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Zirconium(IV)- and Hafnium(IV)-Catalyzed Highly Enantioselective Epoxidation of Homoallylic and Bishomoallylic Alcohols

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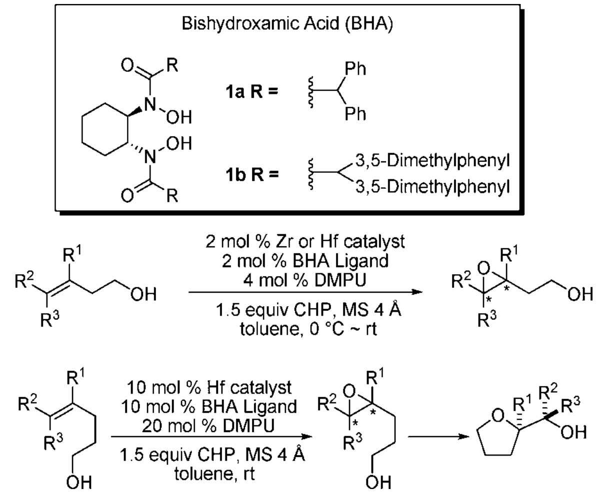
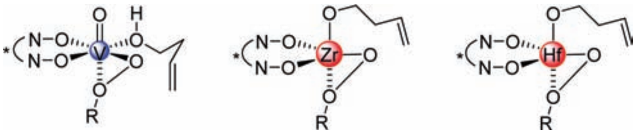
Despite the tremendous success of asymmetric epoxidations,[1] more efficient epoxidation reactions are still of great importance. For example, there are only sporadic reports of catalytic enantioselective epoxidation of challenging substrates such as homoallylic alcohols and bishomoallylic alcohols to date.[2] In recent years, our group has developed highly efficient vanadium−hydroxamic acid and −bishydroxamic acid (BHA) catalyst systems for the asymmetric epoxidation of allylic alcohols and homoallylic alcohols.[3] However, asymmetric epoxidation of bishomoallylic alcohols is an even more challenging problem because the longer carbon chain is much more flexible in the transition state.[4] Although syntheses of epoxides, tetrahydrofuran (THF), and tetrahydropyran (THP) derivatives via epoxidation of bishomoallylic alcohols are well established using either achiral metal catalyst[5] or Shi's chiral-ketone-catalyzed epoxidation procedures,[2f,6] a highly efficient metal-catalyzed enantioselective direct epoxidation is still missing from the list. Herein, we would like to report a zirconium(IV)- and hafnium(IV)-catalyzed highly enantioselective epoxidation of homoallylic alcohols and bishomoallylic alcohols (Scheme 1).

Since we depleted the catalytic ability of the vanadium−BHA system with a very bulky BHA ligand,[3d,e] we began to consider solving the problem using another approach. For example, we postulated that using a larger center ion would provide more space around it so that even a smaller ligand could arrange a proper cavity for stereoselective recognition of the substrate and oxidant molecules. There are many transition metals reported to efficiently catalyze epoxidation of alkenyl alcohols, especially group 4 and 5 metals such as Ti, Zr, and V.[7] Additionally, as a strong Lewis acid,[8] Zr(IV) has been applied in asymmetric epoxidation of homoallylic alcohols.[2b,e] Enlightened by this pioneering work, we therefore chose Ti, Zr, Hf, V, and Nb as candidate metal species for our initial experiments. As we examined the candidate metal sources, $\mathrm{Zr(O}t\mathrm{Bu)_4}$ and $\mathrm{Hf(O}t\mathrm{Bu)_4}$ proved to be superior compared to other metals such as $\mathrm{Ti(O}i\mathrm{Pr)_4}$, $\mathrm{Nb(OEt)_5}$, and $\mathrm{VO(acac)_2}$ in terms of both reactivity and enantioselectivity. An explanation is presented in Scheme 2. In vanadium-catalyzed reactions, the transition state is believed to involve hexacoordinate vanadium species,[3d] while, in zirconium and hafnium-catalyzed reactions, the transition state should be a mononuclear pentacoordinate complex[7,9] because (1) the ligand binds with the metal using two hydroxamate oxygens and the size of the ligand prevents catalyst oligomerization;[10] (2) the substrate binds with the metal using one alkoxide; and (3) the alkylhydroperoxide binds with the metal as a bidentate ligand using both oxygens of the peroxy group as ligand donors.[9] Nonlinearity experiments showed the linear relationship between the enantiomer excess of ligand and product, which supported our hypothesis.

Scheme 1. Zr(IV)− and Hf(IV)−BHA Catalyzed Asymmetric Epoxidation of Homoallylic and Bishomoallylic Alcohols



Scheme 2. Comparison of V-, Zr-, and Hf-Catalyzed Reactions



We then started conditions optimization with the Zr(IV)−BHA system (Table 1). Compared with the V(V)−BHA system, Zr−BHA gave a much higher selectivity (entries 1 and 2). The simpler ligand **1a** showed the best reactivity and selectivity (entries 2 and 3). A 1:1 ratio of metal to ligand was crucial; while 2 equiv of ligand completely inactivated the catalyst (entry 4),[11] and $\mathrm{Zr(acac)_4}$ did not work at all as the metal source (entry 5). Since using toluene and dichloromethane as solvent both gave similar levels of enantioselectivity, we chose to use toluene because it is more environment friendly. Interestingly, we also found that the results were significantly improved when a polar aprotic ligand such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was added (entry 7). The additive may serve two functions in the system. First, as seen in Scheme 2, there are vacant coordination sites on Zr and Hf metal during the reaction. These vacant sites could possibly facilitate a slow but significant oligomerization of Zr and Hf species by bridging two or more metals with a primary alkoxide anion generated from the substrate or product. Adding DMPU could help the catalyst stay in its monomeric form by occupying these vacant sites on the metals as well as regeneration of the monomeric catalytic species.[8b,12] Second, the nucleophilic oxygen of DMPU may help release the coordinated product from the metal and complete the catalytic cycle. Final screening showed Hf(IV) gave more promising results than Zr(IV) as the center metal ion (entry

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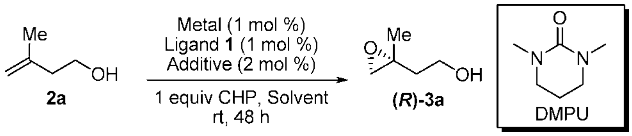
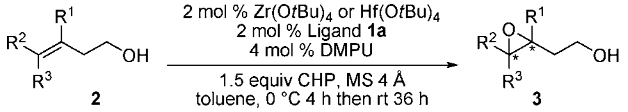
Table 1. Screening of Reaction Conditions

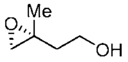
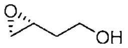
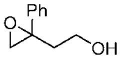
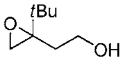
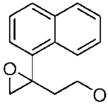
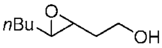
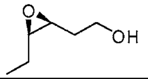
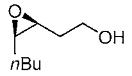
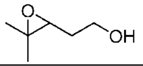
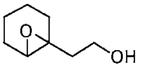


entry[a]	metal	ligand	additive	solvent	%yield[b]	%ee[c]
1	VO(O*i*Pr)$_3$	**1a**[d]	–	toluene	29	69
2	Zr(O*t*Bu)$_4$	**1a**	–	toluene	25	90
3	Zr(O*t*Bu)$_4$	**1b**	–	toluene	28	71
4	Zr(O*t*Bu)$_4$	**1a**[e]	–	toluene	N.R.	–
5	Zr(acac)$_4$	**1a**	–	toluene	N.R.	–
6	Zr(O*t*Bu)$_4$	**1a**	–	CH$_2$Cl$_2$	48	90
7	Zr(O*t*Bu)$_4$	**1a**	DMPU	toluene	56	90
8	Hf(O*t*Bu)$_4$	**1a**	DMPU	toluene	60	95
9[f]	Hf(O*t*Bu)$_4$	**1a**	DMPU MS 4 Å	toluene	81	97

[a] All reactions were performed in the presence of 1.0 equiv of cumene hydroperoxide (CHP) (1 mmol) unless otherwise noted. [b] Isolated yield after chromatographic purification. [c] Enantiomeric excess values were determined by chiral gas chromatography. [d] 1.5 mol % ligand was used. [e] 2.0 mol % ligand was used. [f] Conditions: 2 mol % metal, 2 mol % ligand, 4 mol % DMPU, 1.5 equiv of CHP, and 100 mg MS were used in a 0.5 mmol scale reaction. The reaction is initially cooled to 0 °C for 4 h then left at room temperature for the next 36 h.

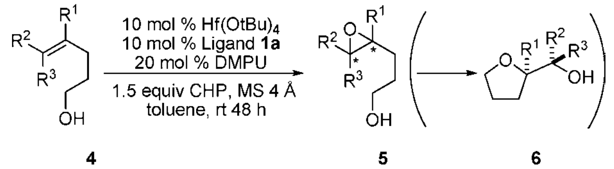
Table 2. Zr(IV)- and Hf(IV)-Catalyzed Asymmetric Epoxidation of Homoallylic Alcohols

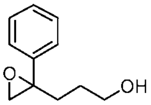
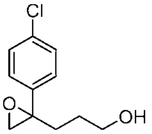
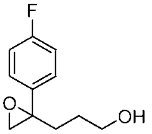
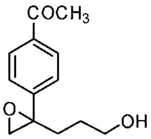
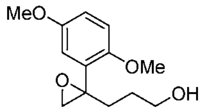
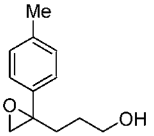
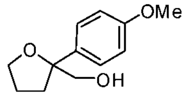
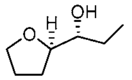


entry[a]	product		metal	%yield[b]	%ee[c]
1		**3a**	Zr Hf	61 81	91 97
2		**3b**	Hf	37	63
3		**3c**	Zr Hf	67 69	92 98
4		**3d**	Zr Hf	67 70	63 71
5		**3e**	Hf	31[d]	91
6		**3f**	Hf	47	73
7		**3g**	Zr Hf	45 82	93 94
8		**3h**	Zr Hf	80 83	92 96
9		**3i**	Hf	41	71
10		**3j**	Zr Hf	72 81	76 89

[a] All reactions were performed in the presence of 1.5 equiv of CHP. [b] Isolated yield after chromatographic purification. [c] Enantiomeric excess values were determined by chiral GC and chiral HPLC. [d] 61% of **2e** was recovered.

Table 3. Zr(IV)- and Hf(IV)-Catalyzed Asymmetric Epoxidation of Bishomoallylic Alcohols



entry[a]	product		%yield[b]	%ee[c]
1		**5a**	75	99
2		**5b**	57	98
3		**5c**	73	97
4		**5d**	79	97
5		**5e**	25[d]	97
6		**5f**	53	99
7		**6g**	47	59
8		**6h**	43	95[e]

[a] All reactions were performed in the presence of 1.5 equiv of CHP. [b] Isolated yield after chromatography purification. [c] Enantiomeric excess values were determined by chiral HPLC. [d] 42% of **4e** was recovered. [e] 30 mol % catalyst loading was used and the reaction was stirred for 72 h. 52% starting material **4h** was recovered. Absolute configuration is determined as (*R*, *R*). See ref 14.

8). Furthermore, addition of molecular sieves (MS) also greatly improved the results, especially the 4 Å powdered molecular sieves (entry 9).[13]

A variety of homoallylic alcohols with different substituted patterns were subjected to the optimum epoxidation conditions of both Zr(IV) and Hf(IV). The results are summarized in Table 2. In general, Hf is better than Zr in terms of reactivity and selectivity. 1,1-Disubstituted (entries 1, 3, and 5) and (*Z*)-substituted substrates (entries 7 and 8) provide higher reactivities and selectivities. It is interesting to note that these two substitute patterns lead to completely reversed enantioface selection as shown in Table 2. Entries 1 and 2 indicated that, without (*Z*)-substituent, the epoxidation gave (3*R*)-product predominately, while entries 7 and 8 showed (*Z*)-substituted substrates mainly provided (3*S*,4*R*)-products.

The reactivity of epoxidation of bishomoallylic alcohols was lower as the length of the carbon chain was increased, requiring 10 mol % of catalyst in most cases. The best substrates for this reaction are 1,1-disubstituted olefins bearing an aromatic group as shown in Table 3. We anticipated that making the δ-carbon a benzylic position would accelerate the THF forming process; however, in most cases, the δ-aromatic group actually suppressed the THF formation in that we were able to isolate a high yield of corresponding epoxides. Several bishomoallylic alcohols bearing a δ-aromatic group were subjected to the optimized conditions, and they underwent smooth reactions. Electron-deficient substrates such as **4b**, **4c**, and **4d** provide corresponding epoxides efficiently (entries 2, 3, and 4). Electron-rich but sterically hindered substrate **4e** gave epoxide in high ee but low reactivity, presumably due to the size of the *ortho*-methoxy group which is very close to the double bond (entry 5). Substrate **4g** which contains a *para*-methoxyphenyl substituent was converted to THF products with lower ee presumably because the *para*-methoxy effect stabilizes the benzylic cation therefore facilitating the S_N1 type racemizing cyclization. (*Z*)-Substituted substrates such as **4h** also exhibited high enantioselectivity although the reactivity was much lower. THF formation was also exclusively observed in this reaction.

In conclusion, we discovered that, in combination with BHA ligands, Zr(IV) and Hf(IV) are able to catalyze highly enantioselective epoxidation of homoallylic alcohols and bishomoallylic alcohols in a very efficient manner. Further efforts are being employed to investigate the reaction mechanism and potential application in asymmetric synthesis.

Acknowledgment. National Institutes of Health (NIH) is greatly appreciated for providing financial support (GM068433-05).

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

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(11) It is probably due to a stable complex Zr(BHA)$_2$ was formed. See: Fouché, K. F.; le Roux, H. J.; Phillips, F. *J. Inorg. Nucl. Chem.* **1970**, *32*, 1949.

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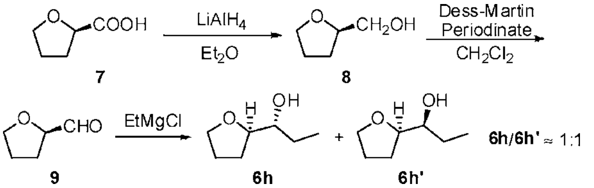
(13) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (b) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. We also examined 3 Å and 5 Å MS as additive. No significant rate or ee improvement was observed with 3 Å MS, while 5 Å MS favored the formation of THF compounds.



(14) The absolute configuration of substituted THF was established by the synthesis of diastereomers of products from known chirality compound and comparison of chiral gas chromatography retention times.

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