

Catalytic Enantioselective Epoxidation of Tertiary Allylic and Homoallylic Alcohols

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S Supporting Information

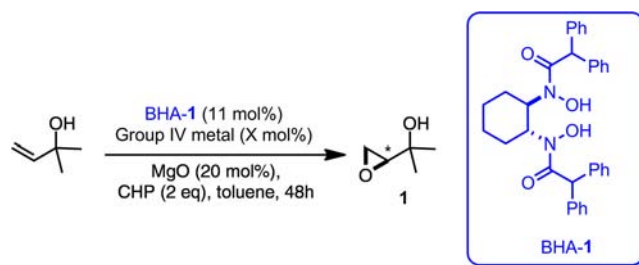
ABSTRACT: An efficient and versatile method for the enantioselective epoxidation of both tertiary allylic and homoallylic alcohols catalyzed by Hf(IV)–bishydroxamic acid (BHA) complexes is described. Asymmetric epoxidation, kinetic resolution, and desymmetrization have been developed, demonstrating the flexible nature of the Hf(IV)–BHA system. This is the first report in which these substrates were obtained with enantioselectivities of up to 99%.

Enantioselective epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides, which are crucial building blocks for the synthesis of natural products and biologically active substances.^{1,2} Recently, our group has described efficient protocols for epoxidation of not only primary and secondary allylic alcohols but also *N*-alkenyl sulfonamides and *N*-tosylimines with excellent yields and enantioselectivities.^{3,4} Nonetheless, the preparation of enantioenriched tertiary 2,3-epoxy alcohols is still a long-standing problem, especially in view of the fact that they could be highly versatile building blocks containing quaternary carbon centers. Unfortunately, the Sharpless asymmetric epoxidation⁵ is not an efficient protocol for preparing enantioenriched tertiary epoxy alcohols from the corresponding tertiary allylic alcohols. Indeed, there are only two (isolated) examples that showed moderate yields and suffered from low enantioselectivities using a stoichiometric chiral reagent,⁶ and no truly efficient and reliable catalytic asymmetric epoxidation of tertiary olefinic alcohols has been described. It is clear that development of a catalytic enantioselective protocol for the epoxidation of tertiary olefinic alcohols remains urgent and highly desirable.

The major problem with these substrate classes is their extremely low reactivity, probably due to steric hindrance, which diminishes the coordinating ability with the metal center. This drawback can be solved using another approach. For instance, Zr and Hf have longer metal–oxygen bonds than titanium, and the use of a larger center ion would provide more space around it.^{7,8} As a consequence, less steric interaction between the substrate and the complex would be anticipated, especially in the case of tertiary olefinic alcohols. This would lead to much higher reactivity for these previously unreactive compounds. Herein we report a Hf(IV)-catalyzed enantioselective epoxidation of challenging tertiary olefinic alcohols.

The studies were initiated by examining complexes of bishydroxamic acid (BHA) with Hf, Zr, and Ti. Compared with

Table 1. Screening of Group IV Metal Catalysts



entry	group IV metal ^a (mol %)	T	t (h)	% yield ^b	% ee ^c
1	[Hf] (10)	rt	12	99	96
2	[Zr] (10)	rt	12	96	91
3	[Ti] (10)	rt	12	98	30
4	[Hf] (10)	0	48	99	98
5	[Hf] (5)	0 °C	96	84	98
6	[Hf] (3)	0 °C	96	71	87
7	[Hf] (1)	0 °C	96	76	74
8 ^d	[Hf] (1)	0 °C	96	78	80

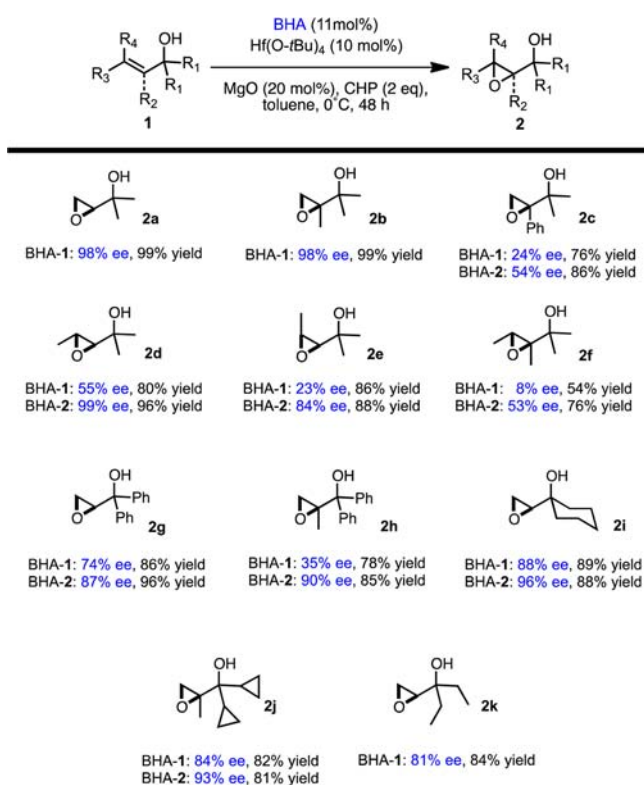
^a[Hf] = Hf(O*t*-Bu)₄; [Zr] = Zr(O*t*-Bu)₄; [Ti] = Ti(O*i*-Pr)₄. ^bIsolated yields. ^cDetermined by chiral gas chromatography. ^dThe reaction was carried out at 0.4 M.

the Zr(IV)–BHA system, Hf(IV)–BHA gave a higher selectivity (Table 1, entries 1 and 2). As expected, the same reaction based on the Ti(IV)–BHA system gave poor selectivity (entry 3). The temperature, concentration, and catalyst loading were also examined, and the optimum reaction conditions were found to involve a catalyst loading of 10 mol % at 0 °C (entries 4–8).

With these optimized reaction conditions, the asymmetric epoxidation of various tertiary allylic alcohols was performed, and the results are summarized in Scheme 1. Initially the oxidations of the α,α' -*gem*-dimethyl and 2-methyl- α,α' -*gem*-dimethyl alcohols were carried out in high yields with enantioselectivities of up to 99% ee (**2a** and **2b**). Unfortunately, when a series of different tertiary allylic alcohols containing different substitution patterns (**1c–h**) were oxidized using BHA-1, they gave moderate enantioselectivities. For instance, the epoxidation of *E* and *Z* tertiary alcohols gave **2d** and **2e** with 55 and 23% ee, respectively. Thus, we attempted to improve the enantioselectivity for these more sterically demanding tertiary allylic alcohols using BHA-2 (Figure 1),

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Scheme 1. Enantioselective Epoxidation of Tertiary Allylic Alcohols^{a,b,10}

^aIsolated yields are shown. ^bEnantiomeric excess values were determined by chiral HPLC or chiral gas chromatography.

and to our delight, the selectivity improved dramatically (99 vs 55% ee for **2d**). The extra methylene group at the C α position relieved steric congestion and provided a larger pocket, allowing for higher selectivity. It was found that the reaction was more enantioselective for *E* olefins than *Z* olefins (99 vs 84% ee for **2d** and **2e**, respectively). Encouraged by these results, we next performed the epoxidation of aromatic and cyclic tertiary olefins. Gratifyingly, the enantioselectivities were improved significantly: the selectivity using **1h** was enhanced from 35 to 90% ee (**2h**), and that for the cyclic substrate was superior, up to 96% ee (**2i**). Substrates bearing α,α' -gem-dicyclopropyl or α,α' -gem-diethyl substitution could also be oxidized with high enantioselectivities of up to 93% (**2j** and **2k**).

Next, the epoxidation of tertiary homoallylic alcohols under the optimized conditions was tested, and the results are shown in Scheme 2. The reaction of α,α' -gem-dimethyl homoallylic

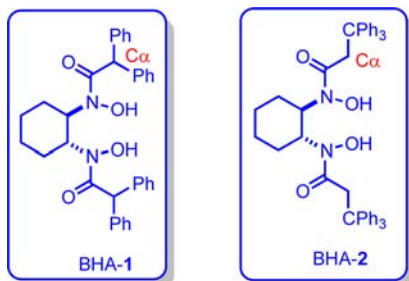
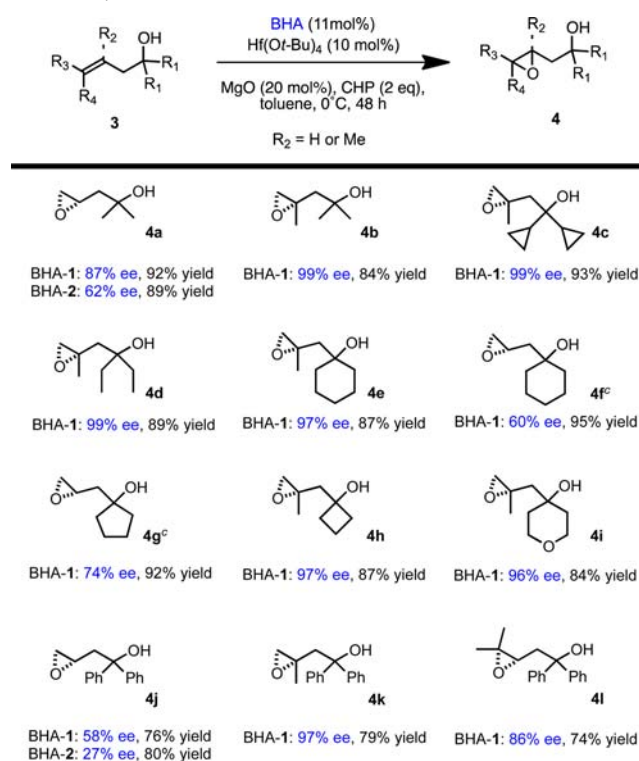


Figure 1. Chiral bishydroxamic acids BHA-1 and BHA-2.

Scheme 2. Enantioselective Epoxidation of Tertiary Homoallylic Alcohols^{a,b,10}

^aIsolated yields are shown. ^bEnantiomeric excess values were determined by chiral HPLC or chiral gas chromatography. ^cThe ee was determined by ¹H NMR analysis in the presence of Eu(hfc)₃.

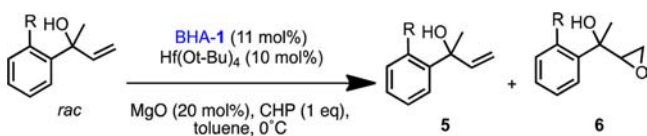
alcohol proceeded in high yield with good enantioselectivity (**4a**). With the incorporation of the methyl group at the C3 position, the epoxidation took place with up to 99% ee (**4b**). Substrates containing α,α' -gem-dicyclopropyl and α,α' -gem-diethyl substitution furnished the desired epoxy alcohols with excellent enantioselectivities (**4c** and **4d**). Tertiary olefinic alcohols bearing a cyclic moiety in the α,α' -geminal position also furnished the corresponding epoxides with enantioselectivities of up to 97% (**4e–I**). The epoxidation was accomplished with up to 97% ee for α,α' -gem-diphenyl substrates (**4j** and **4l**). The epoxidation of **3a** and **3j** using BHA-2 gave lower enantioselectivity. In general, tertiary olefinic alcohols having exo methylenes were the best substrates for the reaction.

With the successful results of the asymmetric epoxidation of tertiary allylic and homoallylic alcohols in hand, we applied this catalyst system to the kinetic resolution of aromatic tertiary olefinic alcohols (Table 2). Amazingly, both the starting allylic alcohol and the epoxy alcohol were obtained with up to 90% enantiopurity ($s > 15$).⁹

Finally, the scope of the reaction was further expanded to the desymmetrization of meso tertiary bisallylic and bishomoallylic alcohols. The combination of lower temperature and a catalyst loading of 10 mol % provided the epoxy alcohols with high diastereoselectivities and excellent enantioselectivities (Table 3).

In conclusion, we have successfully applied our Hf(IV)–BHA catalyst system to the enantioselective epoxidation, kinetic resolution, and desymmetrization of tertiary olefinic alcohols. To the best of our knowledge, this is the first general protocol

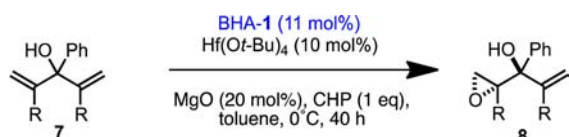
Table 2. Kinetic Resolution of Tertiary Olefinic Alcohols



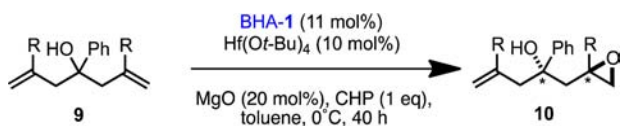
entry	R	t (h)	% conv.	% ee ^a (% yield ^b)		s ^c
				5	6	
1	H	36	51	80 (46)	84 (49)	24
2	Me	38	50	90 (47)	90 (50)	58

^aDetermined by chiral HPLC. ^bIsolated yields. ^cThe selectivity factor *s* was calculated as $s = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$, where *C* is the conversion.

Table 3. Desymmetrization of Meso Tertiary Olefinic Alcohols



entry	R	% yield	dr (anti/syn)	% ee (anti)
1	H	54	97:3	90
2	CH ₃	51	60:40	87



for catalytic enantioselective epoxidation of tertiary alcohol substrates. Further studies of Hf(IV)–BHA-catalyzed asymmetric oxidation in other applications are ongoing.

■ ASSOCIATED CONTENT

📄 Supporting Information

Representative experimental procedures and necessary characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For reviews, see: (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 621. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (d) Chatterjee, D. *Coord. Chem. Rev.* **2008**, *252*. (e) Díez, D.; Núñez, M. G.; Antón, A. B.; García, P.; Moro, R. F.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Curr. Org. Synth.* **2008**, *5*, 186. (f) Matsumoto, K.; Sawada, Y.; Katsuki, T. *Pure Appl. Chem.* **2008**, *80*, 1071. (g) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.
- (2) (a) Illa, O.; Arshad, M.; Ros, A.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 1828. (b) Egami, H.; Oguma, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 5886. (c) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. (d) Tanaka, H.; Nishikawa, H.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 12034. (e) De Faveri, G.; Ilyashenko, G.; Watkinson, M. *Chem. Soc. Rev.* **2011**, *40*, 1722.
- (3) (a) Murase, N.; Hoshino, Y.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* **1999**, *64*, 338. (b) Hoshino, Y.; Murase, N.; Oishi, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1653. (c) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452. (d) Makita, N.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 941. (e) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389. (f) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286. (g) Barlan, A. U.; Zhang, W.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 6075. (h) Li, Z.; Zhang, W.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7520. (i) Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 7878.
- (4) Olivares-Romero, J. L.; Zhi, L.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 5440.
- (5) Singh, S.; Guiry, P. J. *Tetrahedron* **2010**, *66*, 5701.
- (6) (a) Wang, Z. M.; Zhou, W. *Tetrahedron* **1987**, *43*, 2935. (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1991**, *32*, 3527.
- (7) (a) Jørgensen, K. A. *Chem. Rev.* **1989**, *89*, 431. (b) Ikegami, S.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, *83*. (c) Okachi, T.; Murai, N.; Onaka, M. *Org. Lett.* **2003**, *5*, 85.
- (8) Semiempirical PM3 calculations predicted that the metal–oxygen bond lengths in Ti(OMe)₄, Zr(OMe)₄, and Hf(OMe)₄ are 1.953, 2.088, and 2.070 Å, respectively.
- (9) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
- (10) The absolute stereochemistries of 2a and 4a were assigned by comparison with known compounds (see the Supporting Information). The stereochemistries of the remaining tertiary alcohols were assigned by analogy, assuming a common reaction pathway.

■ NOTE ADDED AFTER ASAP PUBLICATION

In the version of this article posted ASAP on February 19, 2013, a portion of Table 3 was missing because of a production error. The corrected article was reposted on February 20, 2013.