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Amino acid-derived hydroxamic acids as chiral ligands in the vanadium catalysed epoxidation†

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New sulfonamide-derived hydroxamic acids **7–11** have been developed as chiral ligands for the V-catalysed asymmetric epoxidation, showing high reactivity at subzero temperatures and moderate to good enantioselectivity. The strong accelerating effect exhibited by the ligands of this type can be attributed to the sulfonamide functionality. A range of cinnamyl type allylic alcohols were epoxidised with up to 74% ee.

Introduction

Hydroxamic acid derivatives have been used as ligands in coordination chemistry of transition metals for a long time.[1] However, only a few examples of their application in asymmetric catalysis are known, and asymmetric epoxidation is the major object.[2] In general, olefin epoxidation has become a powerful tool for the preparation of chiral intermediates in organic synthesis.[3] To-date, the most successful protocols rely on the Ti-catalysed epoxidation of allylic alcohols, pioneered by Sharpless and Katsuki,[4] Mn-catalysed epoxidation of *cis*-olefins, developed by Jacobsen,[5] Cr-catalysed epoxidation of *trans*-olefins designed by Gilheany,[6] and organocatalytic epoxidation of *cis*- and *trans*-disubstituted and trisubstituted olefins introduced by Shi.[7]

The setbacks of titanium catalysis are the necessity of strictly anhydrous conditions and high catalyst loading, resulting in a tedious workup. Compared to the titanium systems, the use of other metals lags far behind. A few examples of molybdenum(VI)-catalysed reactions are known, though the enantioselectivities do not exceed 30–40%.[8] Vanadium(V) complexes, on the other hand, have been more successful. Thus, Sharpless reported that a complex of hydroxamic acid **3** (Scheme 1) and $VO(acac)_2$ catalysed epoxidation of selected allylic alcohols (**1** → **2**) with up to 44% ee, which was later improved to 80% ee (for **2**, $R^1 = R^2 = Ph$) by using ligand **4** and $(i\text{-PrO})_3VO$ as the metal source.[9,10] However, in this case, coordination of the chiral ligands to vanadium resulted in a significant deactivation of the catalyst, so that this method was not considered to be of practical use.

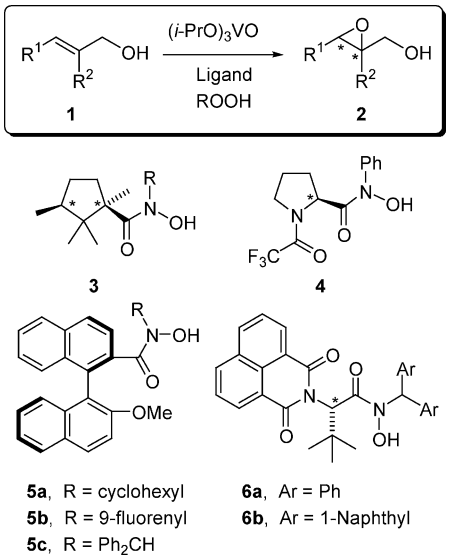
The last five years or so, have witnessed the renewed interest in vanadium(V)-catalysed epoxidation of allylic alcohols. Thus, Yamamoto described the preparation of hydroxamic acids **5**, derived from 2,2′-binaphthol, which allowed to achieve 41–91% ee with a range of allylic alcohols.[11] Several other reports on the application of chiral hydroxamic acids in V-catalysed epoxidation[12] and mechanistic studies[13] have then followed. Recently, while our work was in progress, Yamamoto[14] disclosed the new amino acid-derived ligands, in particular **6b** that, for the first time, came close to the Ti(IV) systems in terms of reactivity and enantioselectivity.

Herein, we report on the synthesis of chiral hydroxamic acids with an appended sulfonamide group,[15] and demonstrate their application in vanadium(V)-catalysed asymmetric epoxidation of allylic alcohols. In particular, the effect of the sulfonamide moiety on the reactivity and selectivity of the catalyst is discussed.

Results and discussion

The selection of chiral hydroxamic acids **7–11**, employed in this work, is shown in Chart 1. We have varied the amino acid backbone (**7a–d**, and **10**), the sulfonyl group (**8a–d**), and the substitution pattern at the stereogenic centre (**7a**, **9**, and **11**). The bulky diphenylmethane substituent at the hydroxylamine part of the molecule remained constant as the use of smaller groups led to a considerable reduction in selectivity.[11,16]

† Electronic supplementary information (ESI) available: Experimental procedures; ^1H and ^{13}C NMR spectra for new compounds. See http://dx.doi.org/10.1039/b505324b



Scheme 1

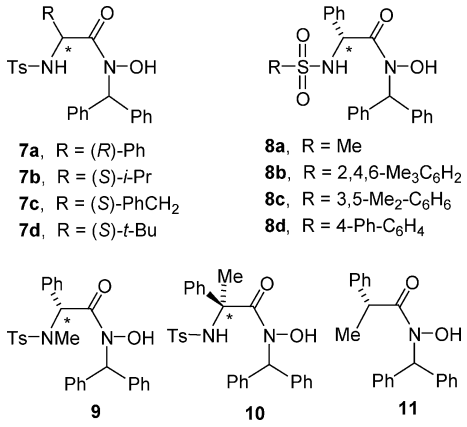
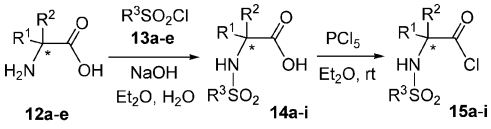


Chart 1

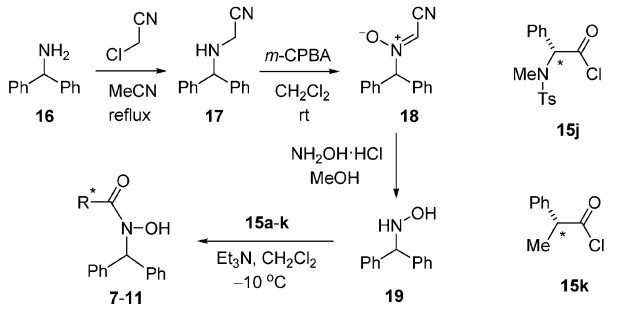
DOI: 10.1039/b505324b



12a, R^1 = (*R*)-Ph, R^2 = H
12b, R^1 = (*S*)-*i*-Pr, R^2 = H
12c, R^1 = (*S*)-PhCH$_2$, R^2 = H
12d, R^1 = (*S*)-*t*-Bu, R^2 = H
12e, R^1 = (*S*)-Ph, R^2 = Me

13a, R^3 = 4-MeC$_6$H$_4$
13b, R^3 = Me
13c, R^3 = 2,4,6-Me$_3$C$_6$H$_2$
13d, R^3 = 3,5-Me$_2$C$_6$H$_3$
13e, R^3 = 4-PhC$_6$H$_4$

14a, 15a, R^1 = (*R*)-Ph, R^2 = H, R^3 = 4-MeC$_6$H$_4$
14b, 15b, R^1 = (*S*)-*i*-Pr, R^2 = H, R^3 = 4-MeC$_6$H$_4$
14c, 15c, R^1 = (*S*)-PhCH$_2$, R^2 = H, R^3 = 4-MeC$_6$H$_4$
14d, 15d, R^1 = (*S*)-*t*-Bu, R^2 = H, R^3 = 4-MeC$_6$H$_4$
14e, 15e, R^1 = (*R*)-Ph, R^2 = H, R^3 = Me
14f, 15f, R^1 = (*R*)-Ph, R^2 = H, R^3 = 2,4,6-Me$_3$C$_6$H$_2$
14g, 15g, R^1 = (*R*)-Ph, R^2 = H, R^3 = 3,5-Me$_2$C$_6$H$_3$
14h, 15h, R^1 = (*R*)-Ph, R^2 = H, R^3 = 4-PhC$_6$H$_4$
14i, 15i, R^1 = (*S*)-Ph, R^2 = Me, R^3 = 4-PhC$_6$H$_4$



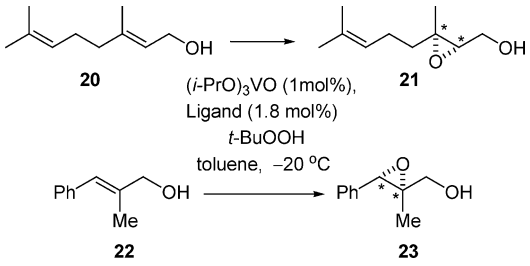
Scheme 2

Ligand synthesis

The general synthetic strategy towards the hydroxamic-type ligands relied on reacting the corresponding amino acid chlorides **15** with benzhydryl hydroxylamine (**19**) at low temperature (Scheme 2). Chlorides **15a–i** were prepared in two steps from the respective amino acids **12a–e**, which were first *N*-derivatized with the corresponding sulfonyl chloride **13a–e** in a biphasic ether–1 M aqueous NaOH system and the resulting sulfonamides **14a–i** were then converted into acid chlorides **15a–i**; the best results in the latter reaction were obtained with PCl_5 in ether. Acid chlorides **15j**, **k** were prepared in a similar fashion from the corresponding acids.[17] Benzhydryl hydroxylamine (**19**) was prepared using the published protocol[18] that involves cyanomethylation of benzhydrylamine (**16**), followed by oxidation with *m*-CPBA. Treatment of the resulting nitrone **18** with hydroxylamine hydrochloride furnished the desired benzhydryl hydroxylamine **19**. The reaction of chlorides **15a–k** with **19** produced the required hydroxamic acid **7–11**. Under these conditions, the competing *O*-acylation of the hydroxylamine was reduced to a minimum (less than 5%). Chiral HPLC analysis of **7a** revealed that the latter coupling proceeded without any loss of the stereochemical integrity (>99% ee).

Vanadium catalysed epoxidation

Hydroxamic acids **7a** and **11** were employed as chiral ligands in the epoxidation of geraniol **20** and 2-methylcinnamyl alcohol **22**, selected as model substrates to allow direct comparison with the results published earlier[10–12,14] (Scheme 3).



Scheme 3

With ligand **7a**, derived from (*R*)-phenylglycine, the reaction turned out to be very fast, almost matching the rate observed for VO(acac)$_2$ alone. Epoxidation of **20** afforded **21** in quantitative yield and 64% ee at −20 °C in 6 h, while the epoxidation of **22** was complete in 24 h, giving **23** in 80% yield and 62% ee, both with 1 mol% catalyst loading (Table 1, entry 1). The level of asymmetric induction attained with ligand **7a** for geraniol (**20**) matched the enantioselectivities obtained with ligand **5c** and was only slightly lower than that reported for ligand **6b**. By contrast, the catalytic system based on ligand **11**, lacking the sulfonamide functionality, proved sluggish, even with geraniol, producing less than 5% of epoxide **21** of 43% ee (entry 6) after 24 h, which clearly demonstrates the importance of the toluenesulfonamide group (as in **7a**).

The influence of the amino acid backbone on the ligand efficacy was examined next (Table 1). Ligands **7b–d** predictably exhibited excellent reactivities; however only **7d**, derived from *tert*-leucine, produced enantioselectivity similar to **7a**. Surprisingly, ligands **7b–d**, despite having the opposite configuration at the stereogenic centre (compared to **7a**), gave rise to the same enantiomers of the products (though with lower enantioselectivity).

The mechanism of enantiodifferentiation in vanadium(V)-catalysed epoxidation has not been established in detail. The NMR investigation of the complexes of V(V) with hydroxamic acids showed that the axial alkoxide ligand is fairly labile and rapidly exchanges with neutral alcohol added to the solution.[13a,b] It can be assumed that diastereoisomeric complexes **A–D** (Chart 2), chiral at vanadium, are the major components present in solution. With chiral hydroxamic acids, complexes **A**/**B** and **C**/**D** form two sets of diastereoisomeric pairs, whose relative reactivity would be responsible for the observed overall enantioselectivity of the epoxidation.

It can be suggested that, in the case of sulfonamide ligands, hydrogen bonding between the sulfonyl group[19] and the approaching allylic alcohol may facilitate displacement of the labile axial ligand (the *i*-PrO group or the epoxy alcohol produced), followed by a fast oxygen transfer (**E** → **F**, Scheme 4). Furthermore, if such an interaction exerts a considerable effect on the reaction rate, then structures **A** and **B**, where the transferable oxygen of the peroxide and the sulfonamide moiety are

Table 1 Asymmetric epoxidation of allylic alcohols catalysed by V-complexes of chiral hydroxamic acids **7a–d** and **10–11** (Scheme 3)[a]

		Geraniol (**20**)		2-Methylcinnamyl alcohol (**22**)	
Entry	Ligand	Yield (%)	Ee (%), config.[b,c]	Yield (%)	Ee (%), config.[b,c]
1	(*R*)-**7a**	95	64 (*S*,*S*)	90	62 (*S*,*S*)
2	(*S*)-**7b**	84	15 (*S*,*S*)	79	17 (*S*,*S*)
3	(*S*)-**7c**	95	<5	88	<5
4	(*S*)-**7d**	93	66 (*S*,*S*)	87	51 (*S*,*S*)
5	(*S*)-**10**	87	32 (*R*,*R*)	—	—
6	(*R*)-**11**	<5	43 (*S*,*S*)	—	—

[a] The reaction was carried out in toluene at −20 °C for 20 h on a 1 mmol scale. The catalyst was generated *in situ* from (*i*-PrO)$_3$VO (1 mol%) and the ligand (1.8 mol%). [b] Determined by chiral GC (see the Experimental). [c] The absolute configuration of the products was deduced from their optical rotation (see the Experimental).

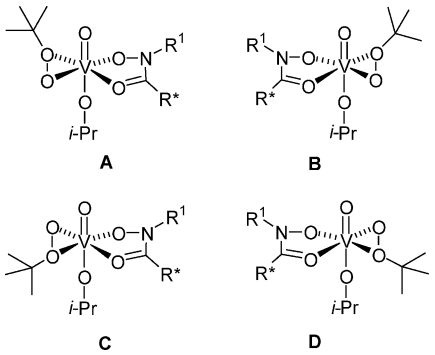
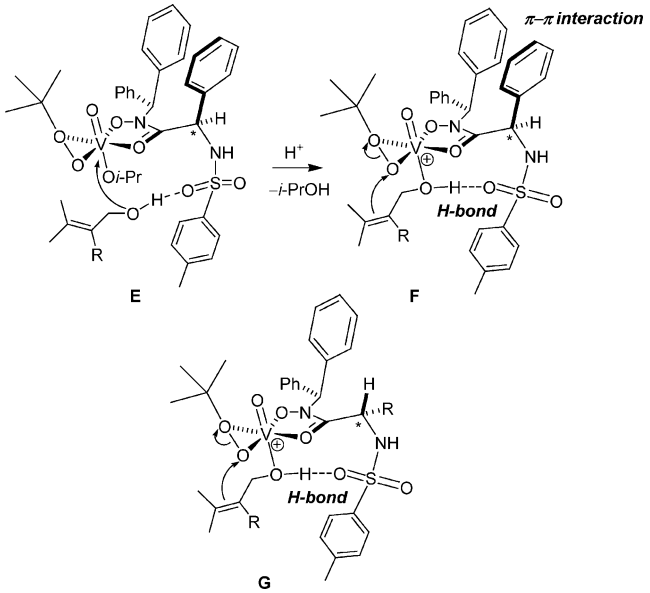


Chart 2



Scheme 4

positioned *cis* to each other, should exercise the main influence on the reaction outcome; the relative reactivity of **A** and **B** will be reflected in the enantioselectivity of the reaction. Note that methanol, a protic polar solvent, is likely to disrupt intramolecular hydrogen bonding. As a result, the reactivity and selectivity of ligand **7a** in MeOH was reduced to that of the ligand **11** where no functional group is present (compare entry 6, Table 1 and entry 5, Table 2). In addition, π–π interactions between the phenyl groups of the phenylglycine and the hydroxylamine units may constitute a significant factor in controlling the structure of the active complex. These aromatic interactions can be suggested to account for the observation that the ligands derived from (*R*)-phenylglycine and aliphatic (*S*)-amino acids produced epoxides of the same configuration (*vide supra*, Table 1). In the latter case, a steric repulsion between the substituent in the amino acid backbone and the phenyl group of the hydroxylamine moiety should force them apart, creating a transition state similar to **E**, where the hydrogen atom and the substituent at the stereogenic centre of the amino acid have traded places (**G**).

The results of a brief investigation of the effects of solvent, temperature, and the vanadium : ligand ratio, carried out with ligand **7a** and employing geraniol as substrate, are summarized in Table 2. Among the solvents, toluene proved to be superior (entry 1), while the use of other solvents (acetonitrile and methanol in particular) led to lower selectivities (entries 2–5). The reaction at room temperature was very fast (complete in less than 2 h) but non-selective (entry 9); cooling to −20 °C proved to be beneficial but further lowering the temperature failed to improve the selectivity (compare entries 1 and 10). The minimum ligand : vanadium ratio that does not adversely affect the enantioselectivity was identified as 1.5. An increase to 2.4 : 1 did not improve the asymmetric induction, while reduction to 1.2 : 1 resulted in a considerable drop in the enantioselectivity. To maintain a good reproducibility, the 1.8 : 1 ratio was employed throughout this work. Loading of vanadium can be reduced to 0.5 mol% without any loss of reactivity or selectivity; on the other hand, at 0.1 mol%, the enantioselectivity dropped below 50% ee, although good reaction rate was maintained.

An investigation of the effect of additives on this asymmetric epoxidation revealed that weakly coordinating Lewis-basic additives (up to 5 mol%), such as DMSO, DMF, and pyridine *N*-oxide, slightly decelerated the reaction but did not have an adverse effect on the enantioselectivity. In fact, pyridine *N*-oxide improved the enantioselectivity of geraniol epoxidation (to 68% ee). On the other hand, addition of the coordinating Et_3N resulted in a dramatic decrease in both reactivity and selectivity (42% ee). It can be hypothesized that the additives assist the displacement of the product from the axial position but, in the same time, impair further displacement by the allylic alcohol, resulting in an overall deceleration of the reaction.

In the Yamamoto imides, the environment of the nitrogen is flat (Chart 1, ligands **6a,b**).[14] By contrast, in the sulfonamide group of our ligands, the sulfur atom adjacent to the nitrogen is tetrahedral,[19] which creates a different spatial environment. Note that sulfonamide derived ligand **7d** and Yamamoto's ligands **6a,b** sharing the same (*S*)-*tert*-leucine backbone produced opposite epoxide enantiomers.

The effect of the steric properties of the sulfonamide moiety on the selectivity of epoxidation of geraniol and 2-methylcinnamyl alcohol is highlighted in Table 3. It appears from these results that the aromatic group in the sulfonamide unit plays a key role in the creation of the chiral cavity, since the smaller methylsulfonyl group gave nearly racemic products (entry 2).

Recently, we have demonstrated[20] that *N*-methylation of the amino acid-derived ligands can improve their catalytic performance by inducing favourable conformational restrictions.

Table 2 Effect of temperature, solvent, and ligand : vanadium ratio on the asymmetric epoxidation of geraniol **20** catalysed by V-Complexes with Ligand **7a**[a]

Entry	Temp./°C	Ratio ligand : V	Solvent	Yield (%)	Ee (%)[b]
1	−20	1.8 : 1	toluene	98	64
2	−20	1.8 : 1	CH_2Cl_2	96	47
3	−20	1.8 : 1	$CHCl_3$	96	55
4	−20	1.8 : 1	MeCN	95	37
5	−20	1.8 : 1	MeOH	<5	39
6	−20	1.2 : 1	toluene	98	34
7	−20	1.5 : 1	toluene	95	64
8	−20	2.4 : 1	toluene	82	64
9	20	1.8 : 1	toluene	95[c]	30
10	−40	1.8 : 1	toluene	98	58

[a] The reaction was carried out for 20 h at a 1 mmol scale. The catalyst was generated *in situ* from $(i\text{-PrO})_3VO$ (1 mol%) and ligand **7a**. [b] Determined by chiral GC (see the Experimental section). [c] The reaction was complete in less than 2 h.

Table 3 The influence of the sulfonamide group on the asymmetric epoxidation of allylic alcohols[a]

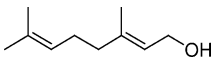
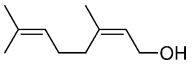
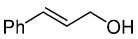
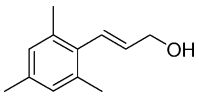
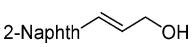
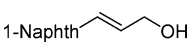
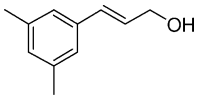
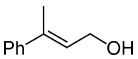
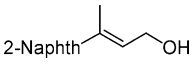
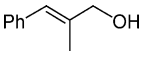
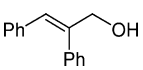
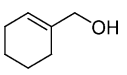
		Geraniol (**20**)		2-Methylcinamyl alcohol (**22**)	
Entry	Ligand	Yield (%)	Ee[b] (%)	Yield (%)	Ee[b] (%)
1	**7a**	95	64	90	62
2	**8a**	86	4	69	8
3	**9**	96	7	93	14
4	**8b**	55	41	52	39
5	**8c**	62	61	85	48
6	**8d**	95	64	76	56

[a] The reaction was carried out in toluene at −20 °C for 20 h at a 1 mmol scale. The catalyst was generated *in situ* from $(i\text{-PrO})_3VO$ (1 mol%) and the ligand (1.8 mol%). [b] Determined by chiral GC, the products had (*S*,*S*) absolute configuration deduced from their optical rotation (see experimental part).

However, in this case, the *N*-methylated ligand **9** turned out to exhibit poor enantioselectivity (entry 3). In terms of the size, *p*-toluenesulfonamide appears to be optimal, as additional substituents in the aromatic ring did not bring about any enhancement of enantioselectivity (entries 4–6). In fact, introducing *ortho* substituents decreased the selectivity (entry 4).

The efficacy of the sulfonamide ligand **7a** was assessed in the epoxidation of a range of allylic alcohols **20**, **22**, and **24–33** (Table 4). It is pertinent to note that monosubstituted allylic alcohols, particularly aromatic cinnamyl derivatives **25–29**, are renowned for their poor reactivity in V-catalysed epoxidation.[11,12,14] With the most reactive ligand **6b** (reported to date) it took 80 h at 0 °C to achieve 92% conversion in epoxidation of **25** (58% yield, 87% ee).[14a] By contrast, with our catalytic system, based on the sulfonamide-derived hydroxamic acid **7a**, comparable conversion (82%) of **25** into the corresponding epoxide was attained in 20 h at −20 °C (67% yield and 63% ee, entry 3). Other cinnamyl derivatives, such as **26–29**, behaved in a similar way; a moderate drop in reactivity was observed for bulky substrates **26** and **29** (entries 4 and 7). All the cinnamyl derivatives exhibited moderate to good enantioselectivity (entries 4–7). The (*E*)-3,3-disubstituted allylic alcohols **20**, **30**, and **31** reacted rapidly, affording the corresponding epoxides in moderate to good ee (entries 1, 8, and 9), while nerol **24**, with (*Z*)-configuration of the double bond, showed reduced reactivity and selectivity (entry 2). In the case of 2,3-disubstituted alcohols **22**, **32**, and **33**, the reactivity was not compromised but selectivity displayed strong dependency on the size of the 2-substituent. When ligand **7a** was employed, groups larger than methyl caused ee plummeting (entries 10–12), which contrasts with ligand **6** that gave excellent selectivity for this type of substrates.[14a] This comparison serves as an indication that structural changes in the part of the ligands **6** and **7a,d**, seemingly remote from the active metal centre, can dramatically affect the mechanism

Table 4 Catalytic epoxidation of allylic alcohols using ligand **7a**[a]

Entry	Substrate		Yield (%)	Ee (%) config.[b,c]
1		**20**	95	68[d] (*S*,*S*)
2		**24**	40	41 (*R*,*S*)
3		**25**	67	63 (*R*,*R*)
4		**26**	32	74 (*R*,*R*)
5		**27**	95	63 (+)
6		**28**	91	62 (−)
7		**29**	46	63 (+)
8		**30**	49	72 (−)
9		**31**	95	61 (+)
10		**22**	90	62 (*S*,*S*)
11		**32**	85	20 (*S*,*S*)
12		**33**	55	56 (*R*,*R*)

[a] The reaction was carried out in toluene at −20 °C for 20 h at a 1 mmol scale. The catalyst was generated *in situ* from $(i\text{-PrO})_3VO$ (1 mol%) and the ligand (1.8 mol%). [b] Determined by chiral GC (see the Experimental section). [c] The absolute configuration of the products was deduced from their optical rotation (see the Experimental section). [d] Pyridine *N*-oxide was used as an additive (5 mol%).

of enantiodifferentiation, implying that sulfonamide or imido group might be involved in shaping up the transition state.

In conclusion, new sulfonamide-derived hydroxamic acid ligands were developed for V-catalysed asymmetric epoxidation, showing fast reactivity at subzero temperatures and moderate to good selectivity (in particular, ligand **7a**). The strong accelerating effect exhibited by the ligands of this type can be attributed to the hydrogen bonding between the sulfonamide moiety and the incoming alcohol that brings and holds the reactants together. The reactions only require 1 mol% catalyst loading. A range of cinnamyl type allylic alcohols (Table 4) were epoxidised with up to 74% ee.

Experimental

General methods

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated with an error of $<\pm 0.1$. The $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, ^{1}H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0 ^{13}C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between KBr plates or for $CHCl_3$ solutions. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware twice evacuated and filled with nitrogen. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether from lithium aluminium hydride; tetrahydrofuran from sodium–benzophenone; dichloromethane from calcium hydride, toluene from sodium. Petroleum ether refers to the fraction boiling in the range of 40–60 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR and MS data and by TLC behaviour. Synthesis of chiral ligands is illustrated by the synthesis of hydroxamic acid **7a**.

Hydroxamic acid (*R*)-(−)-7a

Step A. A solution of *p*-toluenesulfonyl chloride **2a** (1.372 g, 7.2 mmol) in ether (12 mL) was added to a mechanically stirred solution of D-(−)-phenylglycine **1** (906 mg, 6 mmol) and NaOH (600 mg, 15 mmol) in water (12 mL) at room temperature. The mixture was stirred at room temperature for 16 h and then acidified to pH ~2 with 12 M HCl to produce a white precipitate. The precipitate was separated by filtration and washed with water. Crystallization from ether afforded acid **14a** as a white solid (1.2 g, 66%), which was used in the next step without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.33 (s, 3H), 4.86 (d, $J = 9.2$ Hz, 1H), 7.12–7.29 (m, 7H), 7.61 (d, $J = 8.2$ Hz, 2H), 8.60 (d, $J = 9.2$ Hz, 1H), 12.8 (bs, 1H), consistent with the literature data.[21]

Step B. Phosphorus pentachloride (0.875 g, 4.2 mmol) was added portion wise to a stirred solution of acid **14a** (1.068 g, 3.5 mmol) in anhydrous ether (8 mL) in a 100 mL round bottom flask under nitrogen atmosphere. After stirring for 2 h at room temperature, 35 mL of *n*-hexane was added and the mixture was left in a freezer overnight. Precipitated crystals were quickly separated by filtration and washed with *n*-hexane. A white solid of acid chloride **15a** (535 mg, 47%) was used immediately in the next step.

Step C. A solution of benzhydryl hydroxylamine **19** (200 mg, 1 mmol) in dry dichloromethane (3 mL) was added to a solution of acid chloride **15a** (323 mg, 1 mmol) in dry dichloromethane (3 mL) under nitrogen atmosphere at −10 °C (cryocooler). The resulting mixture was stirred at −10 °C for 30 min and then the mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched with triethylamine (150 μL). A saturated solution of ammonium chloride was added and the mixture was extracted with dichloromethane. The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil. Purification, using column chromatography on silica gel (15 × 3 cm) with an *n*-hexane–ethyl acetate mixture (4 : 1) furnished **7a** (115 mg, 24%) as white crystals, which gave positive red-wine coloured stain with $FeCl_3$ on TLC: mp 172–174 °C (hexane–ethyl acetate), $[a]_D$ −58 (*c* 0.5, $CHCl_3$); Chiral HPLC (Chiralcel OD-H; 0.75 mL min^{-1}; hexane : 2-propanol 90 : 10, $t_S = 13.56$, $t_R = 15.43$) showed >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 5.01 (s, 1H), 5.60 (d, $J = 8.2$ Hz, 1H), 6.08 (d, $J = 8.3$ Hz, 1H), 6.77 (s, 1H), 6.89 (d, $J = 7.3$ Hz, 2H), 7.12–7.37 (m, 15H), 7.62 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 57.8 (CH), 63.5 (CH), 127.4 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 129.8 (CH), 136.3 (C), 137.3 (C), 137.5 (C), 143. 5 (C), 169.6 (CO); IR (KBr) ν 3286, 1615, 1496, 1419, 1335, 1163, 1091, 703 cm^{-1}; HRMS (EI) *m/z* 486.1615 ($C_{28}H_{26}O_4N_2S$ requires 486.1613).

General procedure for asymmetric epoxidation

Ligand (1.8 mol%) and $(i\text{-PrO})_3VO$ (2.5 μL, 10 μmol) were dissolved in dry toluene (3 mL) under nitrogen atmosphere and the resulting deep brown solution was stirred at room temperature for 30 min. Allylic alcohol (1 mmol) was then added in one portion and the mixture was stirred for at room temperature for 10 min and then cooled to −20 °C. A 5 M solution of *t*-BuOOH in nonane (0.3 mL) was added and the mixture was stirred at −20 °C overnight (~20 h). The solution was then washed with water (10 mL), the aqueous phase was extracted with dichloromethane (2 × 20 mL), 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 an *n*-hexane–ethyl acetate mixture (4 : 1). The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using chiral GC or HPLC.

Epoxidation of geraniol 20. (2*S*,3*S*)-(−)-3,7-Dimethyl-2,3-epoxy-oct-6-en-1-ol (**21**) was isolated as a clear, colourless oil: $[a]_D$ −1.9 (*c* 1.00, $CHCl_3$); chiral GC (Supelco α-Dex 120 column, oven temp. 110 °C for 2 min, then 1.0 °C min^{-1} to 200 °C, $t_{S,S} = 24.38$, $t_{R,R} = 24.82$) showed 64% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.41–1.5 (m, 2H), 1.62 (s, 3H), 1.65 (s, 3H), 2.06–2.12 (m, 2H), 2.23 (bs, 1H), 2.98 (dd, $J = 6.6$, 4.3 Hz, 1H), 3.68 (dd, $J = 12.2$, 6.6 Hz, 1H), 3.83 (dd, $J = 12.2$, 4.1 Hz, 1H), 5.08 (t, $J = 6.7$ Hz, 1H), consistent with the literature data.[22]

Epoxidation of alcohol 22. (2*S*,3*S*)-(−)-2-Methyl-3-phenyl-2,3-epoxy-propan-1-ol (**23**) was isolated as a clear, colourless oil: $[a]_D$ −6.1 (*c* 1.00, $CHCl_3$); chiral GC (Supelco β-Dex 120 column, oven temp. 110 °C for 2 min, then 1.5 °C min^{-1} to 200 °C, $t_{R,R} = 33.19$, $t_{S,S} = 33.71$) showed 62% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 2.16 (bs, 1H), 3.77 (d, $J = 12.5$ Hz, 1H), 3.88 (d, $J = 12.5$ Hz, 1H), 4.24 (s, 1H), 7.28–7.39 (m, 5H), consistent with the literature data.[22]

Epoxidation of nerol 24. (2*S*,3*R*)-(+)-[3-Methyl-3-(4-methyl-pent-3-enyl)oxiranyl]-methanol was isolated as a clear, colourless oil: $[a]_D$ +9.8 (*c* 1.00, $CHCl_3$); chiral GC (Supelco β-Dex 120 column, oven temp. 110 °C for 2 min, then 1.5 °C min^{-1} to 200 °C, $t_{S,R} = 46.12$, $t_{R,S} = 46.36$) showed 40% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.38–1.63 (m, 2H) 1.55 (s, 3H),

1.62 (s, 3H), 1.78 (bs, 1H), 1.96–2.10 (m, 2H), 2.9 (dd, $J = 6.8$, 4.4 Hz), 3.58 (dd, $J = 12.0$, 6.9 Hz, 1H), 3.73 (dd, $J = 12.0$, 4.4 Hz, 1H), 5.01–5.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3), 22.6 (CH_3), 24.6 (CH_2), 26.0 (CH_3), 33.5 (CH_2), 61.7 (CH_2), 64.5 (CH), 123.7 (CH-O), 132.9 (C), 138.5 (C-O), consistent with the literature data.[22]

Epoxidation of cinnamyl alcohol 25. (2*R*,3*R*)-(+)-3-Phenyl-oxiranemethanol was isolated as a beige solid: mp 33–36 °C (hexane–ethyl acetate); $[\alpha]_D$ +59 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.7 mL min^{-1}, hexane–2-propanol 95 : 5, $t_{S,S} =$ 35.08, $t_{R,R} = 39.26$) showed 63% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77–1.80 (m, 1H), 3.25 (m, 1H), 3.80–3.87 (m, 1H), 3.94 (d, $J = 2.1$ Hz, 1H), 4.05–4.17 (m, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9 (CH), 61.6 (CH_2), 62.8 (CH), 126.1 (CH), 128.7 (CH), 128.9 (CH), 137.0 (C), consistent with the literature data.[23]

Epoxidation of alcohol 26. (2*R*,3*R*)-(–)-(2,4,6-Trimethyl-phenyl)oxirane-2-methanol was isolated as a white solid: mp 84–86 °C (chloroform); $[\alpha]_D$ −12.4 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.7 mL min^{-1}, hexane–2-propanol 95 : 5, $t_{R,R} =$ 16.13, $t_{S,S} = 20.52$) showed 74% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.8 (dd, $J = 7.6$, 5.6 Hz, 1H), 2.19 (s, 3H), 2.28 (s, 6H), 3.09 (m, 1H), 3.81 (ddd, $J = 12.4$, 7.2, 4.0 Hz, 1H), 3.88 (d, $J = 2.0$ Hz, 1H), 4.03 (ddd, $J = 12.4$, 5.6, 2.4 Hz, 1H), 6.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (CH_3), 20.9 (CH_3), 54.4 (CH), 59.7 (CH), 61.5 (CH_2), 128.7 (CH), 130.3 (C), 137.0 (C), 137.5 (C), consistent with the literature data.[24]

Epoxidation of alcohol 27. (+)-(3-Naphthalen-2-yl-oxiranyl)-methanol was isolated as a beige solid: mp 100–102 °C (hexane–ethyl acetate); $[\alpha]_D$ +23.9 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.7 mL min^{-1}; hexane–2-propanol 98 : 2, $t_{(+)} = 29.88$, $t_{(-)} = 41.68$) showed 63% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (dd, $J = 7.6$, 5.6 Hz, 1H), 3.25 (d, $J = 1.8$ Hz, 1H), 3.78 (ddd, $J =$ 12.0, 7.6, 3.7 Hz, 1H), 4.00–4.05 (m, 3H), 7.15–7.76 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2 (CH), 61.6 (CH_2), 62.8 (CH), 123.2 (CH), 123.3 (CH), 125.8 (CH), 126.6 (CH), 126.8 (CH), 128.2 (CH), 128.8 (CH), 133.5 (C), 133.7 (C), 134.5 (C); IR (KBr *v* 3441, 3055, 2926, 1630, 1510, 1400, 1210, 1076, 1018, 824, 745 cm^{-1}; HRMS (EI) *m*/*z* 200.0839 ($C_{13}H_{12}O_2$ requires 200.0837).

Epoxidation of alcohol 28. (−)-(3-Naphthalen-1-yl-oxiranyl)-methanol was isolated as a colourless oil: $[\alpha]_D$ −15.9 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.7 mL min^{-1}; hexane–2-propanol 98 : 2, $t_{(-)} = 30.27$, $t_{(+)} = 35.79$) showed 62% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (bs, 1H), 3.11–3.13 (m, 1H), 3.86–3.89 (m, 1H), 4.00–4.07 (m, 1H), 4.49 (d, $J = 2.1$ Hz, 1H), 7.33–8.01 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8 (CH), 60.2 (CH_2), 60.6 (CH), 121.3 (CH), 121.8 (CH), 124.8 (CH), 124.9 (CH), 125.4 (CH), 127.2 (CH), 127.7 (CH), 130.2 (C), 131.8 (C), 132.2 (C), consistent with the literature data.[25]

Epoxidation of alcohol 29. (+)-[3-(3,5-Dimethyl-phenyl)-oxiranyl]-methanol was isolated as a colourless oil: $[\alpha]_D$ +14.5 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.7 mL min^{-1}, hexane–2-propanol 95 : 5, $t_{(+)} = 18.69$, $t_{(-)} = 20.43$) showed 62% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 7H), 3.11–3.17 (m, 1H), 3.65–3.68 (m, 1H), 3.76–3.77 (m, 1H), 3.90–3.94 (m, 1H), 6.81 (s, 2H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 56.1 (CH), 61.7 (CH_2), 62.7 (CH), 123.9 (CH), 130.4 (CH), 136.9 (C), 138.6 (C); IR (NaCl) *v* 3483, 2919, 1701, 1655, 1608, 1467, 1160, 1074, 1036, 849, 698 cm^{-1}; HRMS (EI) *m*/*z* 178.0995 ($C_{11}H_{14}O_2$ requires 178.0994).

Epoxidation of alcohol 30. (−)-(3-Methyl-3-phenyl-oxiranyl)-methanol was isolated as a colourless oil: $[\alpha]_D$ −10.2 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.5 mL min^{-1}; hexane–2-propanol 90 : 10, $t_{(-)} = 13.45$, $t_{(+)} = 14.89$) showed 72% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.96 (bs, 1H), 3.01 (dd, $J = 6.4$, 4.4 Hz, 1H), 3.74 (dd, $J = 12.0$, 6.4 Hz, 1H), 3.89 (dd, $J = 12.0$, 4.4 Hz, 1H), 7.14–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3), 60.9 (C), 61.3 (CH_2), 66.0 (CH), 125.1 (CH), 127.6 (CH), 128.4 (CH), 142.0 (C), consistent with the literature data.[26]

Epoxidation of alcohol 31. (+)-(3-Methyl-3-naphthalen-2-yl-oxiranyl)-methanol was isolated as beige solid: mp 58–60 °C (hexane–ethyl acetate); $[\alpha]_D$ +2.4 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.7 mL min^{-1}; hexane–2-propanol 90 : 10, $t_{(+)} =$ 31.46, $t_{(-)} = 41.10$) showed 61% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.96 (bs, 1H), 3.01 (dd, $J = 6.4$, 4.4 Hz, 1H), 3.74 (dd, $J = 12.0$, 6.4 Hz, 1H), 3.89 (dd, $J = 12.0$, 4.4 Hz, 1H), 7.14–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3), 61.2 (C), 61.4 (CH_2), 66.1 (CH), 123.0 (CH), 124.2 (CH) 126.1 (CH), 126.3 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 132.8 (C), 133.1 (C), 139.5 (C); IR (KBr) *v* 3426, 1631, 1599, 1452, 1388, 1136, 1078, 1027, 862, 826, 743 cm^{-1}; HRMS (EI) *m*/*z* 214.0994 ($C_{14}H_{14}O_2$ requires 214.0994).

Epoxidation of alcohol 32. (2*S*,3*S*)-(–)-2,3-Diphenyl-2,3-epoxy-propan-1-ol was isolated as a white solid: mp 57–59 °C (hexane–ethyl acetate) (lit.[27] 54–56 °C, hexane–diethyl ether); $[\alpha]_D$ −14.2 (*c* 1.00, $CHCl_3$); chiral HPLC (Chiracel OD-H; 0.5 mL min^{-1}; hexane–2-propanol 90 : 10, $t_{R,R} = 15.26$, $t_{S,S} =$ 16.91) showed 20% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (s, 1H), 3.96 (s, 2H), 4.44 (s, 1H), 6.96–7.31 (m, 10H), consistent with the literature data.[22]

Epoxidation of alcohol 33. (2*R*,3*R*)-(+)-(7-Oxa-bicyclo-[4.1.0]hept-1-yl)-methanol was isolated as a clear, colourless oil: $[\alpha]_D$ +6.7 (*c* 1.00, $CHCl_3$); chiral GC (Supelco β-Dex 120 column; oven temp. 110 °C for 2 min, then 1 °C min^{-1} to 200 °C, $t_{S,S} =$ 13.16, $t_{R,R} = 13.41$) showed 56% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.33 (m, 2H), 1.39–1.52 (m, 2H) 1.66–2.00 (m, 4H), 2.31 (bs, 1H), 3.25 (d, $J = 3.2$ Hz, 1H), 3.56 (d, $J = 12.4$ Hz, 1H), 3.67 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (CH_2), 19.9 (CH_2), 25.3 (CH_2), 55.9 (CH), 60.3 (CO), 64.6 (CH_2), consistent with the literature data.[22]

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