JOC Article

Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols in Water

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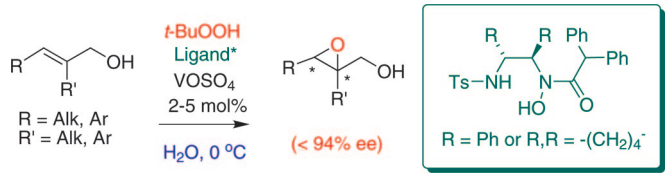
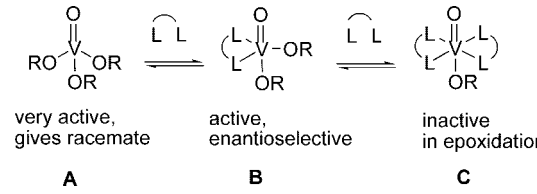


Asymmetric V-catalyzed epoxidation of allylic alcohols can be carried out in water with chiral ligands, which incorporate sulfonamide and hydroxamic acid fragments. Furthermore, the reaction, notorious for its ligand-deceleration effect, in water turned into the ligand-accelerated process. By using this aqueous protocol, a range of allylic alcohols were epoxidized with up to 94% ee.

Introduction

Vanadium-based peroxidases take part in a broad range of synthetically useful oxidative transformations including asymmetric epoxidation, sulfoxidation, and benzylic oxidation, which instigates an interest in designing synthetic biomimetic models with a vanadium core capable of reproducing the action of the biological systems.[1] Among the oxidation products, chiral epoxides occupy a pivotal position due to their unique versatility as synthetic building blocks in the target oriented organic synthesis.[2] Currently, Sharpless Ti-catalyzed epoxidation of allylic alcohols is the method of choice.[3] It is well understood and capable of delivering reliable and reproducible results; however, certain limitations, which include a rather high catalyst loading and requirement for stringently anhydrous conditions, hamper its wider industrial application.

SCHEME 1. Ligand-Deceleration Effect



The alternative methodology, also pioneered by Sharpless,[4] utilizes vanadium complexes, which are less sensitive to moisture, and furthermore, the catalyst loading can be reduced to 1 mol % or less. However, in V-catalyzed systems the mechanism of enantiodifferentiation is not clearly understood and the method is blemished by ligand deceleration effect[5] (Scheme 1): ligand-free species **A** present in equilibrium with coordinated species **B** and **C** is the most reactive but gives a racemic product. To minimize its presence, a large concentration of the chiral ligand is used to shift the equilibrium away from **A** toward the coordinated species **B** and **C**; however, it also substantially reduces the useful concentration of the desired catalytically active chiral species **B**, so that the highest selectivity is achieved at rather low reaction rates, which impeded the

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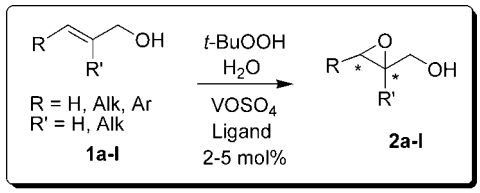
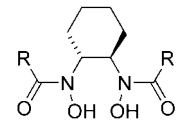
SCHEME 2. Asymmetric Epoxidation





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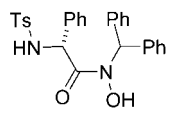

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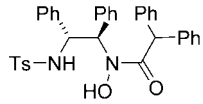

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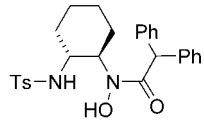

6

practical use of these systems.[4] It is worth noting that even though species **C** appears to be inactive in epoxidation, it may mediate other oxidative processes, such as oxidation of the allylic alcohols to the corresponding unsaturated aldehydes,[6] adding to the complexity of the reacting system.

Following earlier reports on the use of chiral hydroxamic acids in V-catalyzed asymmetric epoxidation of allylic alcohols,[7,8] Yamamoto advanced the field with the discovery of a very efficient family of bis-hydroxamic acids **3**,[9] which matched the Ti systems in terms of the scope and selectivity; however, the reactivity still remains the issue. In parallel with that, we have developed a family of sulfonamide ligands **4** which exhibited high reactivity and promising enantioselectivity in the epoxidation of allylic alcohols in toluene (ee $\leq$78%).[10]

Recently, we discovered that the same reaction (Scheme 2, **1** $\rightarrow$ **2**) can be carried out in water,[10b] where the costly vanadium precursor VO(*i*-OPr)$_3$ and anhydrous *t*-BuOOH are replaced with much cheaper alternatives, such as $VOSO_4$ and aqueous *t*-BuOOH, respectively. Furthermore, the reaction in water turned into the *ligand accelerated* process, where an excess of the ligand was no longer essential. The epoxidation is likely to proceed in the organic phase, as water-soluble vanadium salts exhibited poor conversion. Hydroxamic acid, a well-known key structural fragment of natural siderophores,[11] coordinates to the vanadium ion and transfers it to the organic phase where epoxidation is taking place. In these circumstances, the concentration of the catalytically active vanadium complex will be controlled by the concentration of the ligand. Once extracted from water, vanadium remains in the organic layer as a complex with hydroxamic acid; the aqueous phase turns out to be essentially free from the metal after the reaction is complete. Importantly, the rate of the reaction in water proved generally slower than that in organic solvents and only our sulfonamide ligands of type **4** provided an acceptable level of reactivity and selectivity (up to 72% ee).[10b] Employing water as a solvent[12] offers numerous advantages over traditional organic solvents including favorable environmental impact and low cost. To-date, only a handful of reports related to the asymmetric epoxidation of alkenes in aqueous solutions appeared in the literature.[13,14]

To obtain a full return from performing reactions in aqueous medium, it is important to bring the enantioselectivity to the practically useful level. Herein, we present a further development of the asymmetric V-catalyzed epoxidation of allylic alcohols in water focusing on the synthesis of new chiral ligands and optimization of the reaction conditions to boost reactivity and enantioselectivity.

Results and Discussion

A new set of chiral hydroxamic acids **5** and **6** (Scheme 2) is built around the chiral 1,2-diamine scaffold. Different from hydroxamic acid **4**, the chiral group in **5** and **6** is located in the hydroxylamine part. All the sulfonamide ligands **4**−**6** feature the bulky diphenylmethane substituent in the achiral fragment as smaller groups tend to considerably reduce enantioselectivity.[7c,10a]

Ligand Synthesis. General synthetic strategy toward the hydroxamic acid ligands relies on the coupling of the activated acid derivatives, such as acid chlorides **7**, with hydroxylamines (**12a**,**b**) (Scheme 3). Commercially available monotosylated derivative **9a** was used for the synthesis of hydroxylamine **12a**, while the synthesis of hydroxylamine **12b** commenced with the L-tartrate salt of (*R*,*R*)-(+)-**8b**,[15] which after neutralization with 2 M aqueous NaOH was treated with a solution of tosyl chloride (1.1 equiv) in DCM to afford **9b** (86% yield). Further sequence involved cyanomethylation of the mono-*N*-tosyldiamines **9a**,**b** to furnish the respective **10a** (70%) and **10b** (99%), followed by oxidation with *m*-CPBA. The nitrones **11a** (92%) and **11b** (75%) thus obtained were treated with hydroxylamine hydrochloride to produce the desired hydroxylamines **12a** (73%) and

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SCHEME 3. Synthesis of Hydroxamic Acids 5 and 6

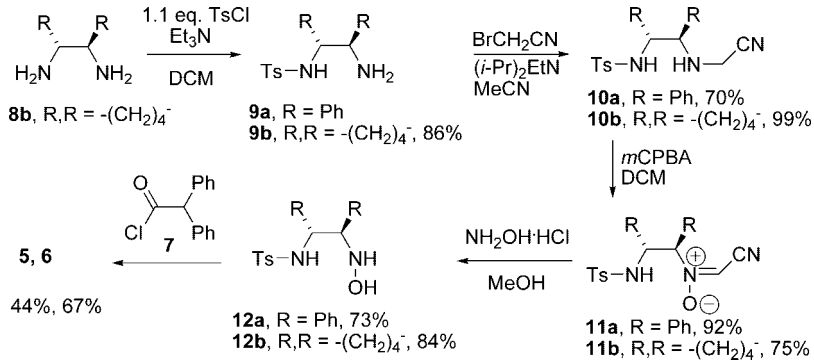
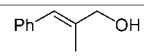
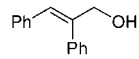


TABLE 1. Optimization of Aqueous V-Catalyzed Epoxidation of Allylic Alcohols[a]

entry	substrate		solvent	catalyst (mol%)	T, °C	yield (%)[b,c]	ee (%)[b,c]
1		**1a**	water	**4** (2)[d]	0	69	59[e]
2		**1a**	water	**5** (2)[d]	0	63	66
3		**1a**	water	**5** (5)	0	89	74
4		**1a**	water	**6** (2)[d]	0	73	82
5		**1a**	water	**6** (5)	0	95	85
6		**1a**	water	**6** (7)	0	94	87
7		**1a**	water/DCM[f]	**6** (5)	0	97	80
8		**1a**	water/tol[g]	**6** (5)	0	97	90
9		**1a**	toluene[h]	**6** (5)	-20	78	58
10		**1i**	water	**4** (2)	0	24	20
11		**1i**	water/tol[g]	**4** (5)	0	40	26
12		**1i**	water/tol[g]	**5** (5)	0	90	86
13		**1i**	water	**6** (5)	0	8	84
14		**1i**	water/tol[g]	**6** (5)	0	92	94

[a] The reaction was carried out at a 1 mmol scale at 0 °C for 12 h unless stated othervise. The catalyst was generated in situ from $VOSO_4$ and the ligand (vanadium/ligand ratio 1:1.1). [b] Determined by chiral GC (see the Experimental Section). [c] The absolute configuration of all the products was (*S*,*S*) as deduced from their optical rotation (see the Experimental Section). [d] Reaction time 48 h. [e] Reference 10b. [f] The reaction was carried out in a 3:1 mixture of water/DCM. [g] The reaction was carried out in a 3:1 mixture of water/toluene. [h] The reaction was carried out at −20 °C for 16 h, using a 5−6 M solution of *t*-BuOOH in nonane. The catalyst was generated from VO(*i*-OPr)$_3$ and the ligand (vanadium/ligand ratio 1:1.1).

12b (84%). In the next step, the hydroxylamines were coupled with commercially available acid chloride **7**. To avoid formation of the unwanted *O*-acylation products, the OH group in hydroxylamines **12a**,**b** was first protected in situ by treatment with a mixture of TMSCl and lutidine[16] followed by acylation with **7** to furnish the target hydroxamic acids **5** (44%) and **6** (67%). Under these conditions, the competing *O*-acylation of the hydroxylamine was reduced to a minimum (less than 5%).

Vanadium-Catalyzed Epoxidation. New hydroxamic acids **5** and **6** were examined as chiral ligands in the epoxidation of 2-methylcinnamyl alcohol **1a** and 2-phenylcinnamyl alcohol **1i** selected as model substrates to allow direct comparison with the results obtained with sulfonamide ligand **4**[10] (Table 1).

In the preliminary report,[10b] the reactions were carried out with 2 mol % of $VOSO_4 \cdot H_2O$ with a slight excess of chiral ligand (2.2 mol %); on average, the process required 48−60 h at 0 °C for completion. Following this protocol, epoxidation of 2-methylcinnamyl alcohol **1a** with aqueous *tert*-butyl hydroperoxide employing the catalyst based on (*R*,*R*)-phenylenediamine ligand **5** after 48 h produced epoxy alcohol **2a** with a slightly improved selectivity (63% yield, 66% ee, entry 2) compared to the original ligand **4** (69% yield, 59% ee, entry 1), whereas the clear winner was ligand **6** derived from (*R*,*R*)-cyclohexyldiamine giving **2a** in 73% yield and 82% ee (entry 4). However, the most dramatic jump in enantioselectivity was observed in the epoxidation of 2-phenylcinnamyl alcohol **1i**: while ligand **4** afforded epoxide **2i** in mere 20% ee (entry 10), ligand **6** delivered **2i** with respectrable 84% ee (entry 13). Epoxidation in water is generally slower than in organic solvents due to the heterogeneous nature of the system. The reaction rate is particularly affected when the substrate allylic alcohol is a solid, such as **1i**, resulting in low conversions (entries 10 and 13). Furthermore, it is important to maintain a high reaction rate in the aqueous epoxidation since prolonged reaction times can lead to a competing hydrolytic opening of the epoxide ring, assisted by a Lewis acidic catalyst, thus affecting the yield of the target product.[17] Therefore, the issues of reactivity were addressed next.

First, we investigated the effect of catalyst loading. Increasing the catalyst content from 2 mol % to 5 mol % reduced the reaction time and increased enantioselectivity. Thus, after just 12 h, the catalyst with ligand **5** afforded epoxy alcohol **2a** in 89% yield and 74% ee, while the complex with **6** produced **2a** in 95% yield and 85% ee (entries 3 and 5, respectively). Catalyst

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(17) (a) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (b) Tetzlaff, H. R.; Espenson, J. H. *Inorg. Chem.* **1999**, *38*, 881.

loading of 5 mol % appears to be optimal since a further increase to 7 mol % offered only marginal benefits (entry 6).

However, the catalyst loading alone cannot cure the problems associated with inefficient mixing of the organic components on the aqueous surface, particularly in those cases when both the substrate alcohol and the ligand are solids. We reasoned that the homogeneity of the organic phase can be improved by addition of a small quantity of organic solvent. Furthermore, in the original aqueous method[10b] the epoxidation is taking place in the organic phase consisting predominantly of the starting alcohol; however, alcohols were shown[10a] to be poor solvents for this process. On the other hand, toluene and dichloromethane (DCM) had a proven record in successful V-catalyzed epoxidation reactions,[7−10] therefore they were chosen as additives. Indeed, addition of DCM to the aqueous mixture in the epoxidation of **1a** with ligand **6** improved reactivity of the system; however, selectivity was slightly diminished (entry 7). At the same time, addition of toluene (entry 8) led to a notable increase in both yield (97%) and selectivity (90% ee). Importantly, the amount of organic solvent should be kept to a minimum, since in the organic medium the ligand deceleration effect comes into play requiring higher ligand-to-vanadium ratios. Thus, when the reaction was carried out in toluene alone with 10% excess of ligand over vanadium, the ratio proved optimal in the aqueous protocol, the selectivity plummeted to 58% ee (compare entries 8 and 9). Epoxidation of 2-phenylcinnamyl alcohol **1i**, so far the slowest reacting substrate, benefited the most from the addition of toluene to the aqueous mixture: epoxide **2i** was obtained in high yield and high enantioselectivity with both new ligands **5** and **6** (entries 12 and 14), the latter reaching 94% ee.

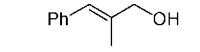
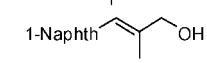
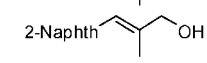
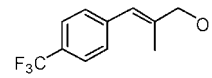
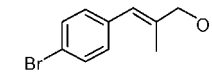
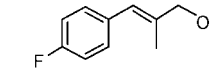
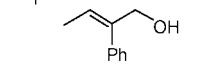
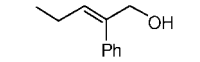
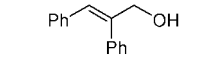
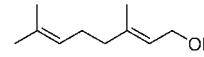
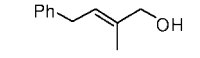
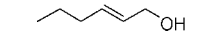
It is pertinent to note that bis-hydroxamic acid (*R*,*R*)-**3** introduced by Yamamoto[9] and our ligand (*R*,*R*)-**6** featuring the same configurations of the stereogenic centers gave rise to opposite enantiomers of the product **2a**, both with high enantioselectivity ((*R*,*R*) 94%[9] and (*S*,*S*) 90% ee, respectively, at 0 °C), suggesting that these systems operate by different mechanisms of enantiodifferentiation. However, we currently do not have sufficient kinetic, spectroscopic, and computational data to speculate on the nature of these differences.

The efficacy of the aqueous protocol employing our best ligand **6** was assessed in the epoxidation of a range of allylic alcohols (Table 2). The conditions in each case were optimized to maximize the yield of the target epoxides.

The reaction proved to be very efficient with all the 2-substitited cinnamyl derivatives **1a**−**f**,**i**, with the enantioselectivity varying in the range of 83−94% ee (entries 1−6 and 9). It is worth mentioning that alcohols **1d** and **1e** produced similar results in both water and water/toluene mixture. In the case of other 2,3-disubstituted alcohols **1g**, **1h**, and **1k**, the selectivity displayed a strong dependency on the size of the substitutents; groups larger than methyl caused a drop in ee (entries 7, 8, and 11), which is somewhat surprising since bulky 2-phenylcinnamyl alcohol **1i** exhibited the highest enantioselectivity (entry 9). Furthermore, alcohols **1h** and **1k** did not benefit from the addition of toluene to the reaction mixture showing slightly higher selectivity in water alone. Other, less sterically demanding substrates, e.g., **1j** and **1*l***, produced selectivities similar to those previously reported for ligand **4**[10b] (entries 10 and 12).

In conclusion, new chiral ligands based on 1,2-diamines featuring sulfonamide and hydroxamic acid functionalities were synthesized for V-catalyzed aqueous asymmetric epoxidation of allylic alcohols. Optimization of the reaction conditions led to development of an efficient protocol that was applied to the synthesis of a range of epoxy alcohol with up to 94% ee.

TABLE 2. Catalytic Epoxidation of Allylic Alcohols in Water with Ligand 6[a]

entry	substrate		yield (%)	ee (%) config.[b,c]
1		**1a**	98[d]	90 (*S*,*S*)
2		**1b**	75[d,e]	83 (*S*,*S*)
3		**1c**	90[d,e]	85 (*S*,*S*)
4		**1d**	61	87 (*S*,*S*)
5		**1e**	60	87 (*S*,*S*)
6		**1f**	65[d]	84 (*S*,*S*)
7		**1g**	97[d]	91 (+)
8		**1h**	71	78 (+)
9		**1i**	92[d]	94[d] (*S*,*S*)
10		**1j**	69[f]	69 (*S*,*S*)
11		**1k**	52	56 (+)
12		**1l**	42	70 (*R*,*R*)

[a] The reaction was carried out at 1 mmol scale with 5 mol % of catalyst (generated from $VOSO_4$ and the ligand in 1/1.1 ratio) at 0 °C for 24 h in water unless specified otherwise. [b] Determined by chiral NMR, GC, or HPLC (see the Experimental Section). [c] The absolute configuration of the products was deduced from their optical rotation (see the Experimental Section). [d] The reactions were carried out in 3:1 mixture of water/toluene. [e] The catalyst was generated in situ from $VOSO_4$ (5 mol %) and the ligand (10 mol %). [f] The reaction was carried out with 2 mol % of catalyst at −20 °C for 48 h in a 3:1 water/methanol mixture.

Experimental Section

Synthesis of *N*-Hydroxy-*N*-((1*R*,2*R*)-2-(4-methylphenylsulfonamido)cyclohexyl)-2,2-diphenylacetamide (6). *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-4-methylbenzenesulfonamide (9b): Following a procedure by Ng,[18] to a stirred solution of L-tartrate salt **8b**[15] (4.0 g, 15.14 mmol) in 2 M aqueous NaOH (18 mL) was added Et_3N (2.19 mL, 20.41 mmol) and DCM (130 mL). The mixture was cooled to 0 °C and a solution of TsCl (3.17 g, 16.65 mmol) in DCM (90 mL) was added dropwise over 30 min. The mixture was warmed to room temperature and stirred for 12 h. The resulting reaction mixture was washed with 2 M aqueous HCl (3 × 50 mL) and the organic phase was removed. The aqueous phase was collected and adjusted to pH 9 by addition of 6 M NaOH. The basic aqueous solution was extracted with DCM (3 × 50 mL). The combined DCM layers were dried over $MgSO_4$ and evaporated in vacuo to give **9b** as a pale yellow solid (3.5 g, 86%). A small sample was recrystallized from ethyl acetate: pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99−1.21 (m, 4H), 1.57−1.66 (m, 3H),

(18) Ng, K. *Tetrahedon: Asymmetry* **2001**, *12*, 1719.

1.86−1.95 (m, 1H), 2.37 (s, 3H), 2.42 (dt, J = 10.3, 3.7 Hz, 1H), 2.66 (dt, J = 10.3, 3.7 Hz, 1H), (br s, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5 (CH_3), 24.7 (CH_2), 25.0 (CH_2), 32.4 (CH_2), 34.9 (CH_2), 54.7 (CH), 60.4 (CH), 127.0 (aromatic CH), 129.7 (aromatic CH), 138.2 (C), 143.1 (C). In agreement with literature data.[19]

***N*-((1*R*,2*R*)-2-(Cyanomethylamino)cyclohexyl)-4-methylbenzenesulfonamide (10b):** Following a procedure by Fukuyama,[20] diisopropylethylamine (2.34 mL, 7.39 mmol) was added to a solution of monotosyl diamine **9b** (1.80 g, 6.72 mmol) in acetonitrile (30 mL) and the reaulting solution was stirred for 5 min. Bromoacetonitrile (0.51 mL, 7.39 mmol) was then added via syringe over 10 min and the mixture was stirred overnight at room temperature. Then the mixture was concentrated on a rotary evaporator to give a yellow oil, which was treated with saturated aqueous $NaHCO_3$ (50 mL). The resulting mixture was extracted with DCM (50 mL), the organic phase was washed with brine (50 mL), and the combined aqueous phases were extracted with DCM (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give **10b** as a yellow solid (1.98 g, 99%), which was used in the next step without further purification. A small sample was recrystallized from ethyl acetate: yellow solid, mp 104−105 °C (petroleum ether/ethyl acetate); $[\alpha]_D$ −9.3 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.20 (m, 4H), 1.38−1.64 (m, 4H), 1.93−2.01 (m, 1H), 2.36 (s, 3H), 2.40 (dt, J = 10.8, 3.9 Hz, 1H), 2.77−2.87 (m, 1H), 3.50 (d, J = 17.7 Hz, 1H), 3.63 (d, J = 17.7 Hz, 1H), 5.10 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7 (CH_3), 21.6 (CH_2), 24.2 (CH_2), 30.4 (CH_2), 32.4 (CH_2), 34.5 (CH_2), 57.4 (CH), 59.5 (CH), 118.1 (C), 126.8 (aromatic CH), 129.8 (aromatic CH), 137.6 (C), 143.6 (CN); IR (NaCl) ν 3353.6 (NH), 2940.9 (C−H), 2253.4 (CN), 1062.6 (O═S═O); MS (FAB) m/z (%) 281.2 (100), 308.3 ((M + H)$^+$ 55), 153.1 (29), 92.9 (25); HRMS (FAB) 308.1430 ($C_{15}H_{22}N_3O_2S$ requires 308.1433).

(1*R*,2*R*)-*N*-(Cyanomethylene)-2-(4-methylphenylsulfonamido)cyclohexanamine Oxide (11b): Following a procedure by Fukuyama,[20] *m*-CPBA (2.14 g, 12.38 mmol) was added in small portions over 30 min to a solution of **10b** (1.52 g, 4.95 mmol) in DCM (23 mL) cooled to 0 °C in an ice bath. After completion of addition, the ice bath was removed and the mixture was stirred at room temperature for 2 h. It was then diluted with DCM (20 mL) and washed with saturated $Na_2S_2O_3$ (30 mL) and saturated $NaHCO_3$ (3 × 30 mL). The aqueous phases were extracted with DCM (2 × 30 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give **11b** as a white solid (1.19 g, 75%), which was used in the next step without further purification. A small sample was recrystallized from DCM: white solid, mp 152−155 °C (DCM); $[\alpha]_D$ −27.3 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.40 (m, 4H), 1.62−2.04 (m, 4H), 2.38 (s, 3H), 3.50−3.59 (m, 1H), 3.82 (td, J = 11.2, 4.4 Hz, 1H), 5.10 (br s, 1H), 6.60 (s, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.6 (CH_2), 24.3 (CH_2), 30.3 (CH_2), 33.1 (CH_2), 54.5 (CH_3), 77.3 (CH), 79.4 (CH), 107.4 (CH), 111.9 (C), 126.8 (aromatic CH), 127.3 (aromatic CH), 129.8 (aromatic CH), 129.9 (aromatic CH), 137.5 (C), 144.2 (CN); IR (NaCl) ν 3303.5 (NH), 2949.6 (C−H), 2253.4 (CN), 1087.7 (O═S═O), 911.2 (N$^+$—O$^-$); MS (CI) m/z (%) 322.3 ((M + H)$^+$ 12), 306.3 (50), 281.3 (40), 125.2 (31); HRMS (CI) 322.1224 ($C_{15}H_{20}N_3O_3S$ requires 322.1225).

***N*-((1*R*,2*R*)-2-(Hydroxyamino)cyclohexyl)-4-methylbenzenesulfonamide (12b):** Following a procedure by Fukuyama,[20] hydroxylamine hydrochloride (1.29 g, 18.5 mmol) was added to a solution of nitrone **11b** (1.19 g, 3.70 mmol) in methanol (32 mL) and the mixture was heated at 60 °C for 2 h. After that time, the reaction mixture was cooled to room temperature and diluted with DCM (50 mL). After stirring for 5 min, the resulting precipitate was collected by filtration and the filter cake was washed with DCM. The filtrate was neutralized with $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous phase was extracted with DCM (25 mL). The organic phase was washed with brine (30 mL) and the combined aqueous phases were back-extracted with DCM (3 × 30 mL). The organic extracts were then dried over $MgSO_4$ and concentrated to give **12b** as a pale yellow solid (0.88 g, 84%), which was used in the next step without further purification. A small sample was recrystallized from DCM: pale yellow solid, mp 100−102 °C (DCM); $[\alpha]_D$ −28.9 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99−1.18 (m, 4H), 1.45−1.84 (m, 4H), 2.34 (s, 3H), 2.43 (td, J = 11.3, 3.9 Hz, 1H), 3.0 (m, 1H), 4.74 (br s, 1H), 5.92 (br s, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.6 (CH_3), 24.4 (CH_2), 24.7 (CH_2), 29.3 (CH_2), 33.2 (CH_2), 54.4 (CH), 64.2 (CH), 127.1 (aromatic CH), 127.3 (aromatic CH), 129.8 (aromatic CH), 136.9 (aromatic CH), 137.7 (C), 143.6 (C); IR (NaCl) ν 3263.9 (NH), 3155.0 (OH), 2938.0 (C−H), 2253.4 (C═C), 1026.9 (O═S═O); MS (FAB) m/z (%) 285.2 ((M + H)$^+$ 100), 92.9 (16), 130.4 (15), 92.9 (13); HRMS (FAB) 285.1274 ($C_{13}H_{21}N_2O_3S$ requires 285.1273).

***N*-Hydroxy-*N*-((1*R*,2*R*)-2-(4-methylphenylsulfonamido)cyclohexyl)-2,2-diphenylacetamide (6):** Following a procedure by Kim,[16] 2,6-lutidine (0.58 mL, 4.94 mmol) and TMSCl (0.63 mL, 4.94 mmol) were added to a solution of hydroxylamine **12b** (0.70 g, 2.47 mmol) in THF (21 mL) at 0 °C and the resulting mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 °C and a solution of diphenyl acetyl chloride (0.57 g, 2.47 mmol) in THF (5.5 mL) was added dropwise. The mixture was stirred at room temperature overnight. Water (0.9 mL) was added and the resulting solution was stirred for 1 h at room temperature. THF was then evaporated in vacuo. Ethyl acetate (20 mL) was added to the residue and the organic layer was washed successively with 10% citric acid (30 mL), 5% $NaHCO_3$ (30 mL), and water (30 mL). The organic solution was then dried over $MgSO_4$ and concentrated in vacuo to give a yellow sticky oil, which was recrystallized from methanol to give **6** as a white solid (0.80 g, 67%): mp 183−186 °C (methanol); $[\alpha]_D$ + 4.8 (c 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.20 (m, 4H), 1.30−1.74 (m, 4H), 2.35 (s, 3H), 3.10 (m, 1H), 4.30 (td, J = 11.0, 3.6 Hz, 1H), 4.76 (d, J = 9.6 Hz, 1H), 5.62 (s, 1H), 7.14−7.31 (m, 12H), 7.61 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6 (CH_3), 23.3 (CH_2), 24.0 (CH_2), 27.1 (CH_2), 31.1 (CH_2), 52.1 (CH), 52.8 (CH), 58.2 (CH), 125.6 (aromatic CH), 125.7 (aromatic CH), 125.8 (aromatic CH), 126.2 (aromatic CH), 126.3 (aromatic CH), 127.3 (aromatic CH), 127.5 (aromatic CH), 127.6 (aromatic CH), 127.7 (aromatic CH), 128.2 (aromatic CH), 128.7 (aromatic CH), 136.5 (C), 138.4 (C), 138.5 (C), 142.5 (C), 172.5 (C═O); IR (NaCl) ν 3154.0 (OH), 2940.9 (C−H), 2253.4 (C═C), 1709.6 (C═O), 1093.4 (O═S═O); HRMS (EI) m/z 478.1929 ($C_{27}H_{30}N_2O_4S$ requires 478.1926).

General Procedure for the Asymmetric Epoxidation (Table 2). Hydroxamic acid (**4**, **5**, or **6**; 5.5 mol %), vanadyl sulfate (5.0 mol %), and allylic alcohol (1 mmol) were added to distilled water (3 mL) or a mixture of distilled water (2.25 mL) and toluene (0.75 mL). The mixture was stirred at room temperature for 30 min and then cooled to 0 °C. A 70% aqueous solution of *t*-BuOOH (0.15 mL) was added and the mixture was stirred at 0 °C for 48 h. The reaction mixture was then quenched with a concentrated solution of Na_2SO_3 (10 mL) and after being stirred for 1 h at 0 °C it was extracted with DCM (3 × 20 mL), then the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a brown oil. Purification of the products was accomplished by column chromatography on silica gel (15 × 3 cm) with a 4:1 mixture of petroleum ether−ethyl acetate. The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined with analysis by chiral GC, HPLC, or NMR.

(19) Balsells, J. *Tetrahedon: Asymmetry* **1998**, *9*, 4135.
(20) Tokuyama, H.; Kuboyama, T.; Fukuyama, T. *Org. Synth.* **2003**, *80*, 207.

(2-Methyl-3-naphthalene-1-yl-oxiranyl)methanol (2b): Biege solid, mp 62−65 °C (petroleum ether/ethyl acetate); $[\alpha]_D$ −73.4 (*c* 0.5, CH_2Cl_2); chiral HPLC (Chiracel IB; 0.70 mL/min; hexane/2-propanol 95:5, $t_{(-)}$ = 15.30 min, $t_{(+)}$ = 22.35 min) showed 83% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 2.02 (dd, J = 8.2, 4.9 Hz, OH), 3.91−3.93 (m, 2H), 4.61 (s, 1H), 7.39−7.48 (m, 4H), 7.71−7.75 (m, 1H), 7.80−7.88 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (CH_3), 59.1 (CH), 63.8 (C), 64.9 (CH_2), 123.0 (CH), 124.1 (CH), 125.4 (CH), 126.0 (CH), 126.4 (CH), 127.8 (CH), 128.7 (CH), 130.9 (C), 131.9 (C), 133.2 (C); IR (NaCl) ν 3588.9 (OH), 3062.4 (C−H), 2929.3 (C−H), 1598.7 (C=C); MS (EI) *m*/*z* (%) 214.1 (M^+ 16), 183.1 (66), 181.0 (19), 141.1 (29), 140.1 (100), 83.9 (26); HRMS (EI) 214.0990 ($C_{14}H_{14}O_2$ requires 214.0994).

[2-Methyl-3-(4-trifluoromethylphenyl)oxiranyl]methanol (2d): White solid, mp 34−36 °C (petroleum ether/ethyl acetate); $[\alpha]_D$ +7.8 (*c* 0.5, CH_2Cl_2); chiral HPLC (Chiracel IB; 0.75 mL/min; hexane/2-propanol 95:5, $t_{(+)}$ = 13.37 min, $t_{(-)}$ = 14.27 min) showed 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.88 (dd, J = 9.1, 4.1 Hz, OH), 3.71 (dd, J = 12.6, 9.1 Hz, 1H), 3.81 (dd, J = 12.6, 4.1 Hz, 1H), 4.19 (s, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5 (CH_3), 60.5 (CH), 64.0 (C), 64.6 (CH_2), 125.1 (CH), 125.1 (C), 125.2 (C), 126.8 (CH), 139.9 (C); IR (NaCl) 3566.7 (OH), 3154.0 (C−H), 2999.7 (C−H), 1620.9 (C=C), 1325.8 (C−F); MS (CI) *m*/*z* (%) 233.1 ($(M + H)^+$ 100), 215.1 (72), 203.1 (40), 175.1 (9); HRMS (CI) 233.0788 ($C_{11}H_{12}O_2F_3$ requires 233.0789).

(3-Methyl-2-phenyloxiranyl)methanol (2g): Yellow oil; $[\alpha]_D$ +33.5 (*c* 1.0, CH_2Cl_2); chiral GC (Supelco β-Dex 120 column, oven temperature 110 °C for 2 min, then 1 °C/min, $t_{R,R}$ = 22.65 min, $t_{S,S}$ = 23.44 min) showed 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 5.5 Hz, 3H), 2.02 (br q, J = 4.2 Hz, OH), 3.53 (q, J = 5.5 Hz, 1H), 3.91−4.02 (m, 2H), 7.31−7.42 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_3), 56.9 (CH), 64.6 (CH_2), 66.0 (C), 127.0 (aromatic CH), 127.9 (aromatic CH), 128.4 (aromatic CH), 135.7 (C); IR (NaCl) 3449.1 (OH), 2966.0 (C−H), 2252.5 (C=C); MS (CI) *m*/*z* (%) 165.2 ($(M + H)^+$ 14), 147.2 (100), 121.1 (94), 85.2 (31), 69.1 (50); HRMS (CI) 165.0915 ($C_{10}H_{13}O_2$ requires 165.0916).

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Supporting Information Available: General experimental methods, experimental procedures, ^{1}H and ^{13}C NMR spectra for new compounds, and GC and HPLC traces for chiral epoxy alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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