J|A|C|S COMMUNICATIONS

Published on Web 06/16/2009

Gold(I)-Catalyzed Enantioselective Ring Expansion of Allenylcyclopropanols

Florian Kleinbeck and F. Dean Toste*

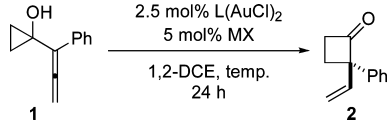
Department of Chemistry, University of California, Berkeley, California 94720

Received May 19, 2009; E-mail: fdtoste@berkeley.edu

Substituted cyclobutanes constitute valuable building blocks for organic synthesis because of their rich chemistry and are additionally found as motifs in numerous natural products.[1] Among the various approaches to cyclobutanes, ring expansion of cyclopropanols by a Wagner−Meerwein shift to the corresponding cyclobutanones is considered one of the most powerful and versatile methods.[2] While ring expansion of small ring systems can generally be induced by coordination of π-acidic transition-metal catalysts to alkenyl-, alkynyl-, and allenylcycloalkanols,[3] only a few reports have described asymmetric catalytic Wagner−Meerwein shifts based on this strategy for the synthesis of cycloalkanones.[4]

In the past decade, cationic gold(I) complexes have evolved as mild Lewis acid catalysts for transformations requiring the activation of π bonds.[5] In 2005, we reported the ring expansion of 1-alkynylcyclopropanols catalyzed by $[(p\text{-}CF_3C_6H_4)_3P]AuSbF_6$, which provides efficient access to a range of alkylidenecyclobutanols.[6,7] We hypothesized that an analogous rearrangement of 1-allenylcyclopropanols using chiral gold−phosphine complexes might allow for the catalytic construction of cyclobutanones possessing a vinyl-substituted quaternary stereogenic center.[8]

Table 1. Optimization of Reaction Conditions

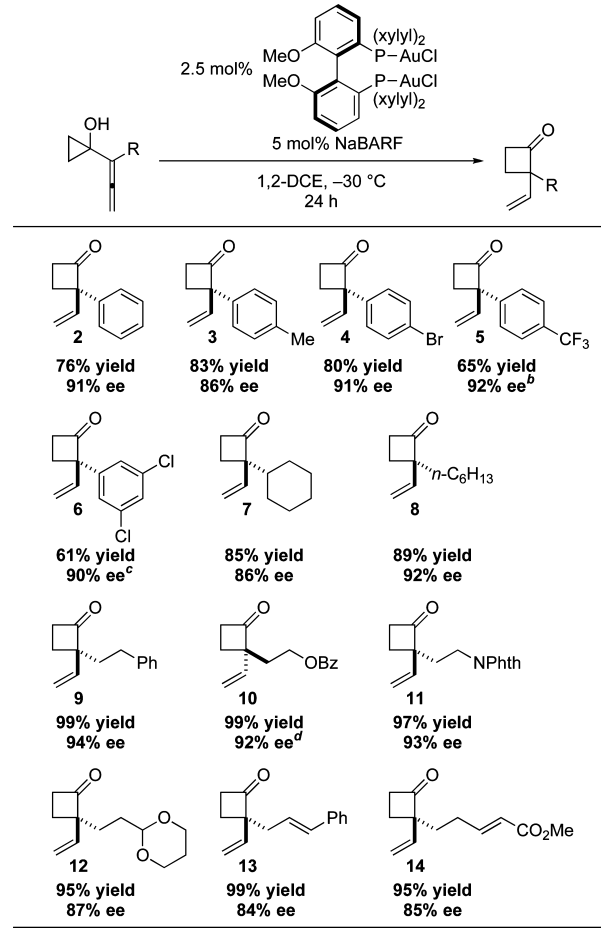


entry	ligand (L)	MX	*T* (°C)	ee (%)
1	(*R*)-xylyl-BINAP	$AgNTf_2$	0	75
2	(*R*)-xylyl-BINAP	$AgNTf_2$	−10	81
3	(*R*)-xylyl-BINAP	$AgNTf_2$	−20	83
4	(*R*)-xylyl-BINAP	$AgNTf_2$	−30	84
5	(*R*)-tolyl-BINAP	$AgNTf_2$	−30	48
6	(*R*)-BINAP	$AgNTf_2$	−30	32
7	(*R*)-MeO-DM-BIPHEP	$AgNTf_2$	−30	86
8	(*R*)-xylyl-BINAP	NaBARF[a]	−30	89
9	(*R*)-MeO-DM-BIPHEP	NaBARF[a]	−30	91

[a] NaBARF = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

During initial experiments to establish standard reaction conditions, (*R*)-xylyl-BINAP was identified as promising ligand. When allenylcyclopropanol **1** was treated with the (*R*)-xylyl-BINAP-derived cationic gold(I) complex at 0 °C, cyclobutanone **2** was isolated in 75% ee (Table 1, entry 1). When the temperature of the reaction was decreased, the enantioselectivity increased, reaching 84% at −30 °C (entry 4). Notably, the enantioselectivity showed a pronounced leveling behavior, with only a small increase in selectivity between −10 and −30 °C (entries 2−4). Decreasing the steric encumbrance around the phosphine led to a drop in the enantioselectivity (entries 5 and 6).[9] A slight improvement in selectivity was obtained with MeO-DM-BIPHEP, giving **2** in 86% ee at −30 °C (Table 1, entry 7). Replacement of $AgNTf_2$ with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) further increased the enantioselectivity, providing **2** in 89 and 91% ee with xylyl-BINAP and MeO-DM-BIPHEP, respectively (entries 8 and 9).[10] Control experiments indicated that the improved selectivity in the case of NaBARF presumably results from suppression of an inherent background reaction by trace amounts of $HNTf_2$ formed under the reaction conditions.[11]

Scheme 1. Substrate Scope[a]



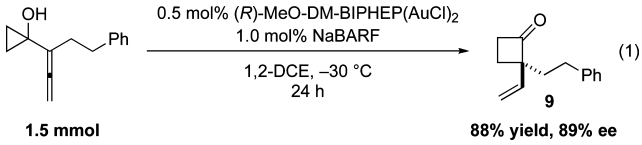
[a] Conditions: 2.5 mol% (*R*)-MeO-DM-BIPHEP$(AuCl)_2$, 5 mol% NaBARF, 0.100 mmol of substrate, 0.12 M in 1,2-DCE, −30 °C, 24 h. Yields refer to isolated material; ee's were determined by chiral HPLC. See the Supporting Information for details. [b] Reaction run at 0.25 M for 48 h. [c] Reaction run with 5 mol% catalyst and 10 mol% NaBARF at 0.08 M for 48 h. [d] Reaction run with (*S*)-xylyl-BINAP$(AuCl)_2$.

With these results in hand, we examined the scope of the gold(I)-catalyzed enantioselective ring expansion of 1-allenylcyclopropanols (Scheme 1). Straightforward access to all of the substrates was achieved using three different strategies: (1) direct allenylation of cyclopropanone generated in situ from 1-ethoxycyclopropanol; (2) Johnson−Claisen rearrangement of propargyl alcohols; and (3) S_N2'

10.1021/ja904055z CCC: $40.75

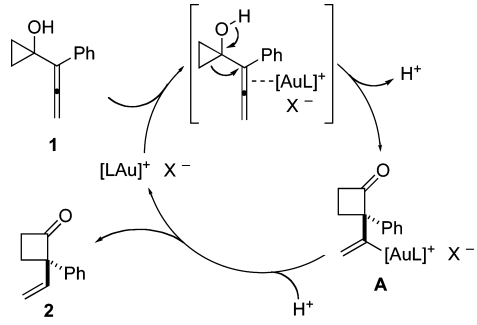
displacement of propargyl mesylates with cuprate reagents (see the Supporting Information for details). A wide range of cyclobutanones were accessible in synthetically useful yields[12] and good to excellent enantioselectivities.[13] Substrates possessing aromatic substituents (**2**−**6**) were generally well tolerated, with the more electron-deficient 1-allenylcyclopropanols **5** and **6** requiring longer reaction times. Alkyl-substituted compounds were excellent substrates for this method, giving cyclobutanones **7** to **9** in high enantioselectivities. The mildness of the method allowed the incorporation of various functional groups in the side chain, e.g., protected alcohols (**10**) and amines (**11**), acetals (**12**), alkenes (**13**), and α,β-unsaturated esters (**14**).

The amount of catalyst could be reduced without significant loss of enantioselectivity or yield. Cyclobutanone **9** was obtained in 88% yield and 89% ee on a 1.5 mmol scale with only 0.5 mol% of the chiral gold(I) catalyst (eq 1). The low catalyst loading combined with the air and moisture of the reaction should make this method suitable for the synthesis of chiral cyclobutanones on a large scale.



A proposed mechanism for the gold(I)-catalyzed enantioselective ring expansion of 1-allenylcyclopropanols is outlined in Scheme 2. Coordination of the cationic gold(I) catalyst to the internal double bond of the allene moiety in **1** triggers a ring expansion by a Wagner−Meerwein shift, generating vinylgold intermediate **A**. A subsequent protodemetalation liberates the catalyst and releases the product **2**. This mechanistic proposal is in agreement with results from computational studies carried out for the related rearrangement of 1-alkynylcyclopropanols.[14]

Scheme 2. Proposed Reaction Mechanism



In summary, we have developed an asymmetric ring expansion reaction of 1-allenylcyclopropanols catalyzed by chiral phosphine gold(I)−phosphine complexes. The method provides access to a wide range of cyclobutanones with a vinyl-substituted quaternary stereogenic center. Moreover, this method constitutes the first report of an enantioselective gold-catalyzed 1,2-alkyl migration[7] and thereby expands the class of reactions amenable to asymmetric catalysis by gold.[15] Further studies of the application of this methodology to the synthesis of natural products are ongoing in our laboratories.

Acknowledgment. We thank Dr. David J. Buchanan and Daniel L. Gray for initial studies. We gratefully acknowledge NIGMS (RO1 GM073932), Bristol-Myers Squibb, and Novartis for financial support. F.K. thanks the German Academic Exchange Service (DAAD) for a postdoctoral fellowship. We acknowledge Solvias and Takasago for the generous donation of phosphine ligands and Johnson Matthey for a gift of $AuCl_3$.

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

References

(1) For general reviews of the chemistry of cyclobutanes, see: (a) Belluš, D.; Ernst, B. *Angew. Chem.* **1988**, *100*, 820. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (c) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.
(2) Lee-Ruff, E. In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons: Chichester, U.K., 2005.
(3) (a) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; (b) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247. (c) Iwasawa, N. *Synlett* **1999**, 13. (d) Iwasawa, N.; Narasaka, K. *Top. Curr. Chem.* **2000**, *207*, 69. (e) Muzart, J. *Tetrahedron* **2005**, *61*, 9423. (f) Muzart, J. *Tetrahedron* **2008**, *64*, 5815.
(4) Cyclobutanones: (a) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162. Cyclopentanones: (b) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (c) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231. For an alternative entry to chiral cyclobutanones based on a Wagner−Meerwein shift induced by a Sharpless asymmetric epoxidation, see: (d) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.
(5) For recent general reviews of gold catalysis, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (g) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.
(6) (a) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. For a ruthenium-catalyzed version of the same ring expansion reaction, see: (b) Trost, B. M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* **2008**, *130*, 17258.
(7) For a review of 1,2-alkyl migrations catalyzed by π acids, see: Crone, B.; Kirsch, S. F *Chem.—Eur. J.* **2008**, *14*, 3514, and references therein.
(8) For reviews of catalytic enantioselective formation of quaternary stereocenters, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.
(9) For all three major bisphosphine ligand families (BINAP, BIPHEP, and Segphos), the same trend was observed, with the xylyl-substituted representatives providing the highest selectivity within each family.
(10) While $AgNTf_2$, $AgPF_6$, and $AgSbF_6$ all provided cyclobutanone **2** in 83% ee at 20 °C with (*R*)-xylyl-BINAP as the ligand, $AgBF_4$, AgOTf, and AgOTs led to formation of **2** in only 67, 34, and 15% ee, respectively.
(11) $AgNTf_2$ was found to slowly catalyze the ring expansion of **1**. While AgOAc was not a competent catalyst, almost instantaneous reaction was observed with $HNTf_2$. These observations suggest that the achiral catalyst causing the background reaction was not the silver cation.
(12) As opposed to 1,1-disubstituted allenes, for which intramolecular addition of the alcohol onto the allene was never observed, tri- and tetrasubstituted allenes generated substantial amounts of dihydrofuran byproducts. For an example of formation of dihydrofurans from alkoxyallenes, see: Yeom, H.-S.; Yoon, S.-J.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817.
(13) The absolute configuration of cyclobutanone **4** was determined by crystal structure analysis of the corresponding tosylhydrazone. The absolute configurations of compounds **2** and **9** were assigned by comparison of the optical rotation with reported values (see ref 4a). The absolute configurations of all the other compounds were assigned by analogy.
(14) Sordo, T. L.; Ardura, D. *Eur. J. Org. Chem.* **2008**, 3004.
(15) For examples of gold-catalyzed enantioselective reactions of allenes, see: (a) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402. (b) Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6670. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (d) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935. (e) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (f) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283.

JA904055Z