Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols Mediated by (+)-Norcamphor-Derived Hydroperoxide

Alessandra Lattanzi,*[a] Sandro Piccirillo,[a] and Arrigo Scettri[a]

Keywords: Optically pure hydroperoxides / Asymmetric synthesis / Epoxidation / Vanadium / Kinetic resolution / Diastereoselectivity

A protocol for the asymmetric epoxidation of allylic alcohols has been established that employs $VO(acac)_2$ as catalyst, the commercial achiral hydroxamic acid, *N*-hydroxy-*N*-phenylbenzamide, and optically pure (+)-norcamphor-derived hydroperoxide as oxygen atom donor and chiral source. Variation of the reaction parameters has a significant effect on the level of asymmetric induction. Under optimized conditions, the epoxy alcohols have been isolated in good yields with up to 67% *ee* and complete control of the diastereoselectivity.

Introduction

Asymmetric epoxidation of allylic alcohols catalyzed by metal complexes in the presence of enantiopure ligands using alkyl hydroperoxide as oxygen donors is the most fundamental process for obtaining epoxy alcohols with a high level of enantioselectivity[1] and impressive results have been obtained by using the Sharpless–Katsuki protocol[2,3] [Ti(O*i*Pr)$_4$/L-DET/TBHP].

A less developed methodology involving the use of $VO(acac)_2$/optically active hydroxamic acids with TBHP as oxidant was previously reported by Sharpless and co-workers[4,5] to afford epoxy alcohols in up to 80% *ee*. Modified versions of this protocol have recently been proposed in which structurally different enantiopure hydroxamic acids derived from binaphthyl,[6,7] α-amino acid,[8] [2.2]paracyclophane,[9] (+)-ketopinic acid[10] and (*R*)-α-phenethylamine compounds were employed.[11] Only one example involving the use of an achiral hydroxamic acid and the optically pure hydroperoxide TADOOH (Figure 1) has so far been reported.[12]

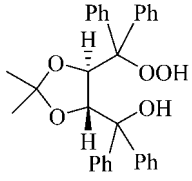
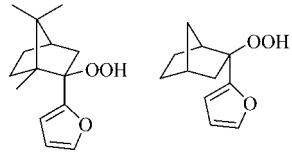


Figure 1. TADOOH hydroperoxide.

Tertiary, sterically demanding TADOOH afforded the epoxy alcohols in up to 72% *ee*, much better than the levels achieved when using enantiopure, secondary alkyl hydroperoxides. In general, the most efficient oxygen atom donors are tertiary hydroperoxides, as confirmed by the data obtained from Sharpless-type oxidations.[13–15] Until now, enantiopure alkyl hydroperoxides have rarely been employed as stereoselective reagents,[16–19] hence this type of investigation provides a new and complementary insight into the field of asymmetric oxidations mediated by alkyl hydroperoxides.

Recently we have become interested in the synthesis of optically pure, tertiary alkyl hydroperoxides **1** and **2** derived from (*R*)-camphor[20] and (*S*)-norcamphor[21] (Figure 2), respectively, in which (unlike TADOOH) the hydroperoxyl group is directly bound to the stereogenic centre.



1 **2**

Figure 2. (*R*)-Camphor- and (*S*)-norcamphor-derived hydroperoxides.

These oxidants have been employed as oxygen donors in the Ti(O*i*Pr)$_4$-catalyzed epoxidation of allylic alcohols[20] and in asymmetric sulfoxidation reactions,[21,22] achieving in some examples the best levels of enantioselectivity reported when using optically pure hydroperoxides.

A recent NMR analysis[23] of the enantiopure [2.2]paracyclophane-based hydroxamic acid protocol[9] supported the original mechanistic proposal[4,5] for the vanadium-catalyzed epoxidation reaction. Sharpless and co-workers[24] suggested that control of vanadium/ligand complexation is important in the epoxidation reaction as different species

[a] Dipartimento di Chimica, Università di Salerno,
Via S. Allende, 84081, Baronissi, Italy
Fax: +39-089-965296
E-mail: lattanzi@unisa.it

 DOI: 10.1002/ejoc.200400736

can equilibrate (Figure 3). With an enantiopure hydroperoxide and an achiral ligand, enantioselective epoxidation reactions can occur via complexes **A** and **B**, unlike the classical methodology, which involves the use of an enantiopure ligand and an achiral hydroperoxide, in which the asymmetric epoxidation takes place only via complex **B**. Up to now, no investigations into the competitive enantioselective epoxidation by species **A** have been reported when using an optically pure hydroperoxide, so it would be of interest to check the efficiency and the sense of asymmetric induction provided by this pathway.

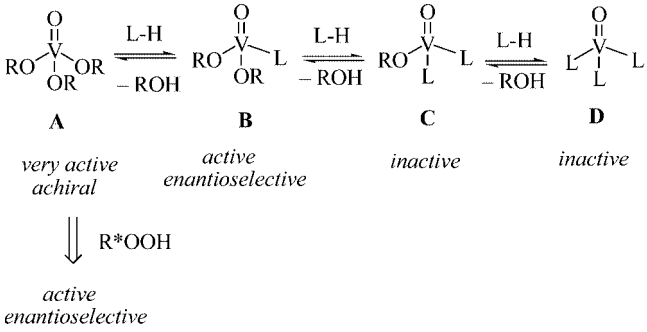
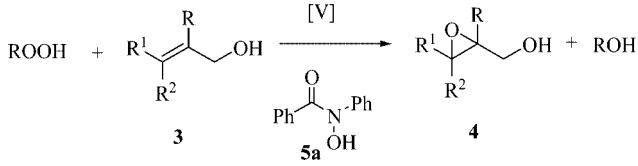


Figure 3. Vanadium/ligand complexation equilibria.

Herein, we report our results of the catalytic asymmetric epoxidation of allylic alcohols using $VO(acac)_2$, the achiral and commercially available *N*-hydroxy-*N*-phenylbenzamide and hydroperoxide **2** as chiral oxidant.

Results and Discussion

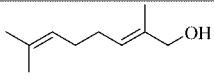
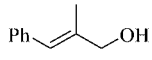
A preliminary study of the catalytic asymmetric epoxidation reaction was carried out under various conditions (Scheme 1, Table 1). It has been demonstrated that the $VO(OiPr)_3$ complex is the most efficient catalyst for the epoxidation reaction and that the nature of the solvent can affect the level of enantioselectivity.[4–11]



Scheme 1. Vanadium-catalyzed epoxidation of allylic alcohols.

Hydroperoxide **1** was found to be less reactive and enantioselective than oxidant **2** in the epoxidation of geraniol under usual reaction conditions [$VO(OiPr)_3$ in toluene] at 0 °C (entries 1 and 2). Taking into account the reaction pathway proposed for the vanadium-catalyzed epoxidation of allylic alcohols[4,5] and as recently supported by NMR studies,[23] the lower reactivity of hydroperoxide **1** could be tentatively ascribed to strong steric interactions in a transition state involving temporary coordination of the encumbered oxygen atom donor and the allylic alcohol. In any case, the possibility of a low reaction rate for the ligand exchange, necessary for the epoxidation reaction to occur under catalytic conditions, cannot be excluded.

Table 1. Vanadium-catalyzed asymmetric epoxidation of allylic alcohols by **1** and **2**.

Entry	ROOH	Catalyst	3		Solvent	*T* [°C]	Time [h]	Yield **4** [%][a]	*ee* **4** [%][b]
1[c]	**1**	$VO(Oi\text{-}Pr)_3$		**3a**	toluene	0	12	98	13 (*R*,*R*)
2[c]	**2**	"	"	"	"	"	5	96	28 (*R*,*R*)
3[c]	**2**	"		**3b**	"	"	5	93	41 (*R*,*R*)
4[d]	**2**	"	"	"	"	–20	24	60	51 (*R*,*R*)
5[d]	**2**	"	"	"	CH_2Cl_2	–20	"	80	51 (*R*,*R*)
6[c]	**2**	$VO(acac)_2$	"	"	toluene	0	22	99	39 (*R*,*R*)
7[d]	**2**	"	"	"	CH_2Cl_2	-20	24	44	54 (*R*,*R*)
8[d]	**1**	"	"	"	"	"	48	–	–
9[c]	**2**	"	"	"	"	"	48	70	61 (*R*,*R*)
10[c]	**2**	"	"	"	"	–40	72	21	67 (*R*,*R*)
11[e]	**2**	"	"	"	"	–20	44	81	38 (*R*,*R*)
12[f]	**2**	"	"	"	"	"	66	47	56 (*R*,*R*)
13[g]	**2**	$VO(Oi\text{-}Pr)_3$	"	"	"	"	23	54	38 (*R*,*R*)

[a] Isolated yields after flash chromatography. [b] Determined by HPLC analysis using a chiral column or by ^1H NMR shift experiments on the acetylated epoxy alcohol using $Eu(hfc)_3$. The absolute configurations given in parentheses were determined by comparison with the optical rotations reported in the literature. [c] The reaction was carried out with 10 mol-% catalyst/15 mol-% hydroxamic ligand. [d] The reaction was carried out with 5 mol-% catalyst/7.5 mol-% hydroxamic ligand. [e] The reaction was carried out in the absence of hydroxamic acid and with 10 mol-% catalyst. [f] The reaction was carried out by using 10 mol-% catalyst/30 mol-% hydroxamic ligand. [g] The reaction was carried out in the absence of hydroxamic acid and with 2 mol-% catalyst.

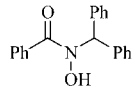
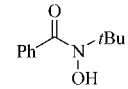
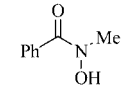
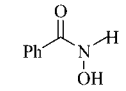
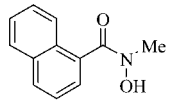
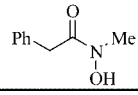
The epoxidation of **3b** (entry 3) using **2** under the same conditions took place to provide the (*R*,*R*)-epoxy alcohol with a better *ee*. Halving the catalyst loading and lowering the temperature to –20 °C reduced the reactivity but improved the enantioselectivity of the reaction (entry 4). Although toluene has been reported to be the best solvent, when the reaction was performed in CH_2Cl_2 (entry 5), the conversion to the epoxide increased while the enantioselectivity was maintained. When the reaction was carried out with 10 mol-% of $VO(acac)_2$ in toluene at 0 °C, the same conversion and enantioselectivity were achieved but with a longer reaction time (entry 6). By using 5 mol-% of catalyst at –20 °C (entry 7) the reactivity was reduced but the *ee* of epoxide improved (compare with entry 5). Hydroperoxide **1** was employed under these conditions, but without success; in fact after two days no trace of epoxide was detected, confirming the poor reactivity of this oxidant. When 10 mol-% of $VO(acac)_2$ was used at –20 °C (entry 9) the epoxide was obtained in good yield and with an improved enantioselectivity (61% *ee*), which increased to 67% *ee* when the reaction was performed at –40 °C (entry 10).

In the absence of the ligand (entry 11) an almost comparable reaction time (compare with entry 9) was required to furnish the (*R*,*R*)-epoxy alcohol in a higher yield but with a lower enantioselectivity. Predictably, complex **A** was more active, although to only a small extent, than complex **B** (Figure 3). In order to be sure that the competing epoxidation by species **A** would be negligible, the equilibria had to be shifted towards complexes **B**, **C** and **D**. Hence, up to 3 equivs. of the ligand (entry 12), with respect to the metal, were used to ensure that only complex **B** was involved in the asymmetric epoxidation pathway. As expected,[24] the reactivity was lowered (compare with entry 9) but the *ee* was almost comparable to that reported in entry 9; thus with a metal/ligand ratio of 1:1.5, we can be assured that species **A** is not involved in the epoxidation process and that only the most enantioselective complex **B** is involved in the asymmetric epoxidation.

Note that the reaction in entry 11 represents the first asymmetric example of the well-known system reported by Sharpless and co-workers for the regio- and diastereoselective epoxidation of allylic alcohols[4,25] [$VO(acac)_2$/TBHP/allylic alcohol]. When the reaction was carried out with only 2 mol-% of $VO(OiPr)_3$ and in the absence of a ligand (entry 13), (*R*,*R*)-epoxy alcohol was isolated after a short reaction time in a satisfactory yield and with the same 38% *ee* (compare with entry 11). In the last case, in order to suppress the involvement of complex **A** in the reaction, the use of a hydroxamic acid/vanadium catalyst ratio[26] >1.5:1.0 equiv. would seem to be better, although it has the disadvantage of lowering the reaction rate.[24]

As suggested by the data in Table 1, the optimized reaction conditions involve the employment of easy-to-handle and inexpensive $VO(acac)_2$ in CH_2Cl_2. Hence, we screened various achiral hydroxamic acids, synthesized according to known procedures,[27,28] in the epoxidation of model alcohol **3b** under the best conditions found previously (Table 2).

Table 2. Asymmetric epoxidation of **3b** by $VO(acac)_2$/**2** and different hydroxamic acids at –20 °C in CH_2Cl_2.[a]

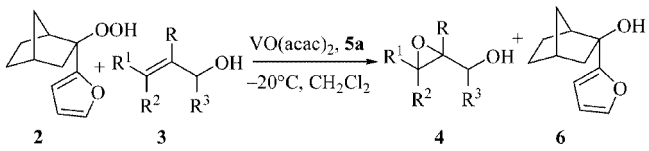
Entry	Hydroxamic acid	**5**	Time [h]	Yield **4b** [%][b]	*ee* **4b** [%][c]
1		**5b**	46	32	40 (*R*,*R*)
2		**5c**	67	45	19 (*R*,*R*)
3		**5d**	48	23	52 (*R*,*R*)
4		**5e**	97	47	24 (*R*,*R*)
5		**5f**	96	–	–
6[d]		**5g**	45	30	55 (*R*,*R*)

[a] The reactions were carried out by using a mixture of **3b**/$VO(acac)_2$/hydroxamic acid/**2** in a molar ratio of 1:0.10:0.15:1.2. [b] Isolated yields after flash chromatography. [c] Determined by HPLC analysis using a Chiralcel OD column and detection at 254 nm; eluent: hexane/*i*PrOH, 97:3. The absolute configurations given in parentheses were determined by comparison with the optical rotations reported in the literature. [d] In this case 10 mol-% of $VO(OiPr)_3$ was used as the catalyst.

Steric hindrance of the substituent on the nitrogen atom significantly reduced the reactivity and the enantioselectivity of the reaction (entries 1 and 2). The *N*-methyl-substituted ligand slowed the conversion but a moderate level of asymmetric induction was observed in the product (entry 3). The *N*-unsubstituted hydroxamic acid furnished a very slow reacting complex with low asymmetric induction (entry 4). The reaction of *N*-methylnaphthohydroxamic acid failed completely (entry 5). The benzyl derivative also afforded an unreactive complex when using $VO(acac)_2$ as the catalyst, while a modest conversion to the epoxide with 55% *ee* was achieved with $VO(OiPr)_3$ (entry 6). In all cases the (*R*,*R*)-epoxide was preferentially obtained. Simple alkyl- or aryl-substituted hydroxamic acids had, as previously reported, pronounced but not easily accountable effects on the reactivity and enantioselectivity of the epoxidation reaction, which were inferior to the levels achieved with the commercial ligand **5a** (Table 1, entry 9).

On the basis of these results, *N*-hydroxy-*N*-phenylbenzamide (**5a**) was the ligand used to assess the scope of the epoxidation reaction (Table 3, Scheme 2).

Geraniol and its (*Z*)-isomer nerol were epoxidized to give the epoxy alcohols in good yields and with moderate enantioselectivities, showing that the asymmetric induction does not depend on the geometry of the double bond (en-



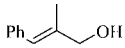
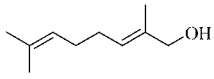
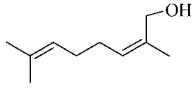
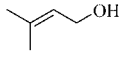
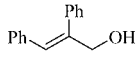
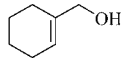
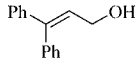
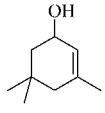
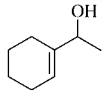
Scheme 2. Asymmetric epoxidation with $VO(acac)_2$/**5a** and hydroperoxide **2**.

tries 2 and 3). The smaller pentenol was epoxidized more quickly (entry 4), while the epoxidation of α-phenylcinnamyl alcohol furnished better results with $VO(OiPr)_3$ in toluene (entry 5). Cyclic alcohol **3f** was also epoxidized in good yield and with a comparable *ee* (entry 6). β-Phenylcinnamyl alcohol, even after a prolonged reaction time, was found to be completely unreactive (entry 7).

Finally, the investigation into the vanadium-catalyzed asymmetric epoxidation turned onto secondary allylic alcohols as substrates, operating under <50% conversion of the alcohol and by using $VO(Oi\text{-}Pr)_3$, since these substrates are less reactive than primary allylic alcohols.

Compound **3h** was epoxidized with complete stereoselectivity to give the *syn* epoxide but with poor enantioselectivity (entry 8). Indeed, kinetic resolution took place with low efficiency as demonstrated by the value of the stereoselectivity factor (S = 2.1).[29] Alcohol **3i** was converted exclusively to the *erythro* epoxy alcohol although with comparable asymmetric induction and efficiency of kinetic resolution[30] (entry 9). The level of diastereoselectivity was better than that observed when using other common systems such as $Ti(OiPr)_4$/L-DET/TBHP, $Ti(OiPr)_4$/TBHP and $VO(acac)_2$/TBHP,[5,31] which preferentially furnished the *erythro*[32–35] isomer of **4i**. Surprisingly, experiments performed in the absence of ligand afforded, in a shorter reaction time, exclusively the *erythro* epoxy alcohol (entry 10)

Table 3. Asymmetric epoxidation of allylic alcohols by $VO(acac)_2$/**5a** and hydroperoxide **2**.[a]

Entry	**3**		Time [h]	Yield **4** [%][b]	*ee* **4** [%][c]	*d.r.* **4** [%][d]
1		**3b**	48	70	61 (*R*,*R*)	–
2		**3a**	45	64	40 (*R*,*R*)	–
3		**3c**	72	61	41 (*R*,*S*)	–
4		**3d**	42	98	44 (*R*)	–
5[e]		**3e**	23	88	44 (*R*,*R*)	–
6		**3f**	23	76	45 (*R*,*R*)	–
7		**3g**	144	–	–	–
8[f]		**3h**	90	29 (70)[g]	13 (1*S*,2*S*,3*R*) 5 (*R*)[h]	*syn*/*anti* >99/<1
9[i]		**3i**	90	52 (43)[g]	17 (2*S*,3*S*,4*S*) 23 (*R*)[h]	*erythro*/*threo* >99/<1
10[l]	"	"	12	58 (40)[g]	11(2*S*,3*S*,4*S*) 15(*R*)[h]	*erythro*/*threo* >99/<1

[a] The reactions were carried out by using a mixture of **3**/$VO(acac)_2$/**5a/2** in a molar ratio of 1:0.10:0.15:1.2. [b] Isolated yields after flash chromatography. [c] Determined by HPLC analysis using chiral columns or by performing ^1H NMR shift experiments on the acetylated epoxy alcohol using $Eu(hfc)_3$or by ^1H NMR analysis of the MTPA-derived ester. The absolute configurations given in parentheses were determined by comparison with the optical rotations reported in the literature. [d] Determined by ^1H NMR analysis (400 MHz) of the crude reaction mixture. [e] The reaction was carried out in toluene using $VO(OiPr)_3$/**5a** in a molar ratio of 0.05:0.075. [f] The reaction was carried out in toluene using $VO(OiPr)_3$/**5a/2/3h** in a molar ratio of 0.30:0.45:0.7:1. [g] Yield of recovered alcohol. [h] Enantiomeric excess of recovered alcohol. [i] The reaction was carried out in toluene using $VO(OiPr)_3$/**5a/2/3i** in a molar ratio of 0.15:0.23:0.7:1. [l] The reaction was carried out in the absence of hydroxamic acid and with 15 mol-% of $VO(OiPr)_3$ in toluene.

with only a marginal effect on the kinetic resolution. The presence of the ligand seems to be of minor importance and does not improve the diastereoselectivity, as observed for the Ti(O*i*Pr)$_4$/L-DET/TBHP system compared with Ti(O*i*Pr)$_4$/TBHP.[32] This result clearly indicates that the structure of the hydroperoxide can be crucial for controlling the diastereoselectivity of the metal-catalyzed epoxidation reactions and improvements can be expected by steric modifications to the oxidant when employing the same metal catalyst in the absence of any ligand.

Conclusions

In summary, we have established a simple protocol for the asymmetric epoxidation of allylic alcohols using VO(acac)$_2$, commercial *N*-hydroxy-*N*-phenylbenzamide and a (+)-norcamphor-derived hydroperoxide as oxidant.[36] The epoxy alcohols have been obtained with moderate levels of asymmetric induction. Although the kinetic resolution of the secondary allylic alcohols has a low efficiency, the diastereoselectivity observed is excellent even in the absence of the ligand.

Experimental Section

General Remarks: All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under argon. CH_2Cl_2 and toluene were distilled from calcium hydride under argon. Petroleum ether showed a boiling range of 40–60 °C. Standard techniques were used for handling air-sensitive reagents. All commercially available reagents were purchased from Aldrich or Fluka. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by a 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Optical rotations were performed on a Jasco Dip-1000 using a Na lamp.

Spectroscopic characterizations of hydroperoxide **2** and alcohol **6** have previously been reported.[22] All the epoxy alcohols are known compounds.[2,3] The hydroxamic acids in Table 2 are known compounds (**5b**,[37] **5c**,[38] **5d**,[27] **5e**,[39] **5f**[28] and **5g**[40]) and were synthesized according to procedures reported in the literature.[27,28] The enantiomeric excesses of the epoxy alcohols **4a** and **4c** were determined by ^{1}H NMR spectral analysis of the corresponding acetylated alcohols using Eu(hfc)$_3$;[2,3] the enantiomeric excesses of **4d**, **4f**, **4h** and **4i** were determined by ^{1}H NMR spectral analysis of the corresponding Mosher esters;[2,3] the enantiomeric excesses of **4b** and **4e** were determined by HPLC analysis on Chiralcel OD and Chiralpak AD chiral columns.[41]

Epoxidation of Allylic Alcohols 3. General Procedure: Ligand **5a** (0.03 mmol, 6.4 mg) was added to a solution of VO(acac)$_2$ (0.02 mmol, 5.3 mg) in dry CH_2Cl_2 (1 mL) under argon at room temperature. The mixture was stirred for 20 min, then allylic alcohol **3** (0.2 mmol) was added and the solution was stirred for a further 40 min at room temperature. The reaction mixture was then cooled to –20 °C and **2** (0.24 mmol, 47 mg) dissolved in dry CH_2Cl_2 (1.5 mL) was added to the flask by means of a cannula. At the end of the reaction, as verified by TLC, the crude reaction mixture was filtered through a small pad of silica gel, eluting with a mixture of petroleum ether/diethyl ether (2:1, 100 mL), to remove the catalyst. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 98:2) to give epoxy alcohols **4** and alcohol **6**.

Acknowledgments

We thank the Università degli Studi di Salerno and the MIUR for financial support.

[1] R. A. Johnson, K. B. Sharpless, *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, p. 231.
[2] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
[3] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
[4] R. C. Michaelson, R. E. Palermo, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 1990–1992.
[5] K. B. Sharpless, T. R. Verhoeven, *Aldrichimica Acta* **1979**, *12*, 63–74.
[6] N. Murase, Y. Hoshino, M. Oishi, H. Yamamoto, *J. Org. Chem.* **1999**, *64*, 338–339.
[7] Y. Hoshino, N. Murase, M. Oishi, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1653–1658.
[8] Y. Hoshino, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 10452–10453.
[9] C. Bolm, T. Kühn, *Synlett* **2000**, *6*, 899–901.
[10] H.-L. Wu, B.-J. Uang, *Tetrahedron: Asymmetry* **2002**, *13*, 2625–2628.
[11] B. Traber, Y.-G. Jung, T. K. Park, J.-I. Hong, *Bull. Korean Chem. Soc.* **2001**, *22*, 547–548.
[12] W. Adam, A. K. Beck, A. Pichota, C. R. Saha-Möller, D. Seebach, N. Vogl, R. Zhang, *Tetrahedron: Asymmetry* **2003**, *14*, 1355–1361.
[13] M. G. Finn, K. B. Sharpless, *Asymmetric Synthesis* Academic Press, New York, **1985**, p. 247.
[14] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
[15] P. Pitchen, E. Duñach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
[16] H.-J. Hamann, E. Höft, D. Mostowicz, A. Mishnev, Z. Urbańczyk-Lipkowska, M. Chmielewski, *Tetrahedron* **1997**, *53*, 185–192.
[17] D. Mostowicz, M. Jurczak, H.-J. Hamann, E. Höft, M. Chmielewski, *Eur. J. Org. Chem.* **1998**, *11*, 2617–2621.
[18] W. Adam, M. N. Korb, K. J. Roschmann, C. R. Saha-Möller, *J. Org. Chem.* **1998**, *63*, 3423–3428.
[19] W. Adam, P. L. Alsters, R. Neumann, C. R. Saha-Möller, D. Seebach, A. K. Beck, R. Zhang, *J. Org. Chem.* **2003**, *68*, 8222–8231.
[20] A. Lattanzi, P. Iannece, A. Vicinanza, A. Scettri, *Chem. Commun.* **2003**, 1440–1441.
[21] A. Lattanzi, P. Iannece, A. Scettri, *Tetrahedron: Asymmetry* **2004**, *15*, 1779–1785.
[22] A. Lattanzi, P. Iannece, A. Scettri, *Tetrahedron: Asymmetry* **2004**, *15*, 413–418.
[23] K. P. Bryliakov, E. P. Talsi, T. Kühn, C. Bolm, *New J. Chem.* **2003**, *27*, 609–614.
[24] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1070.
[25] K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.
[26] From ^{51}V NMR analysis of a benzene solution of VO(O*i*Pr)$_3$ and an α-amino acid based hydroxamic acid,[8] at a V/ligand ratio of 1:1.5, a **B**/**A** ratio of 95:5 was determined (see Figure 3).
[27] R. M. Coates, S. J. Firsan, *J. Org. Chem.* **1986**, *51*, 5198–5209.

[28] R. V. Hoffman, N. K. Nayyar, *J. Org. Chem.* **1994**, *59*, 3530–3539.
[29] H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330.
[30] S = 1.6 was calculated from the equation reported in ref.[29].
[31] Vanadium catalysts have been shown to be the most *erythro*-selective for the epoxidation of allylic alcohols.[5]
[32] The diastereoisomeric (*erythro*/*threo*) ratios obtained for **4i** by using Ti(O*i*Pr)$_4$/L-DET/TBHP, Ti(O*i*Pr)$_4$/TBHP and VO(acac)$_2$/TBHP systems were 98:2, 88:12 and 91:9, respectively.[33]
[33] V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.
[34] W. Adam, B. Nestler, *Tetrahedron Lett.* **1993**, *34*, 611–614.
[35] W. Adam, T. Wirth, *Acc. Chem. Res.* **1999**, *32*, 703–710.
[36] At the end of the epoxidation reactions, alcohol **6** was isolated by flash chromatography in 80–90% yield and recycled for the one-step synthesis of **2**.
[37] D. E. Robinson, M. D. Holladay, *Org. Lett.* **2000**, *2*, 2777–2779.
[38] J. A. Warshaw, D. E. Gallis, B. J. Acken, O. J. Gonzalez, D. R. Crist, *J. Org. Chem.* **1989**, *54*, 1736–1743.
[39] M. Couturier, J. L. Tucker, C. Proulx, G. Boucher, P. Dubé, B. M. Andresen, A. Ghosh, *J. Org. Chem.* **2002**, *67*, 4833–4838.
[40] R. V. Hoffman, N. K. Nayyar, W. Chen, *J. Org. Chem.* **1992**, *57*, 5700–5707.
[41] W. Adam, P. L. Alsters, R. Neumann, C. R. Saha-Möller, D. Seebach, R. Zhang, *Org. Lett.* **2003**, *5*, 725–728.

Received: October 15, 2004

