Pure & Appl. Chem., Vol. 70, No. 5, pp. 1041–1046, 1998.
Printed in Great Britain.

Homogeneous catalysis as a tool for organic synthesis

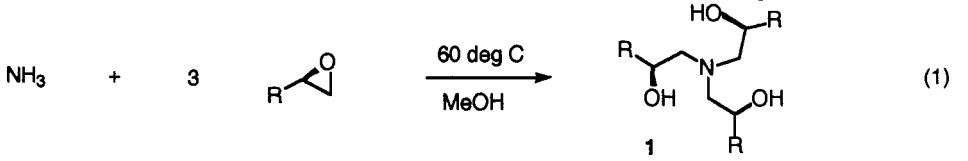
William A. Nugent,[a] Giulia Licini,[b] Marcella Bonchio,[b] Olga Bortolini,[b] M. G. Finn[c] and Brent W. McCleland[c]

[a]*DuPont Central Research, P. O. Box 80328, Wilmington, DE 19880-0328, U.S.A.*
[b]*Dipartimento di Organic Chimica, University of Padova, Via Marzolo 1, I-35131 Padova, Italy*
[c]*Department of Chemistry, University of Virginia, Charlottesville, VA 22901, U.S.A.*

Abstract: Homochiral trialkanolamines are a new class of chiral ligand for enantioselective catalysis. Mononuclear titanium complexes bearing such ligands promote the asymmetric sulfoxidation of alkyl aryl sulfides. In contrast, a dimeric zirconium species is the active catalyst in the desymmetrization of meso epoxides with azides. Mechanistic insight into the latter reaction has led to a new reaction, the enantioselective desymmetrization of meso epoxides using halides as the nucleophilic partner.

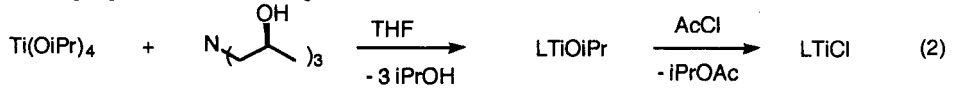
HOMOCHIRAL TRIALKANOLAMINES

Several years ago (ref. 1) we introduced homochiral trialkanolamines **1** as ligands for enantioselective catalysts based on early transition metals. These ligands have several advantages. They are easy to synthesize; many enantiopure epoxides react directly with ammonia according to eq. 1:



1 (1)

Moreover, ligands **1** bind tightly to early transition metals in a tetradentate fashion to form robust complexes which persist even in the presence of water or silylating agents. The three asymmetric centers provide a highly asymmetric environment in coordination sphere of the transition metal. Ligands **1** displace monodentate alkoxides from group 4-6 metal alkoxides to provide the corresponding trialkanolamine(3-) complexes. An example is the reaction of homochiral triisopropanolamine with titanium(IV) isopropoxide shown in eq. 2:



2 (2)

Treatment of the resultant LTiO^{i}Pr with acetyl chloride affords the LTiCl complex, **2**. The x-ray crystal structure of **2** is shown in Figure 1. It can be seen that the ligand adopts a highly symmetrical C_3 stereochemistry and provides a complex whose shape could be described as a "rotor" or "pinwheel".

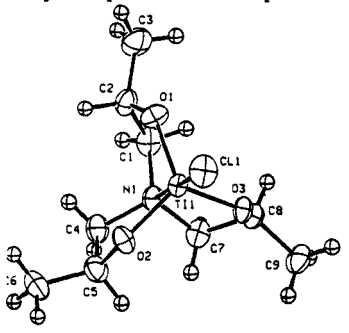


Fig. 1. X-ray crystal structure of **2**.

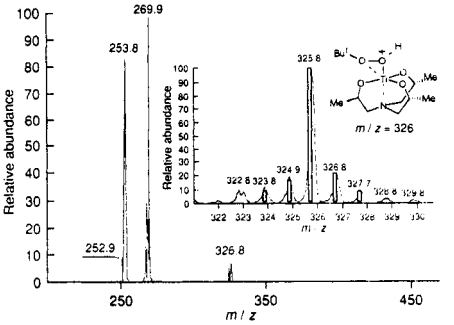
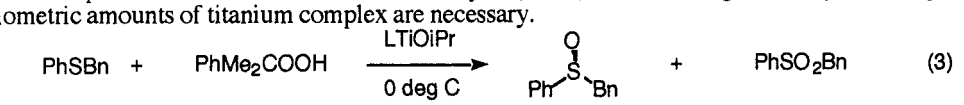


Fig. 2. Electro-spray mass spectrum of LTi(OO^{t}Bu).

ASYMMETRIC SULFOXIDATION

At the beginning of our studies, we assumed that catalysts based on homochiral trialkanolamines would be monomeric species; as in **2** the ligand would create a C_3- symmetric coordination environment. As we soon learned, this is not always true. However, in at least one case - that of catalytic asymmetric sulfoxidation - our initial assumption appears valid.

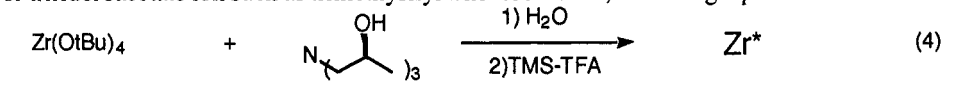
Complexes prepared from **1** and titanium isopropoxide are selective catalysts for the enantioselective sulfoxidation of aryl alkyl sulfides (ref. 2). For example, using ligand **1** (R = phenyl), benzyl p-tolyl sulfide can be oxidized to the corresponding sulfoxide in 84% enantiomeric excess (eq. 3). Reflecting the robust nature of the titanium complex, only a catalytic amount (2%) of titanium complex is required. This contrasts with previous titanium sulfoxidation catalysts (ref. 3) for which higher catalyst loadings or even stoichiometric amounts of titanium complex are necessary.



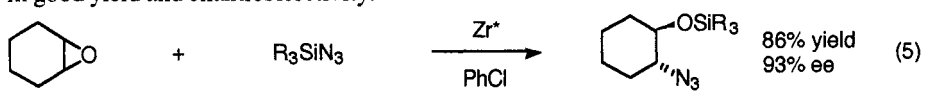
Several lines of kinetic and spectroscopic evidence support the proposal that the active catalyst for eq. 3 is monomeric. Of particular interest are the results of electrospray ionization mass spectroscopic studies (ref. 4). When a methanol solution of $Ti(O^iPr)_4$ and a slight excess of **1** (R = methyl) is injected into the mass spectrometer, a variety of monomeric and polynuclear titanium triisopropanolamine species $LTiX^+$ are observed. These include species where the remaining ligand X is methanol, water, or additional **1**. However, as shown in Figure 2, upon addition of excess tert-butyl hydroperoxide the complex spectrum collapses to a single species with m/e = 326. This m/e is consistent with the formation of mononuclear $LTi(OO^tBu)$ as the predominant species in solution. By comparison with a recent crystal structure (ref. 5) of a triethanolamine titanium *tert*-butylperoxo complex (dimeric in the solid state) we expect the *tert*-butylperoxo ligand to bind to the titanium in an η-2 fashion.

EPOXIDE DESYMMETRIZATION WITH AZIDE AS NUCLEOPHILE

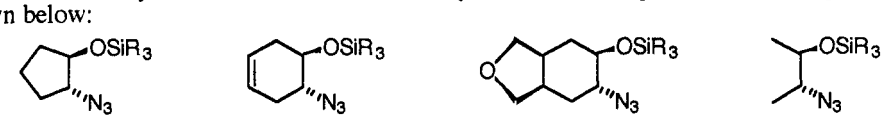
A very different situation pertains in the desymmetrization of meso epoxides which we developed (ref. 6). Preparation of the zirconium catalyst for this reaction requires several steps in which zirconium(IV) *tert*-butoxide is sequentially treated with homochiral triisopropanolamine followed by water and finally a source of trifluoroacetate ion such as trimethysilyl trifluoroacetate, following eq. 4:



The resultant white solid is a complex aggregate which has defied characterization by spectroscopic techniques. Nevertheless, in the presence of trimethylsilyl azide this complex is converted to an active catalyst whose elemental analysis corresponds to the composition $[L_2Zr_2(N_3)(O_2CCF_3)]_x$. As shown in eq. 5, this catalyst allows the desymmetrization of cyclohexene oxide to afford the corresponding azido silyl ether in good yield and enantioselectivity:



Moreover the chemistry could be extended to a variety of other meso epoxides to afford products such as **3**-**6** shown below:

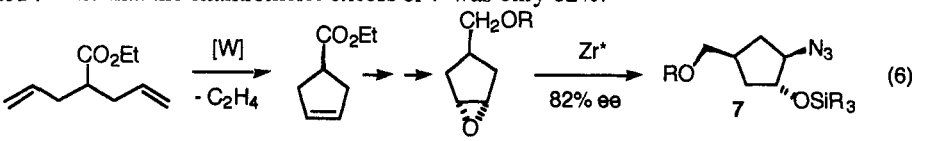


3 83% ee **4** 89% ee **5** 88% ee **6** 87% ee

The limited enantiomeric excess observed for compound **3** seems to be general for other cyclopentene oxide derived azides and became a problem when we applied this chemistry to the synthesis **7** which is a broadly useful intermediate for the synthesis of anti-viral carbocyclic nucleosides.

Our route to **7** is illustrated in eq. 6. It begins with the ring-closing metathesis of a readily available malonate derivative using the inexpensive tungsten metathesis catalyst which we have recently developed (ref. 7). Selective oxidation of the olefinic double bond and reduction/protection of the ester functionality provides the requisite meso epoxide. While desymmetrization proceeds in good chemical yield, we were

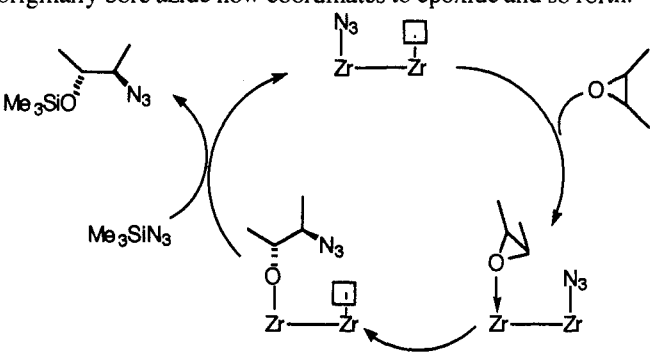
disappointed to find that the enantiomeric excess of **7** was only 82%.



Fortunately, Prof. Eric Jacobsen at Harvard University has recently discovered an alternative catalyst for azide-promoted desymmetrization. Jacobsen's chromium catalyst (ref. 8) is highly effective with cyclopentene oxides generally providing enantiomeric excesses in the 95-98% range. The synthesis of **7** was completed in a collaborative program and is described elsewhere (ref. 9).

Recently several other research groups have developed alternative catalysts which promote the enantioselective addition of nucleophiles other than azidotrialkylsilanes to meso epoxides. In particular, Hoveyda and co-workers (ref. 10) have succeeded in adding trimethylsilyl cyanide to cyclohexene oxide with ee's up to 86% while Shibasaki and co-workers (ref. 11) have achieved the addition of tert-butyl thiol in up to 98% ee. We felt that trimethylsilyl halides would be particularly attractive nucleophiles for enantioselective epoxide desymmetrization. The enantiopure β-halohydrins from such a reaction should be invaluable synthetic intermediates because of their ability to undergo a wide range of subequent (elimination, radical substitution, S_N2 displacement) transformations. Attempts to directly extend eq. 5 by replacing the azidotrimethylsilane with a variety of trialkylsilyl halides produced the desired protected halohydrins but in only modest enantiomeric excess. However, mechanistic studies on eq. 5 have now provided an indirect solution to this problem.

The details of these mechanistic studies will be published elsewhere (ref. 12) but the salient points for the current discussion are shown schematically in Scheme 1. A variety of evidence including kinetic and spectroscopic studies as well as the observation of a very large "chiral amplification effect" indicate that active catalyst is a dimeric species containing two zirconium atoms. One zirconium atom coordinates to the epoxide substrate and activates it toward nucleophilic attack. The other covalently binds the azide nucleophile and delivers it to the backside of the epoxide resulting in a zirconium alkoxide species. Release of this azide-containing alkoxide moiety requires silylation by azidotrimethylsilane and thus regenerates a zirconium azide center. Interestingly, the two zirconium atoms have now reversed their roles - the zirconium that originally bore azide now coordinates to epoxide and so forth.



Scheme 1. Mechanism of zirconium catalyzed epoxide desymmetrization

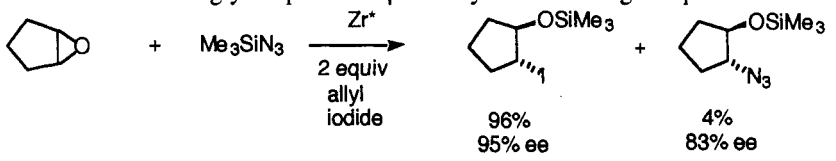
The intermediacy of a homobimetallic zirconium species as the active catalyst in Scheme 1 is noteworthy. Mechanistic proposals have been made for two other catalytic epoxide desymmetrization reactions. The thiol-mediated desymmetrization developed by Shibasaki and co-workers involves a heterobimetallic catalyst where lithium and gallium activate the thiol and the epoxide respectively (ref. 11). The azide mediated desymmetrization developed by Jacobsen and co-workers is second order in the mononuclear chromium catalyst with one chromium center activating azide and a second activating epoxide (ref. 13). Thus nature conspires in three different ways to achieve the same end, the simultaneous activation of the nucleophile and the acceptor while defining their relative positions in three-dimensional space.

EPOXIDE DESYMMETRIZATION WITH HALIDE AS NUCLEOPHILE

It is the presence of covalently bound azide in Scheme 1 which opens the door to new chemistry. In principle, it is only necessary to replace the Zr-bound azide with some other nucleophile in order to detour the organic azide-forming pathway. Of course, for the reaction to be synthetically useful, the rate for this

exchange must be significantly greater than the rate for intramolecular delivery of the azide to the epoxide. Thus we examined the use of highly reactive organic halides as additives to achieve this goal.

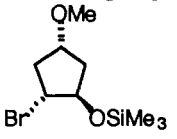
Reaction of cyclopentene oxide with a 2:1 mixture of allyl iodide and azidotrimethylsilane in the presence of Zr* produced overwhelmingly the protected β-iodohydrin according to eq. 7:



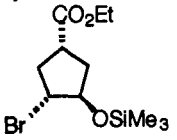
(7)

Interestingly, the iodohydrin is produced in significantly higher enantiomeric excess than the azide product under these conditions. The allyl iodide in eq. 7 could be replaced with allyl bromide. However, a higher allyl bromide to azidotrimethylsilane ratio (20:1) is required to suppress the formation of the azide adduct. The corresponding protected β-bromohydrin is again formed in 95% enantiomeric excess.

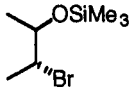
A variety of silylated β-bromohydrins have now been prepared using this reaction as exemplified by **8** - **13**. Synthetically useful ee's can be achieved with epoxides bound to 5, 6, 7 or 8-membered rings. Although we have just begun to explore the functional group compatibility of this chemistry, it is already evident that ester and ether groups are readily accommodated.



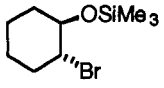
8 96% ee



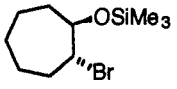
9 94% ee



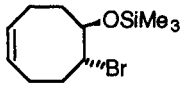
10 85% ee



11 94% ee



12 88% ee



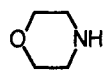
13 85% ee

PARALLEL SYNTHESIS OF ENANTIOPURE AMINOALCOHOLS

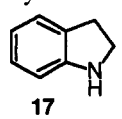
The remarkable simplicity of the aminoalcohol synthesis in eq. 1 inspired us to apply this strategy to prepare a library of enantiopure aminoalcohols via parallel synthesis. Recently Hoveyda, Snapper and co-workers have successfully applied parallel synthesis to prepare a library of chiral ligands bound to polymeric bead (ref. 10). The ligands produced in this way provided the first highly enantioselective desymmetrization of epoxides using trimethylsilyl cyanide as nucleophile. An important conceptual contribution of this work is the recognition that the contributions of the various components can under some circumstances be "independent and additive" (ref. 10). One objective of our study was to circumvent the use of a polymeric support in our synthetic strategy. Eq. 1 suggests the possibility of preparing aminoalcohols without the use of added reagents, solvents, and possibly even purification steps. We would prepare simple aminoalcohols and screen them for the asymmetric addition of diethylzinc to aldehydes, a widely studied reaction (ref. 14) which would serve as a simple testing ground for our approach. A set of amines **14-21** and epoxides **A-D** was chosen for initial study:

14

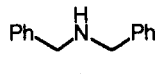
15



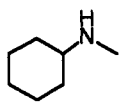
16



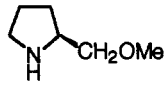
17



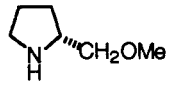
18



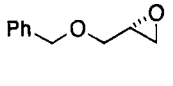
19



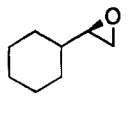
20



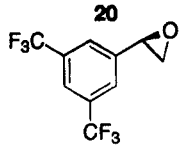
21



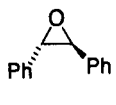
A



B

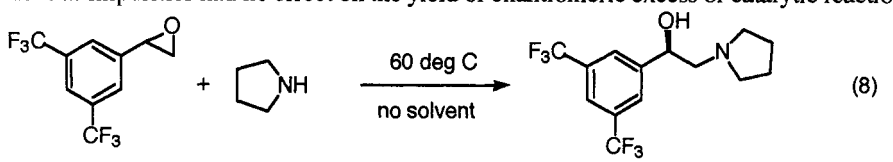


C



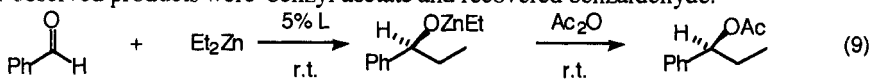
D

The choice of epoxides was governed not only by their availability in enantiopure form but also the expected regiospecificity of their reaction with seconary amines. A typical ligand synthesis is illustrated in eq. 8. Amine **14** and a 5% excess of epoxide **C**, two colorless liquids are heated overnight in a 60°C oil bath. After 24 h the reaction vessel contains a crystalline solid which was shown to be the desired aminoalcohol. In a few cases it was necessary to resort to higher temperatures (typically 90°C). In two cases (epoxide **D** with amines **18** and **19**) it was necessary to heat for several days at 110°C. In almost all cases the ^{1}H and ^{13}C NMR spectra of the crude ligands indicated that their purity was ca. 95% and that the principal impurity was unreacted epoxide. Spiking experiments verified that low concentrations of these epoxides as impurities had no effect on the yield or enantiomeric excess of catalytic reactions.



(8)

A standard screening protocol was adopted involving the addition of diethylzinc in hexane to a toluene solution of aldehyde containing 5 mol % of aminoalcohol ligand at 25°C. To simplify analysis of the enantiomeric excess and product distribution, reactions were quenched directly with acetic anhydride and analyzed by chiral capillary column gas chromatography. The overall reaction in the case of benzaldehyde is shown in eq. 9. Under these conditions, yields of 1-phenyl-1-propyl acetate were typically 80-98%. The other observed products were benzyl acetate and recovered benzaldehyde.



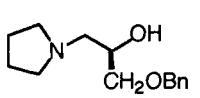
(9)

Observed enantiomeric excesses for four series of ligands are shown in Table 1. The ligands were utilized in crude, unpurified form; nevertheless ee's as high as 88% were observed in the screen. Also shown in parentheses on Table 1 are the corresponding enantiomeric excesses after purification of the ligands by flash chromatography. In the majority of cases it can be seen that chromatographic purification has little effect on the enantioselectivity of the reactions. For the ligands derived from (R,R)-stilbene oxide **D** and 2-(methoxymethyl)pyrrolidines **20** and **21** the ee's increased 23% after chromatography and this was not unexpected. The ligand synthesis did not proceed to completion in this hindered system. Moreover, it could be shown that free methoxymethylpyrrolidine was an efficient but unselective catalyst for organozinc addition to benzaldehyde. But how does one explain a case like ligand **22** where the enantiomeric excess *drops* 42% after chromatography?

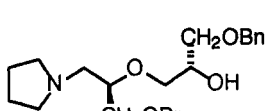
TABLE 1. Enantiomeric Excess for Eq. 8 in the Presence of Aminoalcohol Ligands Derived from Epoxides **A-D** and Secondary Amines **14-21** (5% catalyst, 25 deg C)

Amine/Epoxide	A	B	C	D
14	+74 (+32)	-45	-63 (-47)	-84 (-85)
15	+31 (+27)	-68	-67 (-65)	-88 (-89)
16	+27 (+27)	-65	-70 (-61)	-78 (-89)
17	+11 (+11)	-16	-62 (-62)	+15 (+3)
18	-12 (-12)	+11	-23 (-21)	+1 (+4)
19	+13 (+12)	-13	-43 (-14)	-28 (-81)
20	+61 (+64)	+42	+19 (+19)	-57 (-80)
21	-65 (-66)	-55	-79 (-83)	-45 (-68)

Examination of the impurity derived from synthesis of **22** indicates that the crude ligand contains ca. 5% of the 2:1 adduct **23**. Formation of this 2:1 adduct is no doubt favored by the high reactivity of the epoxide, the substantial basicity of the aminoalcohol product, and the volatility of pyrrolidine itself. Adduct **23** was independently synthesized and shown to be an efficient catalyst for eq. 7, producing the acetylated product in 93% yield and 91% enantiomeric excess. The higher enantiomeric excess obtained from this "chain extended" aminoalcohol is not without precedent. Both Hoshino (ref. 15) and Fu (ref. 16) have shown that chain extension of moderately selective aminoalcohols with 1,2-diphenylethylene oxide can significantly enhance their selectivity for diethylzinc addition to aldehydes.



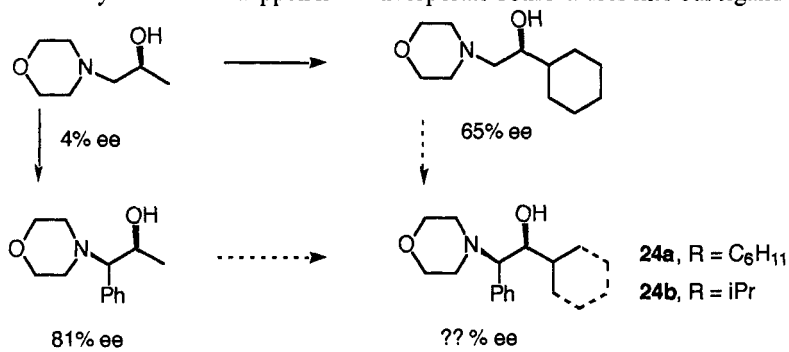
22



23

The last two lines of Table 1 are particularly relevant to the issue of "independence and additivity" as it pertains to eq. 9. Both the amine and epoxide components are chiral in these diastereomeric pairs of ligands. Even within this small set of compounds, three distinctive reactivity patterns are observed. For the ligands derived from epoxide **A**, the enantioselectivity appears to track only the chirality of the amine components, while in the ligands derived from epoxide **D** it is the chirality of the epoxide which dominates. Only in the pair of ligands derived from epoxide **C** is there significant evidence of additive contributions from both constituents.

Nevertheless the additivity concept has proven useful to us in designing an improved aminoalcohol for diethylzinc additions. The simplistic reasoning behind our design is summarized below and draws on the full set of aminoalcohols used in our studies. The ligand derived from (R)-propylene oxide and morpholine gives low selectivity (4% ee) in eq. 9. Increasing the steric bulk of the methyl group to that of cyclohexyl results in a significant enhancement in enantioselectivity (65% ee). Alternatively, a significant increase in enantioselectivity (81% ee) can be achieved by adding a phenyl substituent adjacent to the amine functionality. What will happen if we incorporate both features into our ligand?



Happily, the answer appears to be that these two structural modifications will act cooperatively in to provide an extremely active and selective catalyst for organozinc additions. For convenience, we chose to synthesize the isopropyl derivative **24b** rather than the cyclohexyl analogue **24a**. The resultant ligand promotes the addition of diethylzinc to benzaldehyde according to eq. 9 in 98% enantiomeric excess. Moreover, under the same conditions the addition of diethylzinc to pivalaldehyde proceeds in 97% ee while addition to the α,β-unsaturated *trans*-2-pentenal gives the corresponding product in 85% ee. These enantioselectivities are the highest of any we have seen from our library of β-aminoalcohols and compare favorably with the benchmark ligand DAIB (ref. 14).

REFERENCES

1. Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 6142.
2. Di Furia, F.; Licini, G.; Modena, G.; Motterle, R.; Nugent, W. A. *J. Org. Chem.* **1996**, *61*, 5175.
3. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* 1984, 325; Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188; Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**,*43*, 5132; Brunel, J. M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086.
4. Bonchio, M.; Licini, G.; Modena, G.; Moro, S.; Bortolini, O.; Traldi, P.; Nugent, W. A. *J. Chem. Soc.,Chem. Commun.* **1997**, 869.
5. Boche, G.; Moebus, K.; Harms, K.; Marsh, J. *J. Am. Chem. Soc.* **1996**, *118*, 2770.
6. Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768.
7. Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992.
8. Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897; Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
9. Martinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963.
10. Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668.
11. Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783.
12. McCleland, B. W.; Finn, M. G.; Nugent, W. A., submitted for publication.
13. Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.
14. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823; Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071; Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
15. Ishizaki, M.; Fujita, K.-i.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411.
16. Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *23*, 444.