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

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

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

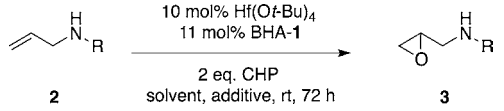
Supporting Information

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 past 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 the '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 a stereochemically wider catalytic space for the oxidation process than that of typical Ti- and V-catalyzed reactions. We therefore anticipated that these catalysts could be effective toward not only the hydroxyl but also other functional groups. The use of amines as directing groups in asymmetric epoxidation[5] is appealing because the chiral epoxide-bearing amine 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 are still a long-standing 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 a 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

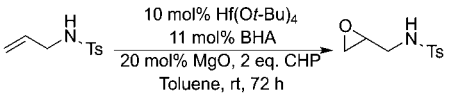
Table 1. Screening of Epoxidation Reaction Conditions

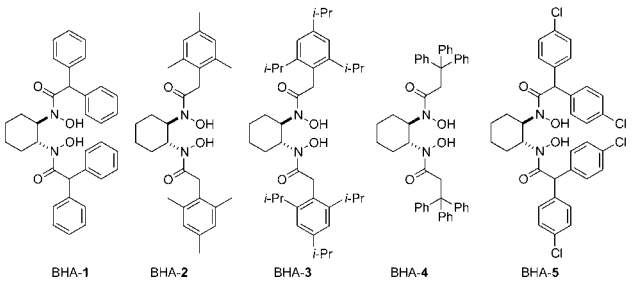


entry	R	solvent	additive	yield[a]/%	ee[b]/%
1	Boc-	toluene	–	9	68
2	Ts-	toluene	–	23	90
3	Ts-	CH_2Cl_2	–	5	75
4[c]	Ts-	toluene	4 Å MS	12	13
5[d]	Ts-	toluene	$MgSO_4$	37	77
6[d]	Ts-	toluene	MgO	46	90
7[d]	Ns-	toluene	MgO	13	89
8[d,e]	Mbs-	toluene	MgO	49	93

[a]Isolated yield after chromatographic purification. [b]Enantiomeric excess values were determined by chiral HPLC or chiral gas chromatography. [c]100 mg of MS were 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.

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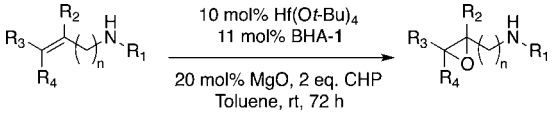
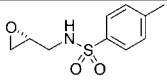
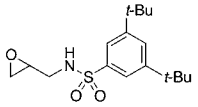
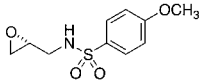
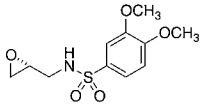
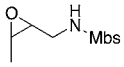
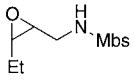
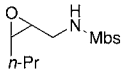
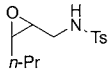
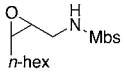
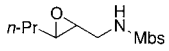
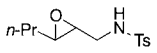
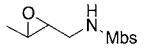
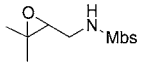
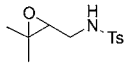
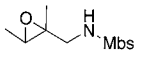
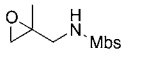
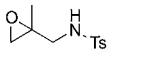
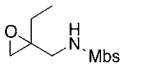
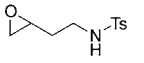
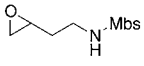
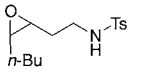
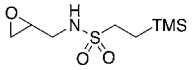
Table 3. Epoxidation of *N*-Alkenyl Sulfonamides



2, n = 1 or 2 **3**

entry[a]	product		yield[b]/%	ee[c]/%
1[d]		**3a**	46	90, *R*
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
15		**3o**	84	62
16		**3p**	92	42
17		**3q**	26	31
18		**3r**	88	9
19		**3s**	9	67
20		**3t**	21	45
21		**3u**	36	31
22		**3v**	88	87

[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 40 mol % additive were used. Ts- = *p*-toluenesulfonyl. Mbs- = 4-methoxybenzenesulfonyl.

and enantioselectivity can be significantly improved by introducing inorganic additives such as magnesium oxide.[6]

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 a 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 the attempts have been unsuccessful since they could not give better enantioselectivity. Even changing the phenyl groups in BHA-**1** to a 2,4,6-trimethyl, 2,4,6-isopropyl, or trityl group will result in a significantly decreased enantioselectivity (entries 2, 3, 4, Table 2). Adding a 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 was 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) compared to 2,3- and 2-disubstituted allylic amines (entries 15−18 Table 3) provide higher reactivities and selectivities. 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 a 4-methoxybenzenesulfonyl group. Finally, we evaluated the selectivity using the 2-(trimethylsilyl)ethanesulfonamide as a

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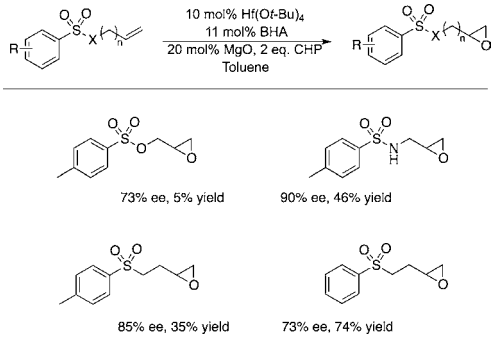
protecting group since this group can be easily removed;[7] to our delight we found almost the same selectivity as that utilizing the *p*-tolylsulfonyl group (entries 1 and 22, Table 3). This result demonstrates that our protocol can be useful in the preparation of enantiomerically enriched epoxides.

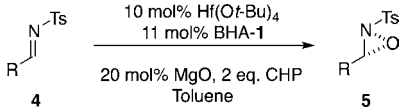
The electronic nature of the sulfonyl group had an effect on both reactivity and enantioselectivity, with the electron-donating *p*-methoxy derivative displaying higher reactivity and selectivity than the Ts- group and the electron withdrawing Ns-group (Table 1, entries 6, 7, 8). To gain more insight into the mode of coordination, a series of control experiments were conducted. Changing the NH-sulfonyl group to the O-sulfonyl or CH_2-sulfonyl group still allowed the asymmetric epoxidation to take place. These facts suggest the sulfonyl oxygen, instead of the amide nitrogen, play a 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]

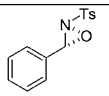
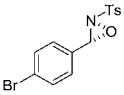
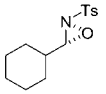
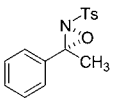
Chart 1. Epoxidation of Allylic Sulfonate, Sulfonamide, and Sulfones[a,b]



[a]Isolated yield after chromatographic purification. [b]Enantiomeric excess values were determined by chiral HPLC.

Table 4. Oxaziridination of *N*-Tosyl Imines



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.

The reaction of Boc-protected allylic amine[9] (entry 1, Table 1) also suggests the weak interaction between the 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, highly enantioselective epoxidation reaction was observed not only for simple aldimines (entries 1−3, Table 4) but also for a 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 a highly enantioselective oxaziridination of *N*-tosyl imines. Utilization of this protocol toward other asymmetric processes and elucidation of the mechanism are underway.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

yamamoto@uchicago.edu

Notes

The authors declare no competing financial interest.

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