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Asymmetric epoxidation of allylic alcohols catalyzed by new chiral vanadium(V) complexes

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Abstract—Vanadium catalysts bearing (+)-ketopinic acid-based chiral hydroxamic acids as constituent ligands are investigated in the asymmetric epoxidation of allylic alcohols. Chiral ligands lacking an *N*-substituent and those having a bulkier aryl group in the bornane skeleton provided better selectivity.

Chiral epoxides have gained immense importance in the domain of organic synthesis in view of their wide applicability as building blocks for many important chiral compounds including complex organic molecules.[1] Prior to the usage of the titanium-based catalytic system, the Sharpless group had reported their first asymmetric epoxidation reactions using chiral vanadium hydroxamate complexes **1**.[2] Yamamoto's vanadium complexes containing axial-chiral hydroxamic acids **2**[3] and Bolm's vanadium catalyst[4] bearing paracyclophane type planar-chiral ligands **3** are subsequent successful catalysts employed in the asymmetric epoxidation of allylic alcohols. The recent disclosure by Yamamoto et al. utilizing an amino acid-based hydroxamic acid ligand **4**[5] for asymmetric epoxidations is another significant contribution to the repertoire of these vanadium catalysts (Fig. 1).

Our ongoing interest in vanadium-catalyzed synthetic methods[6] prompted us to venture into the asymmetric epoxidation of allylic alcohols using vanadium complexes bearing chiral hydroxamic acids and we present the results of this work herein.

At the outset, we studied the effect of the bulkiness of the *N*-substituent of the ligand on the selectivity of the asymmetric epoxidation reaction. Chiral hydroxamic acids **6** with different substituents on nitrogen were accessed from (+)-ketopinic acid **5** by a two-step procedure (Fig. 2). Epoxidation of (*E*)-2,3-diphenyl-2-propen-1-ol **7a** was conducted as a representative example by using the hydroxamic acids **6** in combination with $VO(O^iPr)_3$ and *tert*-butyl hydroperoxide (^{t}BHP 5.5 M in decane) as oxidant.[2–5] Though the corresponding epoxy alcohol (2*S*,3*S*)-**8a**[7] was obtained in good yield (80–90%), the reaction was not rewarding in terms of selectivity. Contrary to Yamamoto's observations,[3,5] we found that increasing the bulk of the

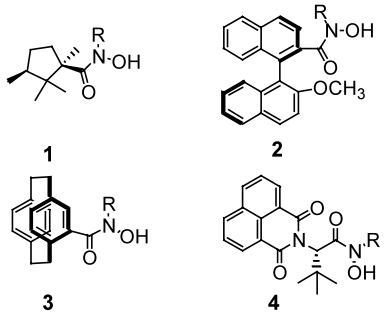
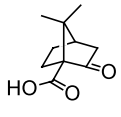


Figure 1. Chiral hydroxamic acids used in asymmetric epoxidations.



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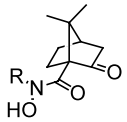

6a R = H; **6b** R = CH_2Ph; **6c** R = Cyclohexyl; **6d** R = $CH(Ph)_2$; **6e** R = Adamantyl

Figure 2. (+)-Ketopinic acid **5** and its derivatives—hydroxamic acids **6a**–**e**.

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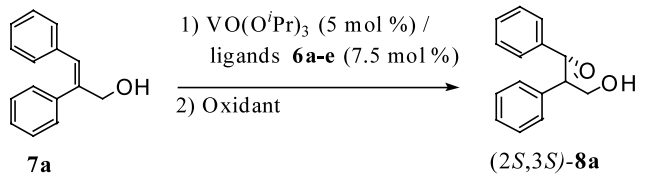
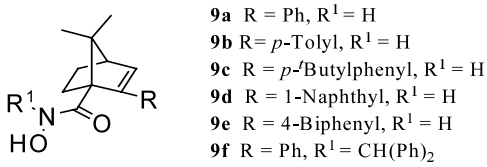


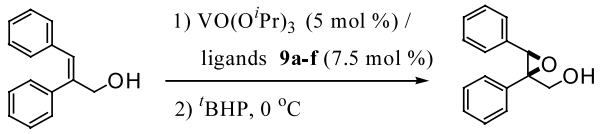
7a (2*S*,3*S*)-**8a**

Scheme 1.



9a R = Ph, R^1 = H
9b R = *p*-Tolyl, R^1 = H
9c R = *p*-^{t}Butylphenyl, R^1 = H
9d R = 1-Naphthyl, R^1 = H
9e R = 4-Biphenyl, R^1 = H
9f R = Ph, R^1 = CH(Ph)$_2$

Figure 3. (+)-Ketopinic acid-derived C-2-substituted hydroxamic acids **9a–f**.



7a (2*R*,3*R*)-**8a**

Scheme 2.

N-substituent reduced the selectivity (Table 1, entries 1–5).

We sought to illuminate the relevant parameters by varying the oxidant and the reaction temperature. Three hydroperoxides, ^{t}BHP, cumene hydroperoxide (CHP) and triphenylmethyl hydroperoxide (TrOOH) were tested as oxidants but no significant selectivity was observed (entries 1, 6 and 7). Among them, ^{t}BHP afforded the epoxide in better yield and selectivity. Variation of the temperature did not have any appreciable effect on the selectivity either (entries 1 and 8–10).

As significant selectivity could not be attained with chiral hydroxamic acids **6**, we modified the structure of these chiral ligands by incorporating bulkier substituents at C-2 of the bornane skeleton. This was a two-pronged strategy—to study the effect of *N*-substituent on selectivity in a modified steric environment of the bornane moiety and also to investigate the impact of the size of the C-2 substituent of bornane on the selectivity. Chiral hydroxamic acids **9** having the required structural features were prepared starting from (+)-ketopinic acid **5** (Fig. 3).

Thus, epoxidation was performed by employing ligands **9a–f** as the constituents of the vanadium catalyst in the presence of ^{t}BHP and the results are collected in Table 2. The observed selectivity with chiral hydroxamic acid **9a** was indeed encouraging, especially when it was used at a concentration of 0.84 M (Table 2, entry 2). Ligands **9a–e** lacking an *N*-substituent imparted good selectivity providing the epoxy alcohol (2*R*,3*R*)-**8a** in good yields, but the selectivity decreased with increasing size of the *N*-substituent, as observed before (Table 2, entry 8).

The steric influence of the bornane C-2 substituent on the enantioselectivity of the epoxidation was evidenced from the enhancement of ee with the size of the substituent (phenyl to 4-biphenyl, Table 2, entries 2–7). It is noteworthy that, (2*S*,3*S*)-**8a** was obtained as the major product when ligands **6** were constituents of the catalyst. On the other hand, (2*R*,3*R*)-**8a** was the major product when ligands **9** were employed. This reversal in enantioselectivity with variation of the ligand could not be rationalized at this stage.

Having attained good selectivity with substrate **7a**, we extended the asymmetric epoxidation to the allylic alcohols **7b–h** to verify the scope of this methodology (Table 3).

Interestingly, the presence of the C-2 phenyl group appears to have a marked influence on the selectivity. Thus, substrates **7a** and **7e** induced good selectivity (entries 1 and 5), while in the case of ligands lacking a C-2 phenyl group, only moderate selectivity was observed (entries 4 and 8). The selectivity was only moderate in the case of long chain allylic alcohols (entries 6 and 7) and for a highly substituted allylic alcohol (entry 3).

Table 1. Effect of the *N*-substituent of chiral hydroxamic acids **6**, oxidant and temperature on the catalytic asymmetric epoxidation of **7a** to (2*S*,3*S*)-**8a** (Scheme 1)

Entry	Ligand	Temp. (°C)	Oxidant	Time (h)	Yield (%)	Ee[a] (%)
1	**6a**	0	^{t}BHP	4	90	44
2	**6b**	0	^{t}BHP	6	87	19
3	**6c**	0	^{t}BHP	7	80	10
4	**6d**	0	^{t}BHP	6	89	5
5	**6e**	0	^{t}BHP	4	88	0
6	**6a**	0	CHP	4	85	35
7	**6a**	0	TrOOH	9	52	39
8	**6a**	rt	^{t}BHP	1	89	41
9	**6a**	−10	^{t}BHP	32	89	44
10	**6a**	−20	^{t}BHP	72	80	43

[a] See refs. 7 and 8.

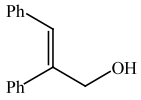
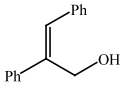
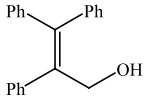
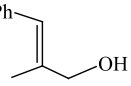
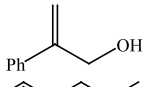
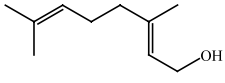
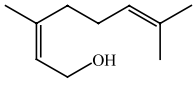
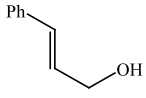
Table 2. The effect of the ligand and concentration in catalytic asymmetric epoxidation of **7a** to (2*R*,3*R*)-**8a** (Scheme 2)

Entry	Ligand	Conc. (M)	Time (h)	Yield (%)	Ee[a] (%)
1	**9a**	0.42	8	60	60
2	**9a**	0.84	6	85	70
3	**9a**	1	5	90	65
4	**9b**	0.84	5	89	70
5	**9c**	0.84	3	86	75
6	**9d**	0.84	9	88	73
7	**9e**	0.84	12	89	89
8	**9f**	0.84	6	85	25

[a] See refs. 7 and 8.

In conclusion, we have achieved moderate to high enantioselectivities in the vanadium-catalyzed asymmetric epoxidation of allylic alcohols employing readily accessible new chiral hydroxamic acids with diverse structural features as ligands for the vanadium catalyst. The origin of the reversal in the sense of asymmetric induction by ligands **6** and **9**, which possess the same chiral (+)-ketopinic acid unit is not clear at this stage. Interestingly, the observed trend in enantioselectivity with the variation in size of the *N*-substituent of the ligand in the present catalytic asymmetric epoxidation is opposite to that of Yamamoto's findings, although further investigation is required. Further studies of this methodology involving the modification of the bornane skeleton to provide better selectivity are under active exploration.

Table 3. Asymmetric epoxidation of allylic alcohols **7a**–**h** to **8a**–**h** using **9e** as ligand[a]

Entry	Allyic alcohol		Epoxide/Yield (%)	Ee[b] (%)
1		**7a**	**8a**/89	89
2		**7b**	**8b**/88	73
3		**7c**	**8c**/80	46
4		**7d**	**8d**/86	55
5		**7e**	**8e**/91	81
6		**7f**	**8f**/83	46
7		**7g**	**8g**/85	55
8		**7h**	**8h**/70	56

[a] Except in the case of **7a**, the oxidations could be completed within 24h. [b] See refs. 7 and 9.

Acknowledgements

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7. The enantiomeric excess was determined by HPLC using a chiral column (Chiralcel OD-H; *n*-hexanes:^{i}PrOH = 98:2; flow rate: 1 ml/min).
8. The absolute configuration was determined by comparing the sign of the specific rotation with that of known samples.[2a]
9. The enantiomeric excess of **8a**–**e**,**h** was determined as mentioned in ref. 7. In the case of **8f** and **8g**, ee was determined from the corresponding benzoate derivatives (Chiralcel OD-H; *n*-hexanes:^{i}PrOH = 98:2; flow rate: 0.5 ml/min). Absolute configuration of all epoxy alcohols except **8c** was determined on the basis of the sign of the specific rotation reported in the literature.[2a]