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Chirality Transfer in Au-Catalyzed Cyclization Reactions of Monoallylic Diols: Selective Access to Specific Enantiomers Based on Olefin Geometry

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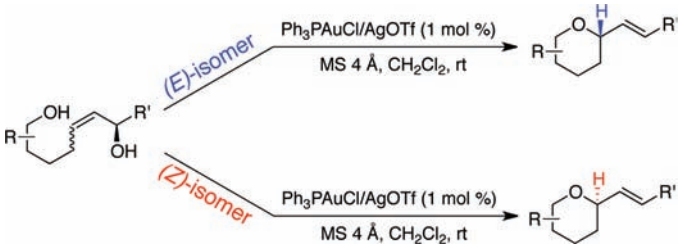
ABSTRACT



The gold(I)-catalyzed cyclization of monoallylic diols to form tetrahydropyrans is shown to be highly stereoselective when chiral allylic alcohols are employed. Substrates that differ only in olefin geometry provide enantiomeric products from formal S_N2' reactions in high yields with excellent chirality transfer. The allylic alcohol stereochemistry also efficiently controls the facial selectivity when the substrates include additional stereocenters.

The area of homogeneous gold catalysis continues to progress at an extremely rapid pace with many new and interesting advancements appearing almost daily.[1] These transformations rely on the ability of gold complexes to activate π-bonds leading to the development of new catalysts and selective new reactions of alkynes, allenes, and alkenes through inspired substrate design. While reactions of alkynes and allenes are the most prevalent and occur under mild conditions, reactions of alkenes typically require more forcing conditions[2] and Au-catalyzed reactions of this substrate class are far less developed.[3] Although the addition of heteroatoms to prochiral olefins with a variety of nucleophiles has been reported,[4] currently Au-catalyzed alkene addition[5] reactions that proceed with discrimination of heterotopic

(1) For recent reviews on Au-catalysis, see: (a) Hashmi, A. S. K.; Buhrle, M. *Aldrichimica Acta* **2010**, *43*, 27. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232. (c) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675. (d) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3366. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (h) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (i) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885.

(2) In comparison to reactions of alkynes and allenes, elevated temperatures and prolonged reaction times are typically required for alkenes. For representative examples see refs 1 and 4.

(3) Au-catalyzed cycloisomerization reactions of enynes have been extensively reported, but the catalyst activates the alkyne component in these substrates. For leading references, see: Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. Additionally, selective addition to enantiotopic alkynes has been explored: (a) Hashmi, A. S. K.; Hamzic, M.; Rominger, F.; Bats, J. W. *Chem.—Eur. J.* **2009**, *15*, 13318. (b) Wilckens, K.; Uhlemann, M.; Czekelius, C. *Chem.—Eur. J.* **2009**, *15*, 13323.

(4) For leading references, see: (a) Zhang, J. L.; Yang, C. G.; He, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (b) Liu, X. Y.; Li, C. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 2707. (c) Shi, M.; Liu, L. P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043. (d) Han, X. Q.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (e) Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (f) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (g) Yao, X. Q.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 6884. (h) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828. (i) Iglesias, A.; Muñiz, K. *Chem.—Eur. J.* **2009**, *15*, 10563. (j) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (k) Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885.

(5) For examples of selective addition to norbornene, see refs 4a, 4b, 4g, 4e. For diastereoselective reactions, see: (a) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (b) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143. (c) Li, H.; Widenhoefer, R. A. *Org. Lett.* **2009**, *11*, 2671.

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π-faces to selectively prepare chiral products have seldom been reported. This is likely due in part to the propensity of Au-complexes to catalyze *anti*-addition reactions across π-bonds placing the ligands in a fairly distal position from the newly formed stereocenter. Herein we report a highly selective Au(I) catalyzed reaction of alkenes where the absolute configuration of the product is controlled by the olefin geometry of the substrate.

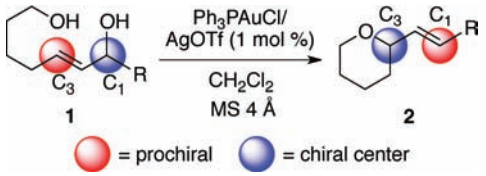

Figure 1. Chirality transfer.

Recent reports from our laboratory and others have demonstrated that heteroatom nucleophiles readily add to the π-bond of unsaturated alcohols in Au-catalyzed processes.[6] In our systems, the reactions proceed with concomitant loss of water and constitute a formal S_N2' reaction to form substituted tetrahydropyrans.[6a,b] The reaction generates a new chiral center, and due to the ubiquity of the tetrahydropyran moiety in natural products,[7] we were interested in exploring methods to control the stereochemistry at the newly formed stereogenic center. We envisioned that chirality could be transferred from the allylic alcohol carbon to the newly formed center and in the course of the reaction erase the stereocenter that guided its formation (Figure 1). This process would be advantageous because it should be possible to selectively obtain either tetrahydropyran enantiomer by controlling the olefin geometry, and highly functionalized chiral allylic alcohols are readily prepared by a variety of reliable methods.

Substitution reactions of allylic alcohols (inter- and intramolecular) have been reported using a variety of other metal-based catalyst systems including palladium,[8] platinum,[9] rhodium,[10] ruthenium,[11] iron,[12] and bismuth.[13] For chirality transfer to be successful, a highly organized transition state is necessary. Several mechanistic scenarios have been suggested including formation of a stabilized allyl cation (Fe^{3+}, Bi^{3+}), π-allyl metal complex formation (Pd^0, Pt^0, Rh^{1+}, Ru^{2+}), and a *syn* S_N2' pathway (Pd^{2+}).[8−13] Enantioselective reactions of π-allyl metal complexes are well-known, and Uenishi has reported very nice examples of chirality transfer under Pd(II)-catalysis.[8e−h] In his examples, Pd(II) is proposed to be complexed to both the olefin and alcohol of the allylic alcohol as well as the incoming nucleophile. In contrast to the ability of Pd(II) to form a highly coordinated catalyst−substrate complex, Au(I) complexes are known to coordinate to two ligands and prefer a linear geometry.[1] We were interested in determining if the stereochemistry of the allylic alcohol could be transferred to the product upon cyclization of chiral substrates even though a linear alkene/Au(I) complex with more degrees of freedom would be formed. Additionally, the low loadings and functional group tolerance should allow for a wide variety of products to selectively be formed by changing either the olefin geometry or the absolute configuration of the allylic alcohol.

To test this premise, monoallylic diols with the same absolute configuration but differing in olefin geometry were prepared by selective reduction of a common propargylic alcohol[14] to both the *cis*- and *trans*-olefins.[15] The simple substrates **5** and **7** were prepared and subjected to the reaction conditions (Table 1, entries 1 and 2). To our delight, the tetrahydropyran **6** was isolated in high yield with both substrates. Interestingly, the products of the two reactions were enantiomers with only a small loss of ee observed in the cyclization event. The scope of the reaction was then explored and found to be fairly general, also smoothly producing enantiomeric methylene tetrahydropyrans and morpholines (entries 3−6) with

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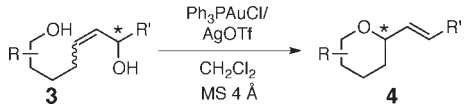
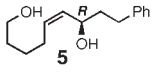
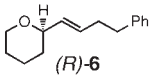
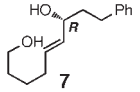
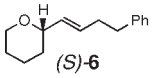
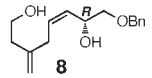
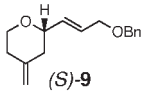
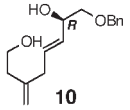
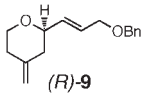
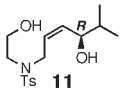
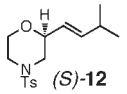
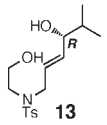
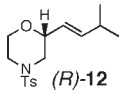
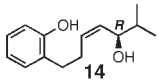
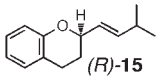
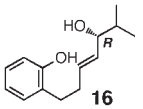
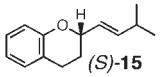
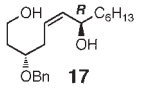
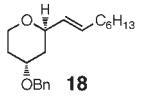
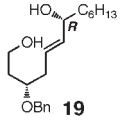
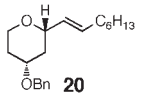
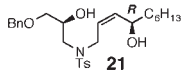
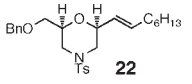
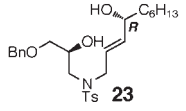
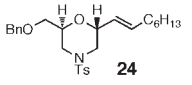
Table 1. Olefin Dependent Chirality Transfer



entry	substrate	substrate ee (dr)[a]	product	product ee (dr)[a]	yield (%)[b]
1	 **5**	96%	 *(R)*-**6**	93%[c]	94
2	 **7**	96%	 *(S)*-**6**	93%[c]	91
3	 **8**	98%	 *(S)*-**9**	97%	92
4	 **10**	98%	 *(R)*-**9**	98%	85
5	 **11**	97%	 *(S)*-**12**	95%[c]	93
6	 **13**	94%	 *(R)*-**12**	93%[c]	91
7	 **14**	97%	 *(R)*-**15**	75%[c]	89
8	 **16**	97%	 *(S)*-**15**	70%[c]	92
9	 **17**	99% (97:3)	 **18**	99% (96:4)[d]	84[e]
10	 **19**	99% (97:3)	 **20**	99% (4:96)[d]	87[e]
11	 **21**	97% (93:7)	 **22**	97% (93:7)[d]	83[e]
12	 **23**	97% (93:7)	 **24**	97% (8:92)[d]	79[e]

[a] Determined by HPLC. [b] Isolated yield. [c] Absolute configuration determined by conversion to a known derivative and comparison of the sign of the optical rotation. [d] Diastereomeric ratio determined by ^{1}H NMR. Major diastereomer shown. [e] Isolated yield of the major diastereomer.

excellent ee transfer. With phenolic nucleophiles chirality transfer was observed but the ee's of the products were lower than than the case with aliphatic alcohol nucleophiles (entries 7, 8). The absolute configuration of the products was consistent, however, with the other examples.

Interestingly, when additional stereocenters were present, the combination of allylic alcohol stereochemistry and olefin geometry controlled the stereochemical outcome of the reaction overriding any inherent bias of the system to selectively provide the *cis*- or *trans*-diastereomers **18**/**20** and **22**/**24** respectively (entries 9−12).

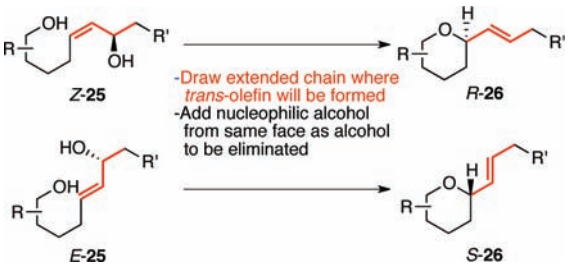


Figure 2. Predictive stereochemical mnemonic.

Analysis of the stereochemistry should provide insight into how the allylic alcohol influences π-face discrimination and enhances olefin reactivity. In the systems studied to date, the sense of chirality transfer is consistent. From these data it can be seen that if the substrate is drawn as is shown for *E*- and *Z*-**25**, in a position to form the tetrahydropyran and the *trans*-olefin (Figure 2), adding the nucleophilic alcohol to the π-face *syn* to the allylic hydroxyl group provides the observed products. This mnemonic has proven to be a reliable stereochemical predictor for reactions that provide both enantiomeric and diastereomeric products.

Mechanistically, the reaction provides products that result from a *syn* S_N2' reaction.[8e−h,16] Although a concerted mechanism with catalyst coordination to the allylic alcohol cannot be ruled out at this point, a two-step formal *syn* S_N2' process with the Au-catalyst activating the π-bond toward nucleophilic addition[1] followed by elimination of a gold hydroxide species[17] is likely. The two stereochemical elements in the products allow the stereochemistry of each step to be determined; however, they are interdependent. In a two-step process, both *syn*-alkoxyauration/*syn*-β-hydroxide elimination and *anti*-addition/*anti*-elimination are consistent with the stereochemistry observed. *Syn*/*anti* or *anti*/*syn* pathways would yield products with either opposite absolute configuration or olefin geometry. To date, only *trans*-olefins have been observed as products in this system.[18]

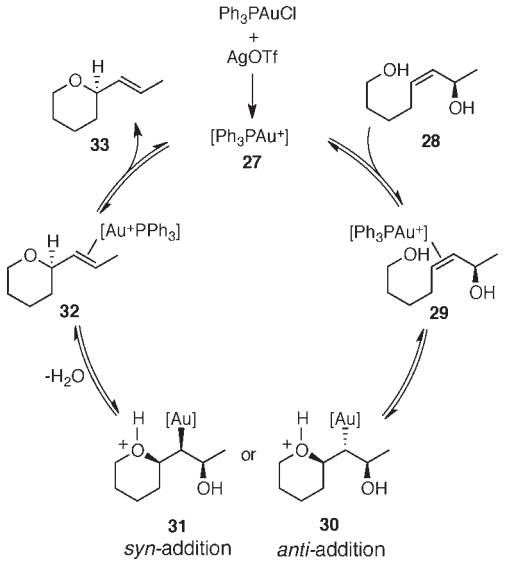
A probable catalytic cycle is shown in Scheme 1. The cationic complex **27** is generated from the precatalyst Ph_3PAuCl and AgOTf. Complexation to the allylic alcohol π-bond then forms **29** which undergoes nucleophilic attack

(16) Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. D.-H. *J. Org. Chem.* **2008**, *73*, 9426.

(17) Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 2742.

(18) Widenhoefer recently reported an amination reaction of a chiral allylic alcohol where both enantiomer/olefin isomer combinations were observed. See ref 6e.

Scheme 1. Probable Catalytic Cycle



forming the tetrahydropyran **30** or **31** in an *anti*- or *syn*-addition process respectively. Loss of water and decomplexation regenerate the catalyst and provide the product **33**.

While both *syn*-addition/*syn*-elimination and *anti*-addition/*anti*-elimination processes lead to the correct stereochemistry, an *anti*-/*anti*- mechanism is likely to be preferred due to the nucleophilic addition step. *Anti*-alkoxyauration involves the outer sphere attack of the nucleophile on a catalyst π-complex, which is the role typically invoked with gold(I) catalysts.[1,19] From complex **29**, *anti*-addition would give **30** that then must lose a proton and undergo *anti*-elimination to provide the *trans*-olefin. It is possible that this is facilitated by hydrogen bonding (in **34** and **35**, Figure 3) and direct loss of water

(19) Recent computational studies support the *anti*-addition mechanism for addition to alkynes: Krauter, C. M.; Hashmi, A. S. K.; Pernpointner, M. *ChemCatChem* **2010**, *2*, 1226.

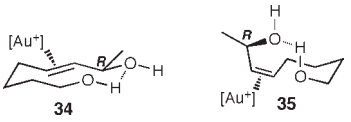


Figure 3. Potential hydrogen bonding.

without any intermolecular proton transfer steps.[6e] Additionally, *syn*-processes should be disfavored because of the preference for Au(I)-complexes to contain only two ligands in a linear geometry.[1a] In comparison to other noble metal based catalyst systems, this preference is unique to Au(I)-complexes.[20] Experiments to conclusively distinguish between the two mechanistic scenarios are underway and should aid in the further development of Au-catalyzed reactions of olefins with π-facial selectivity.

In conclusion, we have demonstrated that Au-catalyzed reactions of alkenes can exhibit a high degree of π-facial selectivity to provide tetrahydropyrans in high ee or de. The desired enantiomer or diastereomer can easily be produced from a given chiral propargylic alcohol by reduction to the correct olefin isomer and cyclization. Applications in natural product synthesis and mechanistic studies are underway and will be reported in due course.

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

(20) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.