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Catalytic Enantioselective Epoxidation of Tertiary Allylic- and Homoallylic Alcohols

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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 system, Hf(IV)-BHA. This is the first report in which these substrates were obtained with enantioselectivities up to 99%.

Enantioselective epoxidation of olefins presents a powerful strategy for the synthesis of enantiomerically enriched epoxides that are crucial building blocks for the synthesis of natural products and biologically active substances.^{1,2} Recently, our group has described efficient protocols to perform the epoxidation not only for primary and secondary allylic alcohols but also for *N*-alkenyl sulfonamides, and *N*-Tosyl imines with excellent yields and enantioselectivities.^{3,4} Nonetheless, the preparation of enantioenriched tertiary 2,3-epoxy alcohols is still a long-standing problem, especially when considering they could be highly versatile building blocks containing quaternary carbon centers. Unfortunately, the Sharpless asymmetric epoxidation⁵ is not an efficient protocol to prepare enantio-enriched tertiary epoxy alcohols from corresponding tertiary allylic alcohols. Indeed, there are only two (isolated) examples that show moderate yields and suffer from low enantioselectivities using stoichiometric chiral reagent⁶ and, no truly efficient and reliable catalytic asymmetric epoxidation of tertiary olefinic alcohols has been described. It is clear that development of the 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 leads to much higher reactivity of these previously unreactive compounds. Herein, we would like to report a hafnium(IV)-catalyzed enantioselective epoxidation of challenging tertiary olefinic alcohols.

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

The authors declare no competing financial interest.

The studies were initiated by the examination of Hf, Zr, and Ti. Compared with the Zr(IV)-BHA system, Hf(IV) 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 (Table 1, entry 3). Temperature, concentration, and catalyst loading were examined, and the optimum reaction conditions were found to be with 10 mol% catalyst loading at 0°C (Table 1, 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 oxidation of the α,α' -gem-dimethyl, and 2-methyl- α,α' -gem-dimethyl alcohols were carried out, with high yields and enantioselectivities up to 99% (**2a** and **2b**). Unfortunately, when a series of different tertiary allylic alcohols containing different substitution patterns (**1c** to **1h**) were oxidized using BHA-**1**, they gave moderate enantioselectivities. For instance, the epoxidation of *E* and *Z* tertiary alcohols gave 55 and 23% ee, respectively (**2d** and **2e**).

The enantioselectivity was compared with even more sterically demanding tertiary allylic alcohols using BHA-**2**.

To our delight, the selectivity was improved dramatically using BHA-**2** (99% vs. 55% ee for **2d**). The extra methylene group at C α position released sterical congestions and provided a larger pocket, allowing for higher selectivity (Figure 1).

It was found that the reaction was more enantioselective for *E*-substituted olefins than *Z*-olefins, 99% ee and 84% ee, respectively (**2d** and **2e**). Encouraged by these results, the epoxidation of aromatic and cyclic tertiary olefins was also performed. Gratifyingly, the enantioselectivities were improved significantly: the selectivity using **1h** was enhanced from 35 to 90% ee (**2h**), also the cyclic one was superior up to 96% ee (**2i**). Substrates bearing α,α' -gem-dicyclopropyl or α,α' -gem-diethyl could also be oxidized with highest enantioselectivities up to 93% (**2j** and **2k**).

Next, the epoxidation of the 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 alcohol proceeded with high yield and good enantioselectivity (**4a**). With the incorporation of the methyl group at the C-3 position, the epoxidation took place with up to 99% ee (**4b**). Substrates containing α,α' -gem-dicyclopropyl and α,α' -gem-diethyl furnished the desired epoxy alcohols with excellent enantioselectivities (**4c** and **4d**). Tertiary olefinic alcohols bearing cyclic moiety in the α,α' -gem-position also furnished the epoxides with enantioselectivities up to 97% (**4e-4i**). 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, this catalyst system was applied to the kinetic resolution of aromatic tertiary olefinic alcohols (Table 2). Amazingly, both the starting allylic alcohol and epoxy alcohol were obtained with up to 90% of enantiopurity (*s* > 15).¹⁰

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 10 mol% catalyst loading provided the epoxy alcohols with high diastereoselectivities and excellent enantioselectivities (Table 3).

In conclusion, we have successfully applied our Hafnium/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 for the catalytic enantioselective epoxidation of tertiary alcohol substrates. Further studies on hafnium/bishydroxamic acid catalyzed asymmetric oxidation toward other applications are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. For reviews see: Katsuki T, Martin VS. *Org React*. 1996; 48:1.; Katsuki T. *Comprehensive Asymmetric Catalysis*. Jacobsen EN, Pfaltz A, Yamamoto H. SpringerBerlin1999; 2:621.; Keith JM, Larrow JF, Jacobsen EN. *Adv Synth Catal*. 2001; 343:5.; Chatterjee D. *Coord Chem Rev*. 2008;252.; Díez D, Núñez MG, Antón AB, García P, Moro RF, Garrido NM, Marcos IS, Basabe P, Urones JG. *Curr Org Synth*. 2008; 5:186.; Matsumoto K, Sawada Y, Katsuki T. *Pure Appl Chem*. 2008; 80:1071.; Wong OA, Shi Y. *Chem Rev*. 2008; 108:3958. [PubMed: 18590339]
2. (a) Illa O, Arshad M, Ros A, McGarrigle EM, Aggarwal VK. *J Am Chem Soc*. 2010; 132:1828. [PubMed: 20102201] (b) Egami H, Oguma T, Katsuki T. *J Am Chem Soc*. 2010; 132:5886. [PubMed: 20359219] (c) Lifchits O, Reisinger CM, List B. *J Am Chem Soc*. 2010; 132:10227. [PubMed: 20662497] (d) Tanaka H, Nishikawa H, Uchida T, Katsuki T. *J Am Chem Soc*. 2010; 132:12034. [PubMed: 20701287] (e) De Faveri G, Ilyashenko G, Watkinson M. *Chem Soc Rev*. 2011; 40:1722. [PubMed: 21079863]
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 Jap*. 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. [PubMed: 17212403] (g) Barlan AU, Zhang W, Yamamoto H. *Tetrahedron*. 2007; 63:6075. [PubMed: 21152351] (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. [PubMed: 20481541]
4. Olivares-Romero JL, Zhi L, Yamamoto H. *J Am Chem Soc*. 2012; 134:5440. [PubMed: 22420598]
5. Singh S, Guiry PJ. *Tetrahedron*. 2010; 66:5701.
6. (a) Wang ZM, Zhou W. *Tetrahedron*. 1987; 43:2935.(b) Takano S, Iwabuchi Y, Ogasawara K. *Tetrahedron Lett*. 1991; 32:3527.
7. (a) Jørgensen KA. *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. [PubMed: 12509897]
8. Semiempirical PM3 calculations predict that the bond length between the metal and oxygen in Ti(OMe)₄, Zr(OMe)₄ and Hf(OMe)₄ is 1.953 Å, 2.088 Å, and 2.070 Å, respectively.
9. Lubben TV, Wolczanski PT. *J Am Chem Soc*. 1987; 109:424.
10. Martin VS, Woodard SS, Katsuki T, Yamada Y, Ikeda M, Sharpless KB. *J Am Chem Soc*. 1981; 103:6237.
11. Absolute stereochemistry of compounds **2a** and **4a** was assigned by comparison with known compounds (see supporting information). Hence, the remaining tertiary alcohols were assigned by analogy assuming a common reaction pathway.

Figure 1.
Chiral bishydroxamic acids.

Scheme 1. Enantioselective Epoxidation of Tertiary Allylic Alcohols^{a,b,11}^aIsolated yields. ^bEnantiomeric excess values were determined by chiral HPLC or chiral gas chromatography.

BHA-1: 87% ee, 92% yield
BHA-2: 62% ee, 89% yield

BHA-1: 99% ee, 84% yield

BHA-1: 99% ee, 93% yield

BHA-1: 99% ee, 89% yield

BHA-1: 97% ee, 87% yield

BHA-1: 60% ee, 95% yield

BHA-1: 74% ee, 92% yield

BHA-1: 97% ee, 87% yield

BHA-1: 96% ee, 84% yield

BHA-1: 58% ee, 76% yield
BHA-2: 27% ee, 80% yield

BHA-1: 97% ee, 79% yield

BHA-1: 86% ee, 74% yield

Scheme 2.

Enantioselective Epoxidation of Tertiary Homoallylic Alcohols^{a,b,11}

^aIsolated yields. ^bEnantiomeric excess values were determined by chiral HPLC or chiral gas chromatography. ^cEnantiomeric excess values were determined by ¹H NMR in the presence of Eu(hfc)₃.

Table 1

Screening of Group IV metal catalysts

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

^aIsolated yields.^bEnantiomeric excess values were determined by chiral gas chromatography.^cThe reaction was carried out at 0.4 M. [Hf] = Hf(O ι -Bu)₄, [Zr] = Zr(O ι -Bu)₄, [Ti] = Ti(O ι -Pr)₄

Table 2

Kinetic Resolution of Tertiary Olefinic Alcohols

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

^aEnantiomeric excess values were determined by chiral HPLC.

^bIsolated yields.

^cThe selectivity factor *s* was calculated as $s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$. C represents conversion.

Table 3Desymmetrization of *Meso*-Tertiary Olefinic Alcohols

entry	R	yield	d.r. (<i>anti/syn</i>)	% ee (<i>anti</i>)
1	H	54	97:3	90
2	CH ₃	51	60:40	87

entry	R	yield	d.r. (<i>anti/syn</i>)	% ee (<i>anti</i>)
1	H	63	99:1	99
2	CH ₃	74	75:25	95