Published in final edited form as:

J Am Chem Soc. 2012 March 28; 134(12): 5440–5443. doi:10.1021/ja211880s.

Hf(IV)-Catalyzed Enantioselective Epoxidation of *N*-Alkenyl Sulfonamides and *N*-Tosyl Imines

José Luis Olivares-Romero, Zhi Li, and Hisashi Yamamoto*

The University of Chicago, 5735 S Ellis Ave., Chicago, IL 60637

Abstract

Asymmetric epoxidation of allylic and homoallylic amine derivatives catalyzed by Hf(IV)-bishydroxamic acid complexes is described. Under similar conditions, aldimine and ketimine produced oxaziridines. The sulfonyl group is demonstrated to be an effective directing group for these transformations.

The spectacular success of asymmetric epoxidation during the last century is one of the most important achievements in modern organic synthesis.^{1,2} The Sharpless epoxidation of allylic alcohol may be the ground-breaking accomplishment among them. Recently, vanadium-, zirconium- and hafnium-catalyzed asymmetric epoxidation of allylic, homoallylic and bishomoallylic alcohols has been reported in our laboratory.³ In all of these transformations, the hydroxyl group in the substrates acts as an effective directing anchor between the metal catalyst and the olefin. Herein we wish to report that ‘sulfonyl’ group is able to act as a new and excellent directing anchor for the asymmetric epoxidation reactions.

We recently reported zirconium- and hafnium- catalyzed asymmetric epoxidations using *C*₂-symmetric chiral bishydroxamic acid (BHA) ligand **1**³ⁱ for the efficient epoxidation of homoallylic alcohols and bishomoallylic alcohols.⁴ The success of these methods depends on stereochemically wider catalytic space for the oxidation process than typical Ti- and V-catalyzed reactions. We therefore anticipated that these catalysts could be effective toward not only hydroxyl but also other functional groups. The use of amines as directing groups in asymmetric epoxidation⁵ is appealing because the chiral epoxide-bearing amines products will be potentially very useful building blocks for the synthesis of enantiomerically pure complex molecules, in particular, of biologically active compounds. Despite the considerable progress that has been made in asymmetric epoxidation allylic amines is still a longstanding challenge in asymmetric oxidation. We thus naively tested the hafnium-catalyzed epoxidations of various derivatives of allylic amines. Indeed, the Hf(IV)-BHA-**1** complex showed catalytic activity toward various derivatives of allylic amines. Among the various groups tested, *p*-methoxybenzenesulfonyl and *p*-tolylsulfonyl groups are shown to be effective (Table 1): *N*-allyl *p*-methoxybenzenesulfonyl gave 49% yield and 93% ee of its corresponding epoxide (entry 8, Table 1). Careful examination of reaction conditions, including metal, solvent and additive screening disclosed the optimum conditions for this reaction (Table 1). It should be noted that the reactivity and enantioselectivity can be significantly improved by introducing inorganic additives such as magnesium oxide.⁶

yamamoto@uchicago.edu.

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

Inspired by these promising results, the effect of sulfonyl protective groups was investigated (entries 7 and 8, Table 1). Electron-rich 4-methoxybenzenesulfonamide (Mbs) gave better yield than electron-deficient 4-nitrobenzenesulfonamide (Ns).

We further tried to tune the stereochemical environment about the hafnium ion by using different ligands (Table 2). However, most of efforts have been unsuccessful since they could not give better enantioselectivity. Even changing the phenyl groups in BHA-1 to 2,4,6-trimethyl, 2,4,6-isopropyl, or trityl group will result in a significant decreased of enantioselectivity (entries 2, 3, 4, Table 2). Adding chloro substituent to the phenyl groups also decreased both the reactivity and enantioselectivity (entry 5, Table 2).

The scope of the allyl and homoallyl amines with different substituted patterns were subjected to the optimum epoxidation conditions and the results are shown in Table 3. *N*-alkenyl sulfonamides with aromatic substituents having 3,5-di-*tert*-butyl and 3,4-dimethoxy afforded the product with moderate to good enantioselectivity (entries 2 and 4, Table 3). In general, substrates bearing the 4-methoxybenzenesulfonyl moiety afforded the product in high yield and enantioselectivity up to 93 % (entries 3, 7, 10, 13, 16, Table 3) in comparison with substrates having the *p*-tolylsulfonyl group (entries 8, 11, 14, 17, Table 3). The reaction was more enantioselective for *Z*-substituted olefins (entries 5–9) than *E*-olefins (entries 10–12). Also, 3,3-disubstituted (entries 13, 14, Table 3) provide higher reactivities and selectivities than 2,3-, and 2-disubstituted allylic amines (entries 15–18 Table 3). Epoxidation of homoallylic amine derivatives was also performed. Although the reactivity and selectivity was lower than that of allylic amine derivatives, the reaction still gave 67% enantioselectivity (entries 19–21). In general, the best substrates for this epoxidation are 3,3-disubstituted allylic amines bearing 4-methoxybenzenesulfonyl group. Finally, we evaluated the selectivity using the 2-(trimethylsilyl)ethanesulfonamide as protecting group since this group can be easily removed,⁷ to our delight we found almost the same selectivity that the analogous containing the *p*-tolylsulfonyl group (entries 1 and 22, Table 3). This result demonstrates that our protocol can be useful in the preparation of enantiomerically enriched epoxides.

The electronic nature of the sulfonyl group had an effect on both reactivity and enantioselectivity, with electron donating *p*-methoxy derivative displaying higher reactivity and selectivity than the Ts- group and the electron withdrawing Ns- group (Table 1, entries 6, 7, 8). To gain more insight into the mode of coordination, series of control experiments were conducted. Changing the NH-sulfonyl group to O-sulfonyl group or CH₂-sulfonyl group still allowed the asymmetric epoxidation to take place. These facts suggest the sulfonyl oxygen, instead of the amide nitrogen, play the major role as the directing group interacting with the metal and, rather amazingly, the reaction may proceed through a sulfonyl-oxygen directed pathway (Chart 1).⁸ The reaction of Boc-protected allylic amine⁹ (entry 1, Table 1) also suggests the weak interaction between carbonyl oxygen and the metal. This new coordination mode could be useful for many other types of compounds containing Lewis basic oxygen atoms.

In order to expand the scope of the reaction, the sulfonyl-directed oxidation reaction was also applied to the oxidation of *N*-tosyl aldimines and ketimines (Table 4).¹⁰ Gratifyingly, high enantioselective epoxidations reaction was observed not only for simple aldimines (entries 1–3, Table 4) but also for more challenging ketimine (entry 4, Table 4).

In conclusion, we have discovered an unprecedented enantioselective epoxidation of *N*-alkenyl amine derivatives catalyzed by a hafnium-BHA catalyst system. The reaction likely undergoes a sulfonyl-oxygen-directing process. This is the first report on a directing group other than hydroxyl in metal-catalyzed asymmetric epoxidation, and its application will

considerably broaden the avenues for asymmetric epoxidation.¹¹ We have demonstrated that the BHA-Hf(IV) system is able to catalyze highly enantioselective oxaziridination of *N*-tosyl imines. Utilization of this protocol towards other asymmetric processes and elucidation of the mechanism are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The financial support of the National Institutes of Health (NIH) (GM068433-05) is greatly appreciated. Olivares-Romero thanks to CONACYT (México) for the postdoctoral fellowship.

References

1. For reviews see: Katsuki T, Martin VS. *Org React.* 1996; 48:1. Katsuki T, Jacobsen EN, Pfaltz A, Yamamoto H. *Comprehensive Asymmetric Catalysis.* Springer Berlin 1999; 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. Li, Z. PhD dissertation. The University of Chicago; 2011.
5. For stereoselective oxidation of allylic amine derivatives with m-CPBA, see: O'Brien P, Childs AC, Ensor GJ, Hill CL, Kirby JP, Dearden MJ, Oxenford SJ, Rosser CM. *Org Lett.* 2003; 5:4955. [PubMed: 14682738] Bond CW, Cresswell AJ, Davies SG, Fletcher AM, Kurosawa W, Lee JA, Roberts PM, Russell AJ, Smith AD, Thomson JE. *J Org Chem.* 2009; 74:6735. [PubMed: 19642691] Asencio G, González-Núñez ME, Bernardini CB, Mello R, Adam W. *J Am Chem Soc.* 1993; 115:7250. Asencio G, Mello R, Boix-Bernardini C, González-Núñez ME, Castellano G. *J Org Chem.* 1995; 60:3692. Asencio G, Boix-Bernardini C, Andreu C, González-Núñez ME, Mello R, Edwards JO, Carpenter GB. *J Org Chem.* 1999; 64:4705. [PubMed: 11674543] Davies SG, Fletcher AM, Kurosawa W, Lee JA, Poce G, Roberts PM, Thomson JE, Williamson DM. *J Org Chem.* 2010; 75:7745. Aciro C, Claridge TDW, Davies SG, Roberts DM, Russel AJ, Thomson JE. *Org Biomol Chem.* 2008; 6:3751. [PubMed: 18843405] Aciro C, Davies SG, Roberts DM, Russell AJ, Smith AD, Thomson JE. *Org Biomol Chem.* 2008; 6:3762. [PubMed: 18843406] Aggarwal VK, Fang GY. *Chem Commun.* 2005:3448. Edwards AS, Wybrow RAJ, Johnstone C, Adams H, Harrity JPA. *Chem Commun.* 2002:1542. Bagal SK, Davies SG, Fletcher AM, Lee JA, Roberts DM, Scott DM, Thomson JE. *Tetrahedron Letters.* 2011; 52:2216.
6. The role of MgO is still elusive. ZnO and Al₂O₃ also improve the reaction to a lesser extent. The amount of the additive is not very influential. For example, reactions with 5 mol% to 2 equivalent of MgSO₄ all gave similar results.

7. For examples in the use of 2-(trimethylsilyl)ethanesulfonamide as protecting group see: Weinreb SM, Demko DM, Lessen TA, Demers JP. *Tetrahedron Letters*. 1986; 27:2099. Garigipati RS, Weinreb SM. *J Org Chem*. 1988; 53:4143.
8. For an example of sulfonyl oxygen interacting with metal catalyst, see: Tsui GC, Lautens M. *Angew Chem Int Ed*. 2010; 49:8938. Csatayová K, Davies SG, Lee JA, Ling KB, Roberts DM, Russell AJ, Thomson JE. *Tetrahedron*. 2010; 66:8420.
9. For enantioselective oxidation of allylic amines bearing carbamate moiety, see: Shaus SE, Brandes BD, Larrow JF, Tokunaga M, Hansen RB, Gould AE, Furrow ME, Jacobsen EN. *J Am Chem Soc*. 2002; 124:1307. [PubMed: 11841300]
10. Recently, Jørgensen et. al. reported an excellent enantioselective oxaziridination, see: Lykke L, Rodríguez-Esrich C, Jørgensen KA. *J Am Chem Soc*. 2011; 133:14932. [PubMed: 21875125]
11. For an example of existing non-asymmetric synthesis of a biological active molecule via epoxy amine intermediates, see: Sova M, Kovac A, Turk S, Hrast M, Blanot D, Gobec S. *Bioorg Chem*. 2009; 37:217. [PubMed: 19804894]

Chart 1. Epoxidation of Allylic Sulfonate, Sulfonamide, Sulfones.^{a,b}

^aIsolated yield after chromatographic purification. ^bEnantiomeric excess values were determined by chiral HPLC.

Table 1

Screening of Epoxidation Reaction Conditions

entry	R	solvent	additive	yield ^a /%	ee ^b /%
1	Boc-	toluene	–	9	68
2	Ts-	toluene	–	23	90
3	Ts-	CH ₂ Cl ₂	–	5	75
4 ^c	Ts-	toluene	4 Å MS	12	13
5 ^d	Ts-	toluene	MgSO ₄	37	77
6 ^d	Ts-	toluene	MgO	46	90
7 ^d	Ns-	toluene	MgO	13	89
8 ^{d,e}	Mbs-	toluene	MgO	49	93

^a Isolated yield after chromatographic purification.^b Enantiomeric excess values were determined by chiral HPLC or chiral gas chromatography.^c 100 mg of MS was added.^d 20 mol% additive was added.^e Mbs- = 4-methoxybenzenesulfonyl.

Table 2

Screening of Bis-Hydroxamic Acid Ligand

entry	BHA	yield ^a /%	ee ^b /%
1	1	46	90
2	2	9	12
3	3	12	13
4	4	21	23
5	5	traces	4

^a Isolated yield after chromatographic purification.

^b Enantiomeric excess values were determined by chiral HPLC.

Table 3

Epoxidation of *N*-Alkenyl Sulfonamides

$ \begin{array}{c} \text{R}_3 \quad \text{R}_2 \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{R}_4 \quad \text{H} \\ \quad \\ \text{N} - \text{R}_1 \\ \text{2, } n = 1 \text{ or } 2 \end{array} \xrightarrow[\begin{array}{c} 20 \text{ mol\% MgO, 2 eq. CHP} \\ \text{Toluene, rt, 72 h} \end{array}]{ \begin{array}{c} 10 \text{ mol\% Hf(O}t\text{-Bu)}_4 \\ 11 \text{ mol\% BHA-1} \end{array} } \begin{array}{c} \text{R}_3 \quad \text{R}_2 \\ \diagdown \quad \diagup \\ \text{C} - \text{C} \\ \diagup \quad \diagdown \\ \text{R}_4 \quad \text{H} \\ \quad \\ \text{N} - \text{R}_1 \\ \text{3} \end{array} $				
entry ^a	product		yield ^b /%	ee ^c /%
1 ^d		3a	46	90, <i>R</i>
2		3b	32	84
3		3c	49	93
4		3d	74	64
5		3e	92	91
6		3f	86	77
7		3g	98	87
8		3h	90	89
9		3i	91	70
10		3j	56	46
11		3k	40	34
12		3l	48	20
13		3m	97	92
14		3n	69	90

^b Isolated yield after chromatographic purification.

^d 20 mol% catalyst and 40 mol% additive were used. Ts- = *p*-toluenesulfonyl. Mbs- = 4-methoxybenzenesulfonyl.

Table 4Oxaziridination of *N*-Tosyl imines

$ \begin{array}{ccc} \text{R}-\text{C}=\text{N}-\text{Ts} & \xrightarrow[\text{Toluene}]{\begin{array}{l} 10 \text{ mol\% Hf}(\text{O}t\text{-Bu})_4 \\ 11 \text{ mol\% BHA-1} \\ 20 \text{ mol\% MgO, 2 eq. CHP} \end{array}} & \text{R}-\text{C}(\text{Oxaziridine})-\text{N}-\text{Ts} \\ \mathbf{4} & & \mathbf{5} \end{array} $				
entry ^a	product		yield ^b /%	ee ^c /%
1		5a	78	98
2		5b	84	95
3		5c	82	91
4 ^d		5d	38	98

^a All reactions were performed in the presence of 2.0 equiv of CHP as oxidant.^b Isolated yield after chromatographic purification.^c Enantiomeric excess values were determined by chiral HPLC.^d 20 mol% catalyst and 20 mol% additive were used.