# Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides

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ABSTRACT
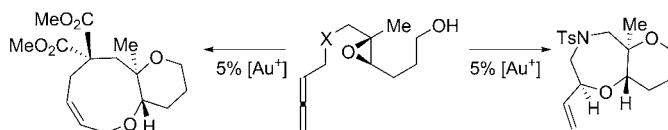
Cationic gold(I) phosphite catalysts activate allenes for epoxide cascade reactions. The system is tolerant of numerous functional groups (sulfones, esters, ethers, sulfonamides) and proceeds at room temperature in dichloromethane. The cyclization pathway is sensitive to the substitution pattern of the epoxide and the backbone structure of the A-ring. It is capable of producing medium-ring ethers, fused 6-5 bicyclic, and linked pyran-furan structures. The resulting cycloisomers are reminiscent of structures found in numerous polyether natural products.

The use of cascade reactions[1] to enhance the molecular complexity of readily prepared starting materials provides great opportunities for the development of novel catalytic protocols. The biosynthesis of molecules like glabrescol,[2] the brevetoxins,[3] and monensin[4] have each been proposed to rely on polyepoxide cascades, a strategy that has also been adopted in natural product synthesis. For example the McDonald synthesis of durgamone/nakorone A[5] and the Jamison assembly of "ladder" polyethers utilize a polyepoxide cascade as the critical step (Scheme 1).[6]

Gold(I)−phosphine and phosphite complexes have recently been shown to activate carbon−carbon multiple bonds for

Scheme 1. Synthesis of Durgamone (McDonald) and Ladder Polyethers (Jamison)
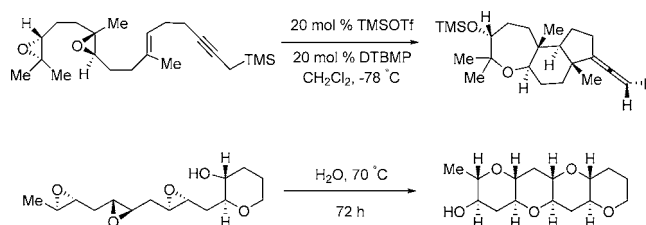
attack by oxygen nucleophiles.[7−9] Most demonstrative of the exquisite chemoselectivity of Au(I) catalysts is the epoxide O-nucleophile class of reactions,[10] which are themselves susceptible to Lewis acid activation. These observations led us to ask if C−C unsaturation could

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be chemoselectively activated toward epoxide nucleophiles to initiate a biomimetic cascade multiether ring forming reaction.[11,12] Starting from our efforts on Au(I)-catalyzed allene activation,[13,14] we designed experiments to determine the feasibility of activating an allene in the presence of a hydroxy-epoxide. To this end, we investigated the cyclization of **1** using a variety of L−AuCl/AgX combinations. From this screen emerged an optimal catalyst formulation: (PhO)$_3$PAuCl (5 mol %) + 5 mol % AgOTf in CH$_2$Cl$_2$.[15] As shown in eq 1, this enabled the cyclization of **1** in <30 min at rt to a diastereomeric mixture of the pyrans **2a** and **2b** in 65% combined yield (2.2:1). No allene activation occurred in the absence of the gold catalyst.[16]
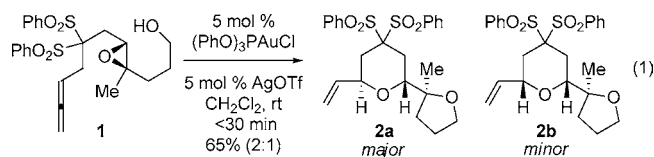
From a combination of NMR data on **2a** and **2b** and X-ray data on **2a** (Figure 1), the two compounds were determined
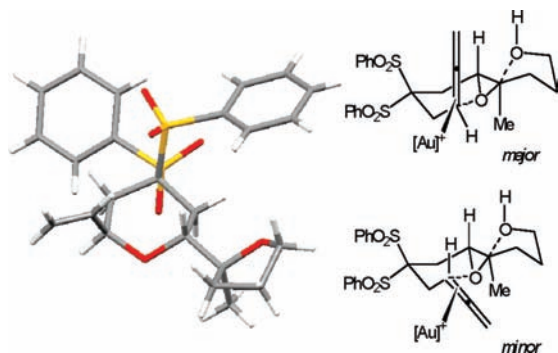
Figure 1. Crystal structure of trans-fused pyran **2a** (sulfur = yellow, oxygen = red, carbon = gray, hydrogen = white).

to be epimeric at the allyl-ether stereocenter. The relative configuration at the pyran-furan linkage was consistent with clean inversion of the original epoxide and adoption of a twist-boat solution conformer. The epimeric allylic ethers

(8) For examples of Au(I)-alkyne-initiated cascade cyclizations, see: (a) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888–2891. (b) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033. (c) Zriba, R.; Gandon, V.; Aubert, C.; Fensterbank, L.; Malacria, M. *Chem.—Eur. J.* **2008**, *14*, 1482–1491. (d) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071. (e) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071. (f) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, D. F. *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133. (g) Nieto-Oberhuber, C.; Muñoz, M. P.; Lopez, S.; Jimenez-Nuñez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M *Chem.—Eur. J.* **2006**, *12*, 1677–1693. (h) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726–6730. (i) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (j) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963. (k) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655. (l) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406.

presumably stem from the competing cyclization geometries shown in Figure 1.[17]

Treating these reactions conditions as optimal, a series of substrates were examined to establish the effect of epoxide stereochemistry, regiochemistry, and backbone functionality (Table 1). The ethereal and malonate-derived backbones, in

Table 1. Scope of the Allene Initiated Cascade Cyclization

substrate		product(s)	yield[a]	selectivity
				(trans:cis)[b]
1	X = (PhO$_2$S)$_2$C	**2a,b**	65%	2.2:1
3	X = O	**4a,b**	60%	1:8
5	X = (MeO$_2$C)$_2$C	**6a,b**	65%[c]	1:8
		6c		
7	X = (PhO$_2$S)$_2$C	**8a,b**	35%	7:1
9	X = NTs	**10a,b**	59%[d]	4:1
11	X = (MeO$_2$C)$_2$C	**12**	40%	--[e]
13		**14a,b**	45%	2.5:1

[a] General conditions: 5 mol % (PhO)$_3$PAuCl/5 mol % AgOTf, CH$_2$Cl$_2$, rt, 15−45 min. Isolated yields after silica gel chromatography. [b] Relative stereochemistry of ethereal α and α′ stereocenters in the vinyl-bearing oxacycle. [c] About 10% of **6c** also generated. [d] Less than 10% of the 9-*endo* product also formed. [e] Only one isomer detected by ^{1}H, ^{13}C NMR.

contrast to **2a,b**, stereoselectively provided the *cis*-pyran in good dr (1:8 by NMR).[18] Worth noting in **5** was a competing (H$^+$ and Ag$^+$ catalyzed) ring-opening of the epoxide by the alcohol and subsequent lactonization to **6c** (∼10% yield). Attempts to further enhance chemoselectivity for allene activation through base addition, lowered catalyst loading, solvent change, or lowered temperature were not fruitful.

In the case of **7**, **9**, and **11**, the alternative positioning of the methyl group on the epoxide led to fused ethers. As noted

by Kozmin,[8j] McDonald,[19] and Fürstner,[8b] the methyl group positioning on an epoxide influences the ring-opening regiochemistry by distorting the epoxonium intermediate to localize charge at the most substituted center.[20,21]

Unexpectedly, 5-Me diester **11** did not yield the expected [5.4.0] bicyclic ether, but instead provided the 9-*endo* product **12** as a single stereoisomer. Traces of this cyclization mode were detected for compound **9** (∼10%), but its production could not be improved. Fused medium-ring ethers are, of course, ubiquitous in marine-derived natural products. Changing the epoxide stereochemistry in **13** led to stereoisomeric **14a**,**b** (c.f. **2a**,**b**), indicative of a cyclization that was stereospecific and invertive at the epoxide.

One mechanistic quandary revolved around whether the reaction initiated at the allene as envisioned in Figure 1, or

proceeded by epoxide opening and allene hydroalkoxylation.[22] This alternative pathway was investigated by precyclizing **1** with 1% TfOH to **15**, and then carrying out a hydroalkoxylation to **2a**,**b** (eq 2). Unlike the direct cyclization of **1**, **2a**,**b** was obtained in a 1:1 ratio, suggesting an allene first mechanism for **1**.
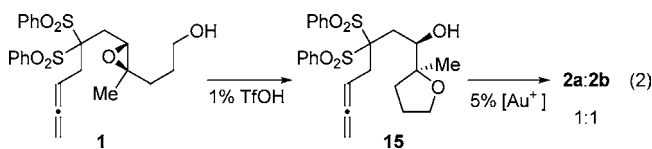
To investigate the feasibility of a tricyclization cascade, the isomerically pure diepoxide **16** was prepared using the asymmetric epoxidation protocols of Sharpless[23] and Shi[24] (eq 3). Upon exposure to the standard reaction conditions, isomerization ensued to form tricyclic ether **17**. Notably, **17** was formed in analogy to product **4** (Table 1) without significant loss in yield or diastereoselectivity, lending further support to the feasibility of the current methodology for multicyclization events in complex molecule synthesis.
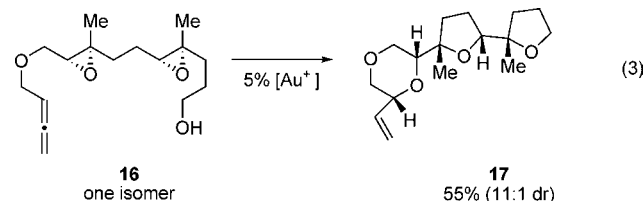
In conclusion, a method to generate polyether skeletons from allene-epoxide cascades has been developed. The method provides access to several ring structures commonly encountered in natural products and promises to yield catalyst control over cyclization regiochemistry. Studies are underway to utilize other heteroatomic traps and to elucidate the cyclization mechanism.

Supporting Information Available: Experimental procedures, spectra of new compounds, and CIF data for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Previous (unpublished) efforts in our laboratories with "carbophilic" Lewis acids always resulted in epoxide activation over alkene, which has also been observed by Yang and He under gold(III)/silver activation catalysis. See for example: (a) Liu, Y.; Li, X.; Lin, G.; Xiang, Z.; Xiang, J.; Zhao, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2008**, *73*, 4625–4629. (b) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964–5965.

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(14) Gold-allene activations were early to appear Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288.

(15) Other silver additives (AgSbF$_6$, AgBF$_4$, AgNTf$_2$, AgClO$_4$, AgOTs) or phosphine ligands (EtPh$_2$P, Cy$_3$P, (4-Cl-Ph)$_3$P, (4-MeO-Ph)$_3$P) led to lower yields of bicyclic product. Other solvents (PhMe, THF) led to complex mixtures.

(16) Exposure to AgOTf in the absence of Au(I) did not produce any discernable allene activation. In preliminary (unpublished) reactivity studies for related transition metal-catalyzed cyclization of allenyl esters, Yb(III) and Pd(II) showed negligible levels of desired reactivity.

(17) A pseudo-axial preference has been noted in previous electrophilic cyclizations, see for example: (a) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517–2518. (b) Koh, J. H.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459–3461. (c) Wan, S.; Gunayadin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915–7923.

(18) The role of the A-ring substituents on cyclization dr is not yet understood.

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(21) Jamison recently showed that water can overturn this propensity, see ref 6a for details.

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