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Gold(I)-Catalyzed Enantioselective Polycyclization Reactions

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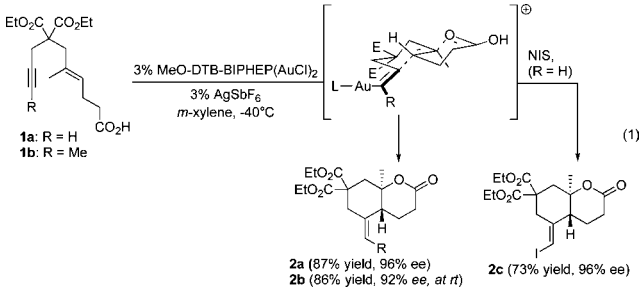
Polycyclization reactions of unsaturated molecules allow for the rapid construction of complex structures in a single operation.[1] Thus, numerous methods that proceed with excellent diastereoselectivity have been developed over the past 50 years.[2] In contrast, enantioselective variants are rare and the majority of reported examples involve cyclization cascades that are promoted by reactions of alkenes with electrophillic reagents.[3,4] Given that the substrates contain multiple alkenes, initiating polycyclization reactions through selective activation of an alkyne[5,6] offers the potential advantage of circumventing unwanted reactions resulting from nonselective alkene activation; however, an example of an enantioselective polycyclization reaction of alkynes has yet to be reported.

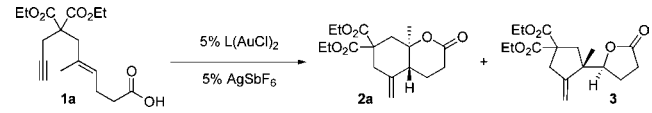
Given that the majority of polycyclization reactions have been induced by an endocyclic process, we first evaluated the use of chiral phosphinegold(I) complexes in a 6-*endo*-dig initiated polycyclization of 1,5-enynes;[7] however, only poor enantioselectivity was obtained (up to 33% ee). While gold(I)-catalyzed enantioselective reactions of alkynes remain rare, the majority of reports involve 5-*exo*-dig additions;[8] however, we have recently reported an example of an enantioselective rearrangement initiated by a 6-*exo*-dig cyclization.[9] Therefore we hypothesized that a related process might be employed to induce enantioselective polycyclization reactions.



(1)

Accordingly, we began a systematic evaluation of ligand effects in the bicyclization of carboxylic acid **1a** (Table 1).[10] Reaction of **1a**, catalyzed by a series of monocationic (BINAP)gold(I) complexes, produced lactone **2a** with 17−40% ee along with small amounts of **3** (entries 1−3). Given the notable improvements in enantioselectivity previously observed in the gold-catalyzed reaction employing sterically encumbered phosphines,[8,11] we examined *tert*-butyl-substituted phosphines as ligands. While the Segphos-based ligand gave poorer enantioselectivity (entry 4), we were pleased to find that the use of MeO-DTBM-BIPHEP resulted in the formation of **2a** in 48% ee (entry 5). The reaction showed a dramatic solvent effect, with nonpolar aromatic solvents providing the desired lactone **2a** in up 87% ee.[12] Switching the ligand to MeO-DTB-BIPHEP furnished fused bicyclic compound **2a** as a single diastereomer[13] in 87% yield and 92% ee (entry 9). A further improvement in enantioselectivity was achieved by conducting the reaction at −40 °C, thereby furnishing **2a** in 96% ee, as a single diastereomer and only trace amounts of **3** (eq 1).[14] Under these conditions, gold(I)-catalyzed cyclization of **1a**, in the presence of an electrophilic iodine source, afforded diastereomerically pure vinyl iodide **2c** in 96% ee. The observation that the enantioselectivity obtained in the formation of **2c** was identical with that of **2a** is in agreement with iodination occurring subsequent to the cyclization event.[15] Internal alkyne **1b** also underwent the gold(I)-catalyzed cyclization to afford **2b** as a single alkene isomer in 86% yield and 92% ee (eq 1), although longer reaction times were required, even at rt, for full conversion.

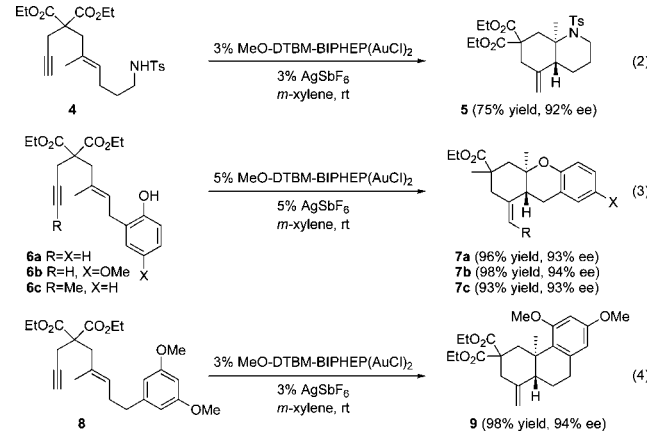
Table 1. Optimization of Reaction Conditions



entry	ligand (L)	solvent	% yield[a] **2a** (**3**)	ee (%)
1	(*S*)-BINAP	CH_2Cl_2	83 (7)	−17
2	(*R*)-tolyl-BINAP	CH_2Cl_2	72 (8)	23
3	(*R*)-xylyl-BINAP	CH_2Cl_2	70 (10)	40
4	(*R*)-DTBM-Segphos	CH_2Cl_2	81 (8)	2
5	(*R*)-MeO-DTBM-BIPHEP	CH_2Cl_2	71 (7)	46
6	(*R*)-MeO-DTBM-BIPHEP	benzene	76 (8)	83
7	(*R*)-MeO-DTBM-BIPHEP	toluene	77 (9)	85
8	(*R*)-MeO-DTBM-BIPHEP	*m*-xylene	76 (12)	87
9	(*R*)-MeO-DTB-BIPHEP	*m*-xylene	86 (11)	92

[a] Yield determined by ^{1}H NMR versus an internal standard (9-bromophenanthrene).

We next evaluated various nucleophiles as terminating groups for the gold-catalyzed polycyclization. We were pleased to find that the catalyst and conditions developed for lactonization of **1** were fairly insensitive to the nature of the terminating group. For example, gold-catalyzed sulfonamide-terminated cyclization of enyne **4** produced decahydroquinoline **5** in 75% yield and 92% ee (eq 2).



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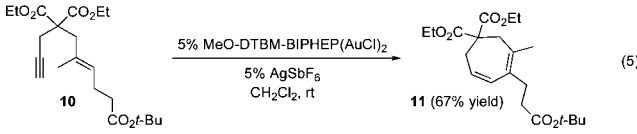
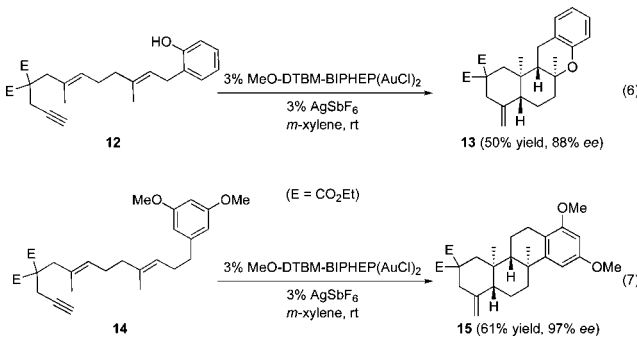
Cyclization of phenoxy-substituted phenyl alkynes also afforded products consistent with a cation-initiated polycyclization reaction. For example, gold-catalyzed reaction of **6a**−**c** produced hexahydroxanthene derivatives **7a**−**c** in excellent yield and enantioselectivity (eq 3). Additionally, the use of an electron-rich aryl group as a nucleophile allowed for the enantioselective formation of **9**, which contains a benzylic quaternary center, in 98% yield and 94% ee (eq 4). The generality of the reaction conditions is noteworthy, allowing a diverse range of nucleophilic terminating groups to participate in the gold-catalyzed polycyclization reaction with excellent chemo-, diastereo-, and enantioselectivity.

In contrast, gold-catalyzed reaction of *tert*-butyl ester **10** afforded only 18% of lactone **2a** along with 27% of **3** and 18% of cycloheptadiene **11**, in xylene at room temperature. Moreover, gold-catalyzed reaction of **10** in methylene chloride generated **11** as the major product (eq 5). These products are consistent with a mechanism in which gold, rather than the trapping nucleophile, stabilizes the developing positive charge in the cyclization.[16] This observation supports the hypothesis that the nature of the nucleophile, and even the solvent, can impact the nature of the gold intermediate in these cyclization reactions.[17,18]



Encouraged by the successful gold-catalyzed bicyclization reactions, we turned our attention to examining the corresponding tricyclization process. To this end, gold-catalyzed reaction of phenol **12** afforded tetracyclic ether in 88% ee (eq 5). Additionally, dieneyne **14** reacted smoothly at room temperature to afford tetracyclic compound **15** as a single diastereomer in 61% yield and 97% ee (eq 7). An X-ray structure **15** provided confirmation of the structure and allowed for assignment of its absolute stereochemistry.



In conclusion, we have developed the first example of a highly enantioselective polyene cyclization reaction in which transition-metal-promoted alkyne activation serves as the cyclization initiating event. The (MeO-DTB-BIPHEP)gold(I)-catalyzed reaction offers an efficient method for the stereoselective synthesis of polycyclic compounds whose stereochemistry is consistent with the Stork−Eschenmoser postulate for polyene cyclization. In this context, a number of nucleophiles can be used to terminate the reaction, and therefore carbo- and heterocyclic structures can be accessed.

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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) (a) Bartlett, P. A. In *Asymmetric Synthesis*, Vol. 3; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; p 341. (b) Van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. (c) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi. (d) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (e) See also: Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812.

(2) For selected examples and relevant discussion, see: (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzika, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890–1904. (c) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9–16. (d) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490. (e) Nishizawa, M.; Takenaka, H.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Am. Chem. Soc.* **1984**, *107*, 522. (f) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999. (g) Bogensättter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206.

(3) (a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (b) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (c) Zhao, Y.-J.; loh, T.-P. *J. Am. Chem. Soc.* **2008**, *130*, 10024. (d) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem., Int Ed.* **2008**, *47*, 6011. (e) Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedron* **2010**, doi: 10.1016/j.tet.2010.03.037.

(4) For exceptions involving organocatalytic polyene cyclization reactions, see: (a) Rendeler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (b) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

(5) Au-Catalyzed: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. Hg-Catalyzed: (c) Imagawa, H.; Iyenaga, T.; Mishizawa, M. *Synlett* **2005**, 703. (d) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451.

(6) For examples of Pd- and Pt-promoted polycyclization reaction intiated by coordination to an alkene, see: (a) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459. (b) Feducia, J. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592. For a catalytic variant, see: (c) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880. For an enantioselective example see ref 3d.

(7) (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (b) Blarre, T.; Toullec, P. Y.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888.

(8) (a) Muñiz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293. (b) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem.—Eur. J.* **2009**, *15*, 1319. (c) Chao, C.-M.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538. For an example of highly enantioselective 6-*endo*-dig initiated cycloisomerization reactions, see: (d) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988.

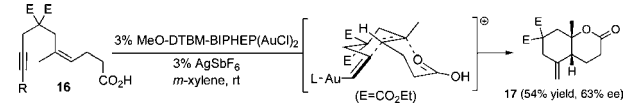
(9) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315.

(10) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030.

(11) (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (b) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283. (c) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402. (d) Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464. (e) Zhnag, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.

(12) Replacing $AgSbF_6$ with either $AgClO_4$ (81% ee) or $AgBF_4$ (82% ee) resulted in a decrease in enantioselectivity.

(13) In accord with the Stork−Eschenmoser hypothesis,[2a,b] cyclization of (*Z*)-alkene **16** selectively afforded *cis*-fused lactone **17** in 54% yield and 63% ee.



(14) In all other examples, the enantioselectivity was identical at rt and−40°C.

(15) (a) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (b) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957. (c) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727. (d) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310.

(16) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306.

(17) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III.; Toste, F. D. *Nature Chem.* **2009**, *1*, 482.

(18) (a) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (c) Michelet, V.; Toullec, P.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268.

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