Collect. Czech. Chem. Commun., **32**, 3897 (1967)).
(10) **3a**: Ir ν_{max}^{Nujol} cm^{-1}: 1595, 1275 (MeCOCHCOMe); 930, 910 (O=Mo=O).[11] NMR (in $CDCl_3$–CD_3OD (1 drop)–Me_4Si): δ 1.05 (3 H, d, J = 6.5 Hz, NCH–CH_3), 2.03 (6 H, s, $CH_3COCHCOCH_3$), 2.83 (6 H, s, $N(CH_3)_2$), 2.8–3.4 (2 H, m, OCH–CH_2N), 5.3–5.5 (1 H, broad s, COCHCO), 7.32 (5 H, s, C_6H_5). Anal. Calcd for $C_{16}H_{23}O_5NMo$: C, 47.42; H, 5.72; N, 3.46. Found C, 47.44; H, 5.74; N, 3.62. **3b**: IR ν_{max}^{Nujol} cm^{-1}: 1595, 1280(MeCOCHCOMe); 930, 910 (O=Mo=O).[11] NMR (in $CDCl_3$–CD_3OD (1 drop)–Me_4Si): δ 0.96 (3 H, d, J = 7 Hz, NCH–CH_3), 1.23 (3 H, t, J = 7 Hz, NCH_2CH_3), 2.01 (6 H, s, $CH_3COCHCOCH_3$), 2.68 (3 H, s, CH_3), 4.0–4.5 (4 H, broad m, OCH–CH_2N and NCH_2CH_3), 5.2–5.6 (1 H, broad s, COCHCO), 7.25 (5 H, s, C_6H_5).
(11) P. C. H. Mitchell, *Q. Rev. (Chem. Soc.)*, **20**, 103 (1966).
(12) When the reaction temperature is lowered, the optical yield of **2** is clearly increased with a remarkable delay of the epoxidation speed. This tendency, which is frequently observed in usual asymmetric synthesis, can be visualized in the following data for the epoxidation of **1b** in the presence of **3a**: reaction temperature, reaction time, chemical yield, optical yield; 30–35 °C, 8 days, 43%, 15%; 40–45 °C, 60 h, 39%, 10%; 70–75 °C, 20 h, 47%, 4.5%. Therefore, the reaction temperature was kept in a range of 40–45 °C to complete the epoxidation within a moderate period.

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Chiral Hydroxamic Acids as Ligands in the Vanadium Catalyzed Asymmetric Epoxidation of Allylic Alcohols by *tert*-Butyl Hydroperoxide

Sir:

In spite of great current interest in asymmetric synthesis[1] little has been achieved in the area of asymmetric oxidations. By contrast asymmetric reductions have been quite successful, and, in the case of hydrogenation of certain olefins,[2] remarkably so. Of all organic oxidations, the epoxidation of olefins would be the most useful to accomplish in an asymmetric manner. The best induction to date with simple olefins is 10% enantiomeric excess (ee) realized using percamphoric acid.[3,18] Recently Wynberg and co-workers have reported substantial (25%) inductions in the epoxidation of α,β-unsaturated ketones by alkaline hydrogen peroxide employing chiral phase transfer agents.[4] We felt that the transition metal catalyzed epoxidations of olefins by alkyl hydroperoxides[5,15d] offered a special opportunity to achieve asymmetric epoxidations. Therefore we have, for the past few years,[9a] been investigating the effects of chiral ligands on these systems and report here our initial successes.

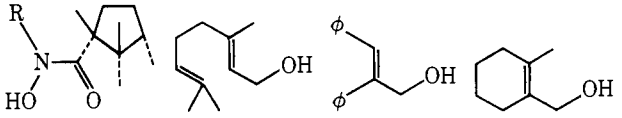
From our earlier results on the vanadium and molybdenum catalyzed epoxidations of allylic alcohols,[5b,5c] we had good evidence that the alcohol function was coordinated to the metal during the oxygen atom transfer step. This attachment of the allylic alcohol substrate to the metal was expected to enhance any asymmetric selection process. All that seemed necessary was to find a chiral ligand which was stable to the conditions and did not block coordination sites essential to the epoxidation process. We first investigated chiral β-diketone[6] complexes of vanadium and molybdenum; these gave poor results and we have since found that β-diketones are rapidly destroyed under the conditions of these oxidations.[7] After trying a variety of other chiral ligands, hydroxamic acids were found to be especially attractive.[9a] They are very resistant to oxidation and seem to bind well to molybdenum and vanadium. Well characterized, chiral molybdenyl bishydroxymates [O_2Mo(hydroxymate)$_2$] were easily prepared from chiral hydroxamic acids such as **1a**.[9a] However, these molybdenum complexes[8] have so far given poor (<2%) asymmetric inductions. On the other hand, although we have not yet managed to prepare a characterizable chiral hydroxymate complex of vanadium,[9b] asymmetric epoxidations with in situ generated vanadium hydroxymates have been encouraging. The results using vanadium catalysis with three related chiral hydroxamic acids (**1a–1c**)[10] and three allylic alcohols (geraniol (**2**), *E*-α-phen-

Table I. Asymmetric Epoxidations of Allylic Alcohols[a]

Hydroxamic acid (*equiv*)[b]	Allylic alcohol	°C	% ee[c]	% conversion[d]
1 **1a** (5)	**2**	−78 → 25	17	83
2 **1a** (3)	**3**	−78 → 25	10	100
3 **1a** (5)	**3**	−78 → 25	21	80
4 **1a** (10)	**3**	−78 → 25	18	22
5 **1b** (4)	**2**	−78 → 25	19	100
6 **1b** (4)	**2**	25	17.5	100
7 **1b** (5)	**2**	25	30	86
8 **1b** (5)	**2**	−78	—	0
9 **1b** (7)	**2**	−78 → 25	10	10
10 **1b** (1)	**3**	−78 → 25	<8	100
11 **1b** (2)	**3**	−78 → 25	8	100
12 **1b** (3)	**3**	−78 → 25	22.5	100
13 **1b** (5)	**3**	−78 → 25	50	30
14 **1b** (5)	**3**	25	40	84
15 **1b** (5)	**4**	25	40	87
16 **1b** (5)	**4**	−10	44	75
17 **1c** (3)	**2**	0	5	70
18 **1c** (4)	**2**	0	19	55
19 **1c** (5)	**2**	0	—	0

[a] All reactions were performed with 1 mmol of allylic alcohol and 2.5 mg (1%) of $VO(acac)_2$ catalyst in 20 mL of toluene under a nitrogen atmosphere. When the appropriate amount of hydroxamic acid was added to these solutions they immediately turned from green to reddish brown in color. Stirring was continued at room temperature for 15 min then, after cooling, 2 equiv of *tert*-butyl hydroperoxide (90+%, Lucidol) was added dropwise. During addition of the hydroperoxide the solution turned ruby red and this color persisted even after warming to room temperature. Reactions were monitored by TLC and acetylation was accomplished in situ by addition of pyridine and acetic anhydride. Acetylation was allowed to proceed for 2 h at room temperature and workup (see ref 5b) afforded the crude epoxyacetates which were purified by PLC and or microdistillation. [b] The figure in parentheses refers to the equivalents of hydroxamic acid added based on the amount of $VO(acac)_2$ catalyst. [c] The enantiomeric excess (ee) was determined by ^1H NMR using Eu-OPTISHIFT II [Eu(hfbc)$_3$] chiral shift reagent on the epoxyacetates (see ref 13 for estimated rotations of the three epoxyacetates). [d] The percent of epoxy alcohol product plus the percent of unreacted allylic alcohol equals 100%. In cases of 100% conversion the isolated yields of epoxy acetates ranged from 70 to 90%.

ylcinnamyl alcohol (**3**),[11] 1-hydroxymethyl-2-methylcyclohexene (**4**)[12] are shown in Table I.[13]



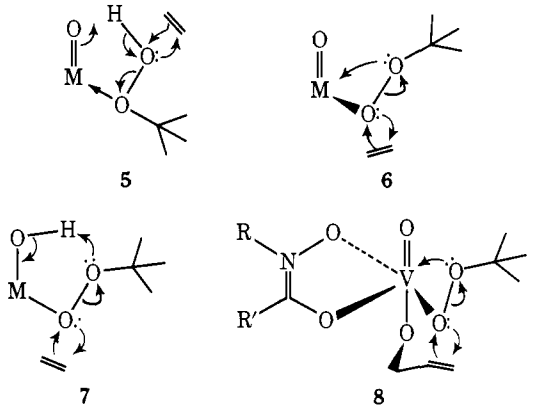
1a, R = CH_3 **2** **3** **4**

1b, R = Ph

1c, R = 2,6-Me_2Ph

The best induction (50% ee) was attained in epoxidation of α-phenylcinnamyl alcohol **3** employing *N*-phenylcampholylhydroxamic acid (**1b**) as the chiral ligand (Table I, entry 13). Trends relating to reaction temperature and the amount of chiral ligand used can be gleaned from Table I. In general, lower temperatures lead to higher inductions (e.g., Table I entries 13 and 14); however, this positive effect is counterbalanced by a tendency toward incomplete conversion as the temperature is lowered. As a rule the optimum inductions were realized when the ratio of hydroxamic acid to $VO(acac)_2$ catalyst was about 5:1. Although not mentioned in Table I, it was found that cumene-hydroperoxide gave substantially poorer inductions than *tert*-butyl hydroperoxide in three different cases where the two were compared. In order to explain such effects one must know the mechanism of these reactions.

We have recently[14] suggested a new possibility for the mechanism of these epoxidations. The previous[15] mechanisms proposed by three different groups, although different in detail, all favor transition states resembling **5** in the scheme; these



5 **6**

7 **8**

mechanisms accomplish activation of the hydroperoxide by coordination to the metal of the oxygen proximal to the alkyl group. In contrast we favor coordination of the hydroperoxide by the oxygen distal to the alkyl group and subsequent oxygen transfer by one or both of the two paths depicted in **6** and **7** of the scheme. The arguments supporting transition states resembling **6** and **7** over those such as **5** are discussed elsewhere;[14] however, an obvious difficulty for the type **5** mechanism is rationalization of the great rate accelerations observed in epoxidations of allylic alcohols with these systems. It is geometrically impossible to coordinate the hydroxyl group of an allylic alcohol to the metal and at the same time allow the olefinic bond to take up the direction of approach to the peroxidic oxygen required in **5**. On the other hand, mechanisms such as **6** and **7** easily accommodate coordination of the allylic alcohol to the metal. For the present reactions with vanadium in the presence of hydroxamic acid ligands we very tentatively suggest a mechanism whose general features are shown in **8** of the scheme.[16]

The results reported here are obviously of a preliminary nature. Much work remains to be done, especially with variation of the chiral ligands. Also underway are investigations on the effects of chiral hydroxamic acids on other transition metal catalyzed processes.

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References and Notes

(1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971.
(2) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauf, *J. Am. Chem. Soc.*, **97**, 2567 (1975), and references cited therein.
(3) (a) D. R. Boyd, D. M. Jerina, and J. W. Daly, *J. Org. Chem.*, **35**, 3170 (1970); (b) F. Montanari, I. Moretti, and G. Tane, *Chem. Commun.*, 135 (1969); (c) R. M. Bowman and M. F. Grundon, *J. Chem. Soc. C*, 2368 (1967); (d) D. R. Boyd and M. A. McKervey, *Q. Rev., Chem. Soc.*, **22**, 111 (1968).
(4) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976).
(5) (a) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970); (b) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973); (c) S. Tanaka, H. Yamamoto, H. Nozaki, K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, *ibid.*, **96**, 5254 (1974); (d) T. Itoh, K. Kaneda, and S. Teranishi, *J. Chem. Soc., Chem. Commun.*, 421 (1976).
(6) We are grateful to our colleagues G. M. Whitesides and L. C. Costa for providing us with several of the chiral β-diketones used in their shift reagent studies (M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974)).
(7) R. C. Michaelson and K. B. Sharpless, unpublished results.
(8) The use of achiral molybdenum(VI) hydroxamates as epoxidation catalysts has been reported by F. Triforò, P. Forzatti, S. Preiti, and I. Pasquon, *J. Less-Common Met.*, **36**, 319 (1974).
(9) (a) The first chiral molybdenyl bishydroxymate was prepared from **1a** in 1973 (R. C. Michaelson, Ph.D. Thesis, Massachusetts Institute of Technology, Jan 1976). (b) It is our impression, based on limited experience, that vanadium hydroxymate complexes are considerably more labile than their molybdenum analogues. For example, the vanadium complexes do not appear to tolerate silica gel chromatography.
(10) All three hydroxamic acids were prepared by acylation of the corresponding hydroxyl amine with campholyl chloride. Different procedures were employed. In the case of **16** 2 equiv of phenylhydroxylamine were added to a solution of campholyl chloride in acetonitrile. We have found this method (developed in our laboratory by Dr. Steven Current) to be very effective for preparing a variety of substituted hydroxamic acids. Hydroxamic acids **1a** and **1c** were prepared by reaction of the lithium salt of the hydroxyl amine with campholyl chloride in THF.
(11) T. Axenrod, E. Bierig, and L. H. Schwartz *Tetrahedron Lett.*, 2181 (1965).
(12) G. Ohloff, *Justus Liebigs Ann. Chem.*, **627**, 79 (1959).
(13) All three allylic alcohols gave dextrorotary epoxyacetates with each of the three (**1a**, **1b**, **1c**) chiral hydroxamic acids. Based on the chiral shift reagent determinations (Table I) and the measured rotations of the enriched epoxyacetate products, the approximate absolute rotations for the epoxyacetates derived from allylic alcohols **2**, **3**, and **4**, respectively, are calculated to be $[\alpha]^{30}_{D}$ 7.8° (*c* 2.0, acetone), $[\alpha]^{30}_{D}$ 44° (*c* 2.7, CCl_4), and $[\alpha]^{30}_{D}$ 34° (*c* 2.8, acetone).
(14) A. O. Chong and K. B. Sharpless, *J. Org. Chem.*, in press.
(15) (a) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970); (b) E. S. Gould, R. R. Hiatt, and K. C. Irwin, *J. Am. Chem. Soc.*, **90**, 4573 (1968); (c) R. A. Sheldon, *Recl. Trav. Chim. Pays-Bas*, **92**, 253 (1973); (c) R. Hiatt in "Oxidation", Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N.Y., 1971, Chapter 3.
(16) The hypothesis that a vanadium monohydroxymate complex (e.g., **8**) is the effective chiral catalyst seems reasonable in light of our experience with molybdenum bishydroxymates. Furthermore, even the most rudimentary mechanistic considerations would seem to require *at least* two available cis-coordination sites for these epoxidations to proceed; it is difficult to see how this criterion could be fulfilled by a vanadium(V) species bearing more than one hydroxamic acid ligand. It might be argued that these considerations are difficult to reconcile with the fact (see Table I) that optimum asymmetric inductions are realized with rather high (~5) hydroxamic acid/vanadium ratios. However, we feel that this phenomenon is likely due to the importance of minimizing the presence of vanadium species bearing no hydroxymate ligands (such species would preduce racemic epoxide) while at the same time maintaining a population of the active monohydroxymate species which is sufficient to sustain a reasonable rate of catalysis. Although a vanadium(IV) catalyst is added we and others (see ref 15b) assume that it is rapidly oxidized to a vanadium(V) species by the *tert*-butyl hydroperoxide. In the molybdenum catalyzed epoxidations it has been proven that a molybdenum(VI) species is rapidly formed regardless of the oxidation state of the molybdenum compound originally added (R. A. Sheldon, *Recl. Trav. Chim. Pays-Bas*, **92**, 367 (1973)).
(17) Yamada, Mashiko, and Terashima *J. Am. Chem. Soc.*, preceding paper in this issue, have found that N-alkyl ephedrine complexes of molybdenum(VI) effect asymmetric epoxidation of allylic alcohols. For geraniol they have nicely correlated the 2,3-epoxide produced with (*R*)-(−)-linalool, thereby establishing the absolute configuration of their (+)-2,3-epoxy-

geraniol as 2(*R*), 3(*R*). We have found that the (+)-2,3-epoxygeraniol acetate produced in our system (entry 7, Table I) gives (−)-2,3-epoxygeraniol upon hydrolysis (K_2CO_3, MeOH). Thus, in the case of geraniol, the two systems selectively form opposite epoxide enantiomers.

(18) Sizeable asymmetric inductions (ca. 50% ee) have been attained in the formation of oxaziridines by the reaction of chiral peracids with imines (see J. Bjørgo, D. R. Boyd, R. M. Campbell, N. J. Thompson, and W. B. Jennings, *J. Chem. Soc., Perkin Trans. 2*, 606 (1976), and references cited therein).

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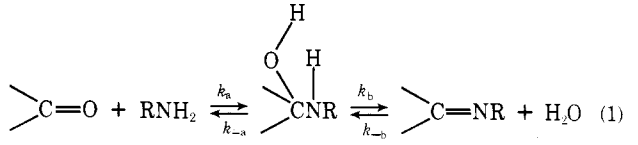
Rate of Carbinolamine Formation between Pyridoxal 5′-Phosphate and Alanine[1]

Sir:

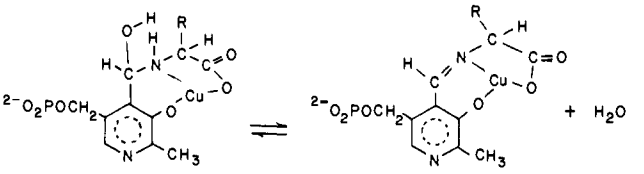
In Schiff base formation reactions between amines and carbonyl compounds a two-step mechanism involving an intermediate carbinolamine is often observed.[2-4] However, in



(1)

the reactions of the physiologically important pyridoxal 5′-phosphate (PLP), 3-hydroxypyridine-4-carboxaldehyde[5] or salicylaldehyde,[6] carbinolamine does not form in readily detectable amounts. The same rate equation, which is first order in each of aldehyde and amine, describes both the disappearance of aldehyde and the formation of aldimine. In two limiting cases which could account for this behavior either a low pre-equilibrium concentration of carbinolamine is formed with dehydration being rate limiting, or carbinolamine formation is rate limiting with dehydration being fast. Arguments in favor of the latter mechanism have been presented.[5,7] Alternatively, an intermediate steady state situation could exist. By trapping the carbinolamine formed during the reaction of PLP and ala with Cu(II) we have been able to determine both the stability of the Cu(II)-carbinolamine complex and the rate law for its formation. Both Cu(II) independent and dependent pathways were found. A comparison of the values of the rate constants found for the former set of reactions with those found for the formation of (*N*-pyridoxylidene 5′-phosphate)alaninate in the absence of Cu(II) shows unequivocally that carbinolamine formation in this system is considerably faster than dehydration.

Intermediates having a lower absorbance in the near-UV than either reactants or products have been observed in the hydrolysis of bis(*N*-salicylideneethylamine)copper(II) in borax buffers at pH 8.5,[8] and during the reaction of PLP with glutamate in the presence of Cu(II).[9] These intermediates have been attributed to Cu(II) carbinolamine complexes. We have found that under certain conditions on mixing PLP with copper(II)-alanine solution[5] the absorbance bands of PLP decrease in intensity owing to a reaction which is complete in 1 min or less, and, concurrently, a new absorption maximum centered at 325 nm appears. In a second reaction which requires about 1 h, the absorption spectrum of the Cu(aldimine) product slowly appears as the 325-nm band disappears. A similar 325-nm band is also observed with the Cu(II) complexes of pyridoxamine 5′-phosphate, in which the 4 position of the aromatic ring is occupied by a saturated substituent.[10] Thus, it appears that this intermediate is, indeed, the carbinolamine complex, I. If too little Cu(II) is present, or if it is extensively bound as alaninate complexes, I is not observed, but PLP is converted to the aldimine complex (II) in an apparent single step reaction. Because the rate of formation of I is so much faster than its dehydration to II, the two steps may very easily be studied separately. We report here the results of a stopped flow spectrophotometric examination of the rates of formation of I as the reaction systems approached the first metastable equilibrium state. The subsequent conversion of I to II was followed using a double beam recording spectrophotometer.



I II

Near equilibrium kinetic data provide information regarding the composition of products as well as formation rates. In this case the results of 96 determinations under a variety of conditions confirmed that I is a 1:1:1 Cu(II)-ala-PLP complex that can add one or two protons, depending on pH. The reaction conditions for a few representative experiments and their observed first-order rate constants as equilibrium was approached are given in Table I.

The data were found to conform to the rate law,

$$k_{obsd} = \left(\sum_{i=0}^{4} k_{a,i} f_{HiPLP} + \sum_{i=0}^{2} k_{a,i}{}^{Cu} f_{CuHiPLP}\right) [ala^-] \left(1 + \frac{1}{K_{cond}}\right) \quad (2)$$

where the $k_{a,i}$ are forward rate constants for the formation of I, the f_x are the fractions of PLP present in the form of species x, and K_{cond} is the conditional equilibrium constant for carbinolamine formation. K_{cond} is equal to the ratio of the sum of the equilibrium concentrations of the unprotonated and protonated forms of I to the sum of all forms of PLP not present

Table I. Some Observed and Theoretical Values of the Near Equilibrium Rate Constants for Cu(carbinolamine) Formation (T = 25 °C, I = 0.5)

	10^3 (Cu_{tot}), M	10^2 (Ala_{tot}), M	10^4 (PLP_{tot}), M	pH	k_{obsd}, s^{-1}	k_{calcd} s^{-1} (no Cu terms)	k_{calcd}, s^{-1} (Cu terms)
1	5.8	5.0	1.0	5.35	0.84	0.90	0.91
2	5.8	10.0	1.0	5.14	2.2	1.7	1.7
3	1.9	2.0	1.0	6.24	3.0	3.2	3.2
4	0.49	1.0	1.0	4.20	0.22	0.17	0.18
5	5.0	1.0	5.2	6.90	0.54	0.59	0.63
6	2.0	4.4	0.8	8.83	12.8	14.5	14.6
7	4.9	1.0	1.0	4.08	0.058	0.031	0.059
8	4.9	1.0	1.0	5.11	0.082	0.044	0.076
9	5.8	0.5	1.0	5.25	0.041	0.004	0.030