Am Chem Soc.* 2010; 132:14070. [PubMed: 20853846]
12. Ye L, He W, Zhang L. *J Am Chem Soc.* 2010; 132:8550. [PubMed: 20521793]
13. a) Hashmi ASK, Weyrauch Jan P, Frey W, Bats Jan W. *Org Lett.* 2004; 6:4391. [PubMed: 15524491] b) Cui L, Li C, Zhang L. *Angew Chem, Int Ed.* 2010; 49:9178.
14. Wuts, PGM.; Greene, TW. *Greene's protective groups in organic synthesis.* 4. Wiley-Interscience; Hoboken, N.J: 2007.
15. Sun P, Weinreb SM, Shang M. *J Org Chem.* 1997; 62:8604. [PubMed: 11672017]
16. a) Robak MT, Herbage MA, Ellman JA. *Chem Rev.* 2010; 110:3600. [PubMed: 20420386] b) Ellman JA, Owens TD, Tang TP. *Acc Chem Res.* 2002; 35:984. [PubMed: 12437323] c) Zhou P, Chen BC, Davis FA. *Tetrahedron.* 2004; 60:8003.
17. a) Gerstenberger BS, Lin J, Mimieux YS, Brown LE, Oliver AG, Konopelski JP. *Org Lett.* 2008; 10:369. [PubMed: 18181633] b) Kirmse W. *Eur J Org Chem.* 2002; 2002:2193.
18. Fors BP, Watson DA, Biscoe MR, Buchwald SL. *J Am Chem Soc.* 2008; 130:13552. [PubMed: 18798626]
19. Mézailles N, Ricard L, Gagosz F. *Org Lett.* 2005; 7:4133. [PubMed: 16146370]
20. CCDC808743 ([BrettPhosAuNTf₂]), 808745 (**7**), and 808744 (**8b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
21. Chen BL, Wang B, Lin GQ. *J Org Chem.* 2009; 75:941. [PubMed: 20041724]
22. Please see the supporting information.

23. Patterson AW, Ellman JA. *J Org Chem.* 2006; 71:7110. [PubMed: 16930078]
24. a) Burkhard JA, Guérot C, Knust H, Rogers-Evans M, Carreira EM. *Org Lett.* 2010; 12:1944. [PubMed: 20356106] b) Wuitschik G, Rogers-Evans M, Buckl A, Bernasconi M, Märki M, Godel T, Fischer H, Wagner B, Parrilla I, Schuler F, Schneider J, Alker A, Schweizer WB, Müller K, Carreira EM. *Angew Chem Int Ed.* 2008; 47:4512.

Scheme 1.
Formation of azetidin-3-ones via alkyne oxidation

Scheme 2.

Design: formation of chiral azetidin-3-ones via *t*-butanesulfinamides

Scheme 3.
Formation of imine **7**

Scheme 4.
Synthesis of oxazaspiro[3.3]heptane **3p**

Scheme 5.
Removal of the Bus group

Table 1

Formation of azetidin-3-ones via oxidative cyclization: condition optimizations.^[a]

entry	gold catalyst	oxidant (2 equiv)	conditions	yield ^[b]	
				3a	4a
1	Ph ₃ PAuNTf ₂	5a (R = 3,5-Cl ₂)	rt, 4 h	28%	27%
2	Ph ₃ PAuNTf ₂	5b (R = 4-Ac)	rt, 12 h	21% ^[c]	19%
3	Ph ₃ PAuNTf ₂	5c (R = 4-Et)	rt, 12 h	<5% ^[d]	-
4	Ph ₃ PAuNTf ₂	5d (R = 2-Br)	rt, 4 h	30%	29%
5	Ph ₃ PAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 4 h	48%	10%
6	Ph ₃ PAuNTf ₂	6	rt, 12 h	22% ^[e]	15%
7	IPrAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 12 h	50%	4%
8	(4-CF ₃) ₃ PAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 4 h	42%	12%
9	Cy-JohnPhosAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 4 h	56%	10%
10	XPhosAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 4 h	58%	12%
11	<i>t</i> -ButylXPhosAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 4 h	50%	10%
12	BrettPhosAuNTf ₂	5e (R = 2,6-Br ₂)	rt, 4 h	70%	4%
13	BrettPhosAuNTf₂	5e (R = 2,6-Br₂)	rt, 6 h^[f]	85%^[g]	-
14	Au(III)	5e (R = 2,6-Br ₂)	rt, 30 m	68%	<1%
15	PCl ₂ /CO (toluene)	5e (R = 2,6-Br ₂)	80 °C, 12 h ^[f]	<5% ^[d]	-

^[a] [2a] = 0.05 M.

^[b] Estimated by ¹H NMR using diethyl phthalate as the internal reference.

^[c] 20 % of **2a** left unreacted.

^[d] Most **2a** left unreacted.

^[e] 10 % of **2a** left unreacted.

[7] No acid additive, 1.2 equiv of **5e**.

[8] 82% isolated yield.

Table 2

Reaction scope study.^[a]

entry	R	sulfonamide		azetidin-4-one		
		1 ^[b]	yield ^[c]	dr	3	yield ^[c] ee ^[d]
1		1a	82%	>99:1	3a	82% 99%
2	<i>n</i> -propyl	1b	71%	>99:1	3b	79% 99%
3	cyclohexyl	1c	78%	>99:1	3c	81% >99%
4	pent-4-en-1-yl	1d	90%	>50:1	3d	80% 97%
5	4-bromobutyl	1e	74%	>99:1	3e	74% 99%
6	4-azidobutyl	1f	78% ^[e]	>99:1	3f	67% ^[f] 98%
7		1g	76% ^[g]	>99:1	3g	84% 98%
8		1h	84%	>99:1	3h	78% 99%
9	Ph	2i ^[h]	71% ^[i]	>99:1	3i	72% ^[j] 98%
10		1j	72%	>99:1	3j	78% 99%

^[a] [1] = 0.05 M.

^[b] Stereochemistry assignment based on literature precedents.

^[c] Two-step overall yield.

^[d] Determined using chiral HPLC.

[e] Prepared from **1e**.

[f] The reaction was run at 40 °C for 24 h.

[g] Prepared from **1f**.

[h] The *m*-CPBA oxidation is done before TBAF desilylation.

[i] Three-step overall yield.

[j] Gold-catalysis yield.