CHEMISTRY
A EUROPEAN JOURNAL

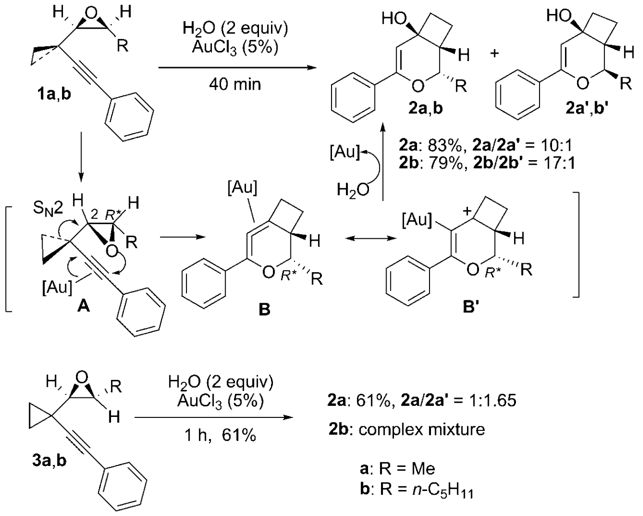
DOI: 10.1002/chem.200903419

Diversity of Products in the Gold-Catalyzed Cyclization of 1-Epoxy-1-alkynylcyclopropanes by Using 1-Oxyallyl Cations

Chun-Yao Yang, Min-Shiun Lin, Hsuan-Hung Liao, and Rai-Shung Liu*[a]

Metal-catalyzed cycloaddition reactions are powerful tools in organic synthesis to access complex molecular frameworks.[1] The gold-catalyzed activation of alkynes enables the generation of unusual intermediates to react with dipolarophiles in a cycloaddition fashion.[2] Although 1-oxyallyl cations[3,4] are versatile intermediates in the [4+2] cycloaddition with dienes, such metal-free cationic species have not been elaborated in gold catalysis. As part of our continued interest in gold-catalyzed reactions of epoxyalkyne substrates,[5,6] we report the diversity of complex oxacyclic products derived from readily available 1-epoxy-1-alkynylcyclopropanes; the success of this catalysis relies on the stereoselective generation of cyclic 1-oxyallyl cations. Herein, we also report the unprecedented [4+2] cycloaddition of enones with such cations.

We prepared *cis*-epoxides **1a** and **1b** and their *trans* isomers **3a** and **3b** to illustrate the effect of epoxy substituents on gold-catalyzed oxacyclization, as depicted in Scheme 1. Treatment of the *cis* forms **1a** and **1b** with a mixture of $AuCl_3$ (5 mol%) and water (2 equiv) in dry CH_2Cl_2 (25°C, 40 min) delivered bicyclic oxacyclic alcohols **2a** and **2b** (79–83% yield) with high diastereoselectivities (d.r.>10:1).[7] Notably, the same catalysis on *trans*-epoxide **3a** lacks stereocontrol in the cyclization, giving a combined 63% yield of products **2a** and **2a′** (**2a′**/**2a**=1.65:1), whereas the other species **3b** gave a complex mixture of products. The structures of products **2a** and **2a′** are confirmed by their ^{1}H NOE spectra.[8] To rationalize the stereochemistry of alcohols **2a** and **2b**, we propose that the mechanism of formation of compounds **2** is likely to involve a concerted electrocyclization as shown by π-alkyne **A**, including an S_N2-type 1,2-migration of the cyclopropyl C–C bond, giving key π-cycloallene species **B** or its resonance structure **B′**.[9] In structure **A**, the epoxy C(2)–O bond is expected to be aligned with the C(4)–C(5) bond to shorten the distance between the interacting C and O atoms, facilitating a 6-*endo-dig* cyclization. Herein, the C(2)–O σ* orbital overlaps efficiently with the cyclopropyl C–C bond near the R group, inducing an S_N2 migration. We attribute the high stereoselectivity of *cis*-epoxides **1a** and **1b** to their *cis* R groups that force the alkynyl group to move toward the epoxy functionality, as depicted in Figure 1. In contrast, the alkynyl group of *trans*-epoxide **3a** is far away from the epoxide and not favorable for the proposed electrocyclization. Accordingly, *cis*-epoxide **1b** (R=*n*-C_5H_{11}) is superior to **1a** (R=Me) in terms of stereoselectivity.[10]



Scheme 1. Gold-catalyzed oxycyclization of epoxy-substituted compounds.

Scheme 2 shows a control experiment to assess a hypothetical S_N2-type cyclopropyl expansion. We prepared chiral trisubstituted (*R*)-epoxide **4** (65% enantiomeric excess (*ee*)) containing only one stereogenic carbon;[11] the same catalysis gave the desired bicyclic oxacyclic alcohol **5** without com-

---

[a] C.-Y. Yang, M.-S. Lin, H.-H. Liao, Prof. Dr. R.-S. Liu
Department of Chemistry, National Tsing-Hua University
Hsinchu, 30043, Taiwan(ROC)
Fax: (+886)3-5711082
E-mail: rsliu@mx.nthu.edu.tw

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903419.

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

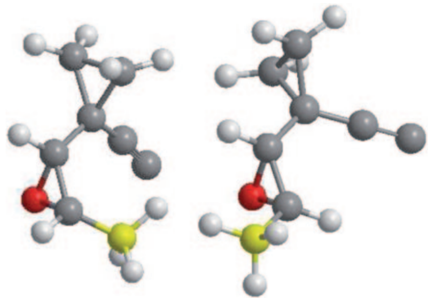
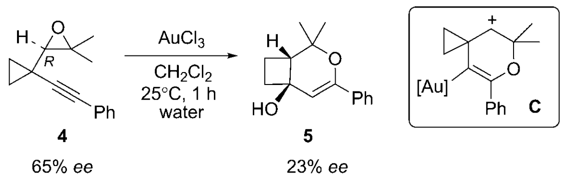


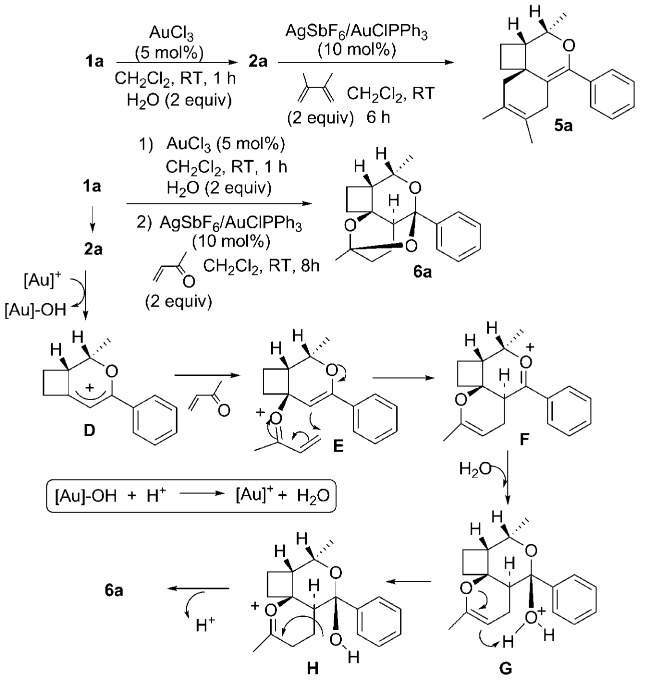
Figure 1. Molecular models for **1a** (left) and **3a** (right). The phenyl group was omitted for clarity; the epoxy oxygen and methyl carbon are marked as red and yellow balls, respectively.



Scheme 2. A control experiment to assess a hypothetical cyclopropyl expansion.

plete loss of chirality. The observed 23 % *ee* supports a hypothetical S_N2 mechanism that is operable for a significant proportion of (*R*)-epoxide **4**. Loss of the chirality is probably attributable to a competitive generation of free cation **C** that is stabilized by dimethyl substituents.

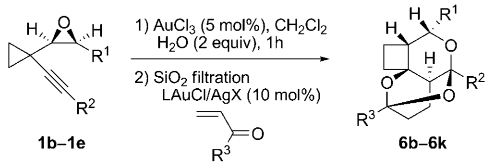
Scheme 3 shows our efforts to achieve a cyclization/cycloaddition sequence on epoxyalkyne **1a**. Treatment of **1a** in a dry CH_2Cl_2 solution with 2,3-dimethylbutadiene (2–5 equiv) and $AuCl_3$ (5 mol %) at 28 °C (1–8 h) failed to give the desired cycloadduct, which was as expected because no intermolecular cycloaddition has been reported for gold–π-allene species, such as **B** (or **B′**) with a dipolarophile.[9,12] We sought to accomplish this cycloaddition with gold-free 1-oxyallyl cation **D**, generated from the ionization of alcohol **2a**. After screening various gold complexes and a Brønsted acid,[13] we found that $PPh_3AuCl/AgSbF_6$ efficiently catalyzed the [4+2] cycloaddition of the 1-oxyallyl cation **D** with 2,3-dimethylbutadienes. In a standard procedure, once the complete conversion of epoxide **1a** to bicyclic oxacyclic alcohol **2a** in the initial $AuCl_3$ catalysis step was observed, the resulting CH_2Cl_2 solution was filtered through a short silica pad before treatment of this filtrate with 2,3-dimethylbutadiene (2 equiv) and $PPh_3AuCl/AgSbF_6$ (10 mol %). This two-step procedure provided tricyclic compound **5a** as a single diastereomer, with an overall 65 % yield. Pleasingly, we found that this tandem reaction is even applicable to substrates, such as but-3-en-2-one, giving the tricyclic oxacyclic compound **6a**, of which the structure was carefully determined with ^{1}H NOE spectra.[8] We envisage that the success of this novel enone cycloaddition relies on the strong s character of the carbocation associated with the cyclobutyl carbon of 1-oxyallyl cation **D**. In this mechanism, the resulting tricyclic oxonium species **F** reacts with water through a bifunctional oxonium–enol (acid–base) pair, ultimately giving the observed product **6a** with the release of one proton.



Scheme 3. Gold-catalyzed cyclization/cycloaddition sequences on epoxyalkyne **1a**.

Table 1 shows additional examples to assess the generality of the enone cycloaddition reaction. This reaction sequence is extendible to the *cis*-epoxides **1b**–**1e** containing an *n*-pentyl group (R^1) and various phenyl groups (R^2 = H, Me, OMe, and F) at their epoxy and alkynyl functionalities, respectively; the resulting tricyclic oxacyclic compounds **6b**–**6e** were obtained with yields exceeding 71 %. Entries 5–10

Table 1. Gold-catalyzed cyclization/cycloaddition reactions with enones.



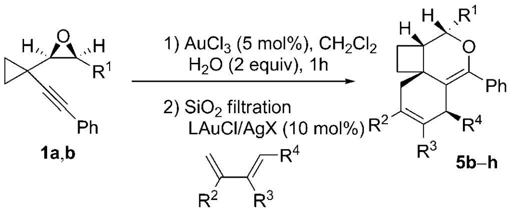
Entry	Epoxide[a] R^1	R^2	Enone R^3	*t* [h]	Product (yield [%])[b]
1	*n*-C_5H_{11}	Ph (**1b**)	Me	10	**6b** (85)
2	*n*-C_5H_{11}	4-MeC_6H_4 (**1c**)	Me	6	**6c** (71)
3	*n*-C_5H_{11}	4-$MeOC_6H_4$ (**1d**)	Me	8	**6d** (81)
4	*n*-C_5H_{11}	4-FC_6H_4 (**1e**)	Me	8	**6e** (73)
5	Me	Ph (**1a**)	Et	6	**6f** (80)
6	*n*-C_5H_{11}	Ph (**1b**)	Et	8	**6g** (79)
7	Me	Ph (**1a**)	*n*-C_5H_{11}	6	**6h** (89)
8	*n*-C_5H_{11}	Ph (**1b**)	*n*-C_5H_{11}	9	**6i** (91)
9	*n*-C_5H_{11}	4-$MeOC_6H_4$ (**1d**)	*n*-C_5H_{11}	10	**6j** (81)
10	*n*-C_5H_{11}	4-FC_6H_4 (**1e**)	*n*-C_5H_{11}	10	**6k** (71)

[a] [epoxide] = 0.05 M, enone (2 equiv), L = PPh_3, X = SbF_6. [b] Yields are reported after separation on a silica column.

(Table 1) illustrate the applicability of this gold catalysis protocol to the cyclization reactions of *cis*-epoxides **1a**, **1b**, **1d**, and **1e** with pent-1-en-3-one and oct-1-en-3-one; we obtained the desired products **6f**–**6k** efficiently and stereoselectively: only one diastereomeric product was formed. ^{1}H NOE spectra were obtained for compounds **6a**, **6f**, and **6h** to confirm their stereochemistry.

As shown in Table 2, various butadienes were suitable for this new [4+2] cycloaddition, including 2,3-dimethylbutadiene, 1-methylbutadiene, 1,3-hexadiene, and 1,2-dimethylbutadiene. Gold-catalyzed cyclization of these dienes with epoxides **1a** and **1b** gave the desired [4+2] cycloadducts **5b**–**5h** with satisfactory yields in most cases. Such a cyclization/cycloaddition sequence proceeds with high stereo- and regiocontrol, allowing the formation of only one diastereomeric product. The ^{1}H NMR spectral data of these products resemble those of compound **5a**, indicative of the same stereochemistry. We have obtained ^{1}H NOE spectra to determine the structure of cycloadduct **5e**.

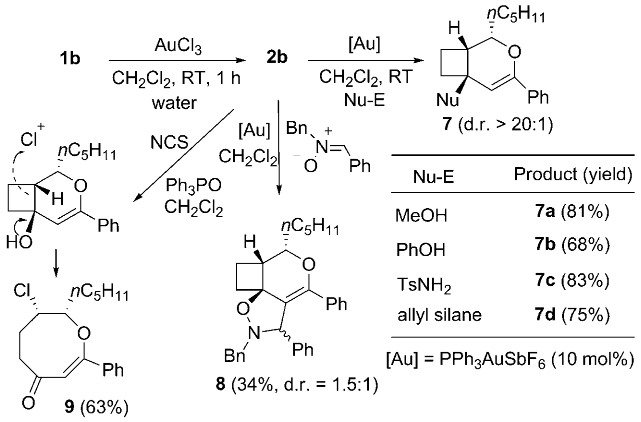
Table 2. Gold-catalyzed cyclization and cycloaddition with dienes.



Entry	Epoxide[a]	Diene			*t* [h]	Product
	R^1	R^2	R^3	R^4		(yield [%])[b]
1	*n*-C$_5$H$_{11}$ (**1b**)	Me	Me	H	7	**5b** (78)
2	Me (**1a**)	Me	H	H	6	**5c** (61)
3	*n*-C$_5$H$_{11}$ (**1b**)	Me	H	H	7	**5d** (61)
4	Me (**1a**)	H	H	Et	6	**5e** (70)
5	*n*-C$_5$H$_{11}$ (**1b**)	H	H	Et	8	**5f** (70)
6	Me (**1a**)	H	Me	Me	6	**5g** (46)
7	*n*-C$_5$H$_{11}$ (**1b**)	H	Me	Me	8	**5h** (45)

[a] [substrate] = 0.05 M, diene (2 equiv). [b] Yields are reported after separation on a silica column.

Scheme 4 shows the availability of various oxacyclic compounds by using alcohol **2b** as the key intermediate. Addition of nucleophiles, namely, MeOH, PhOH, TsNH$_2$ (Ts = tosyl), and allyl silane and addition of the PPh$_3$AuCl/AgSbF$_6$ catalyst (10 mol%) to a CH$_2$Cl$_2$ solution of alcohol **2b**, generated from the AuCl$_3$ catalysis, delivered products **7a**–**7d** in good yields; only one isomeric product was produced here. With nitrone and PPh$_3$AuCl/AgSbF$_6$ (10 mol%), we obtained the [3+2] cycloadduct **8** as a 1.5:1 mixture of two diastereomers. Treatment of species **2b** in the original CH$_2$Cl$_2$ solution with *N*-chlorosuccinimide (NCS, 2 equiv) and Ph$_3$PO provided eight-membered oxacyclic compound **9** in 63% yield; in this one-pot synthesis, Cl$^+$ approaches the cyclobutyl ring opposite the hydroxyl group to facilitate the S$_N$2-type ring opening. Notably, formation of compound **9** from epoxyalkyne **1b** involves two consecutive expansions of carbocyclic rings. The availability of diverse oxacyclic products in this synthesis truly reflects its synthetic value.



Nu-E	Product (yield)
MeOH	**7a** (81%)
PhOH	**7b** (68%)
TsNH$_2$	**7c** (83%)
allyl silane	**7d** (75%)

[Au] = PPh$_3$AuSbF$_6$ (10 mol%)

Scheme 4. Availability of various oxacyclic compounds from the intermediate alcohol **2b**; Bn = benzyl.

In summary, we observed a high stereoselectivity for the AuCl$_3$-catalyzed hydrative cyclization of 1-epoxy-1-alkynylcyclopropanes for the *cis*-epoxides rather than their *trans* analogues. An electrocyclization appears to be a suitable model, as determined with the use of chiral epoxides and control experiments. Since this cyclization produced 1-oxyallyl cations efficiently, we accomplished a two-step [4+2] annulation of epoxyalkynes **1** with dienes, and also with enones, to provide complex oxacyclic compounds with excellent diastereoselectivity. The successful 1-oxyallyl cation/enone cycloaddition is unprecendented in literature reports. To highlight the use of this gold-catalyzed protocol, we demonstrated the diversity of oxacyclic products through the functionalization of alcohol intermediate **2**.

Experimental Section

Compound **1b** (80 mg, 0.30 mmol) and H$_2$O (5.4×10^{-3} mL, 2 equiv) were added dropwise, at 23 °C, to a solution of AuCl$_3$ (4.5 mg, 0.015 mmol, 5 mol%) in dichloromethane (3.0 mL) and the solution was stirred for 40 min. The resulting solution was filtered through a pad of Celite and eluted through a silica-gel column (hexane/ethyl acetate = 10:1) to give compound **2b** as a colorless oil (67 mg, 0.23 mmol, 79%).

Acknowledgements

The authors thank the National Science Council, Taiwan for supporting this work.

Keywords: alkynes · cycloaddition · epoxides · gold · oxycyclization

---

[1] a) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; b) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; c) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; d) A. Fürstner, P. Davies

Angew. Chem. **2007**, *119, 3478; Angew. Chem. Int. Ed.* **2007**, 46, 3410; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; e) S. Md. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269; f) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49.

[2] For gold-catalyzed intermolecular cycloaddition reactions, see: a) N. D. Shapiro; Y. Shi, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654; Y. Shi, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654; b) S. Suárez-Pantiga, E. Rubio, C. Alvarez-Rúa, J. M. González, *Org. Lett.* **2009**, *11*, 13; c) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244; d) G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 12598; e) G. Li, X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 6944; f) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814; g) F. Liu, Y. Yu, J. Zhang, *Angew. Chem.* **2008**, *120*, 5613; *Angew. Chem. Int. Ed.* **2009**, *48*, 5505; h) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244; i) M. Schelwies, A. L. Dempwolff, F. Rominger, G. Helmchen, *Angew. Chem.* **2007**, *119*, 5694; *Angew. Chem. Int. Ed.* **2007**, *46*, 5598; j) Y.-C. Hsu, S. Datta, C.-M. Ting, R.-S. Liu, *Org. Lett.* **2008**, *10*, 521; k) C. C. Lin, T.-M. Teng, C. C. Tsai, H.-Y. Liao, R. S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16417.

[3] For cycloadditions of 2-oxyallyl cations, see selected examples: a) W. K. Chung, S. K. Lam, B. Lo, L. L. Liu, W.-T. Wong, P. Chiu, *J. Am. Chem. Soc.* **2009**, *131*, 4556; b) H. Xiong, J. Huang, S. K. Ghosh, R. P. Hsung, *J. Am. Chem. Soc.* **2003**, *125*, 12694; c) M. A. Walters, H. R. Arcand, *J. Org. Chem.* **1996**, *61*, 1478; d) Y. Wang, A. M. Arif, F. G. West, *J. Am. Chem. Soc.* **1999**, *121*, 876; e) M. Ohno, K. Mori, T. Hattori, S. Eguchi, *J. Org. Chem.* **1990**, *55*, 6086.

[4] Cycloaddition of 1-oxyallyl cations is only operable with dienes, see a) P. G. Gassman, D. A. Singleton, *J. Org. Chem.* **1986**, *51*, 3075; b) P. G. Gassman, D. A. Singleton, J. J. Wilwerding, S. P. Chavan, *J. Am. Chem. Soc.* **1987**, *109*, 2183; c) P. G. Gassman, D. A. Singleton, *J. Am. Chem. Soc.* **1984**, *106*, 6085; d) P. G. Gassman, D. A. Singleton, *J. Am. Chem. Soc.* **1984**, *106*, 7993.

[5] a) R. J. Madhushaw, M.-Y. Lin, S. M. A. Sohel, R.-S. Liu, *J. Am. Chem. Soc.* **2004**, *126*, 6895; b) G.-Y. Lin, C.-W. Li, S.-H. Hung, R.-S. Liu, *Org. Lett.* **2008**, *10*, 5059.

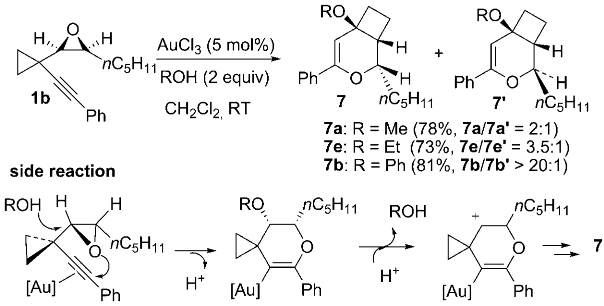
[6] a) F. E. McDonald, C. C. Schultz, *J. Am. Chem. Soc.* **1994**, *116*, 9363; b) C. M. Marson, A. Khan, J. McGregor, *Tetrahedron Lett.* **1995**, *36*, 7154; c) A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem.* **1998**, *110*, 107; *Angew. Chem. Int. Ed.* **1998**, *37*, 101; d) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849; e) C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 8076; f) A. S. K. Hashmi, P. Sinba, *Adv. Synth. Catal.* **2004**, *346*, 432; g) L.-Z. Dai, M.-J. Qi, Y.-L. Shi, X.-G. Liu, M. Shi, *Org. Lett.* **2007**, *9*, 3191; h) X.-Z. Shu, X.-Y. Liu, H.-Q. Xiao, K.-G. Ji, L.-N. Guo, C.-Z. Qi, A.-M. Lian, *Adv. Synth. Catal.* **2007**, *349*, 2493; i) M.-C. Cordonnier, A. Blanc, P. Pale, *Org. Lett.* **2008**, *10*, 1569; j) A. S. K. Hashmi, M. Buhrle, R. Salathe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 2059.

[7] Screening of catalyst activity for this transformation is provided in the Supporting Information.

[8] ^{1}H NOE spectra of key compounds are provided in the Supporting Information.

[9] For metal-catalyzed intramolecular cycloaddition of allenes, see: a) X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 6398; b) G. Zhang, V. J. Catalano, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 11358; c) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614; d) B. Trillo, F. López, M. Gulías, L. Castedo, J. L. Mascareñas, *Angew. Chem.* **2008**, *120*, 965; *Angew. Chem. Int. Ed.* **2008**, *47*, 951; e) D. T. Craft, B. W. Gung, *Tetrahedron Lett.* **2008**, *49*, 5931; f) B. W. Gung, D. T. Craft, *Tetrahedron Lett.* **2009**, *50*, 2685; g) B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas, *Chem. Eur. J.* **2009**, *15*, 3336; h) P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348; i) S. Yudha, Y. Kuninobu, K. Takai, *Angew. Chem.* **2008**, *120*, 9458; *Angew. Chem. Int. Ed.* **2008**, *47*, 9318; j) R. Chaudhuri, H.-Y. Liao, R.-S. Liu, *Chem. Eur. J.* **2009**, *15*, 8895; k) H. Funami, H. Kusama, N. Iwasawa, *Angew. Chem.* **2007**, *119*, 927; *Angew. Chem. Int. Ed.* **2007**, *46*, 909; l) J. H. Lee, F. D. Toste, *Angew. Chem.* **2007**, *119*, 930; *Angew. Chem. Int. Ed.* **2007**, *46*, 912; m) G. Lemière, V. Gandon, K. Cariou, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2007**, *9*, 2207; n) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993.

[10] When the strong nucleophile ROH replaced water in this catalysis, we observed diminished d.r. ratios of the resulting products **7a** and **7e** and their isomers **7a′** and **7e′**. We note that the good d.r. value (d.r.> 20:1) was obtained for **7b**/**7b′** (R = Ph) because the *cis-n*-pentyl group of epoxide **1b** impedes an external attack of the bulky phenol at the epoxy functionality. This side reaction is pronounced for small MeOH, giving **7a** and **7a′** with a low d.r. value.



[11] Preparation of chiral epoxide **4** is described in the Supporting Information.

[12] Intermolecular [3+2] cycloaddition of an allene with an enol ether was reported with a platinum catalyst very recently, see H. Kusama, M. Ebisawa, H. Funami, N. Iwasawa, *J. Am. Chem. Soc.* **2009**, *131*, 16352.

[13] Catalyst screening for the cycloaddition of alcohol **2b** with a diene is provided in the Supporting Information. The lower efficiency of the Brønsted acid is not surprising because cycloadducts **5a** and **6a** are sensitive to free protons.

Received: December 14, 2009
Published online: January 29, 2010

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim