Pure & Appl. Chem., Vol. 66, No. 7, pp. 1463–1469, 1994.
Printed in Great Britain.

Controlling stereochemistry in C–C and C–H bond formation with electronically asymmetric organometallics and chiral poisons

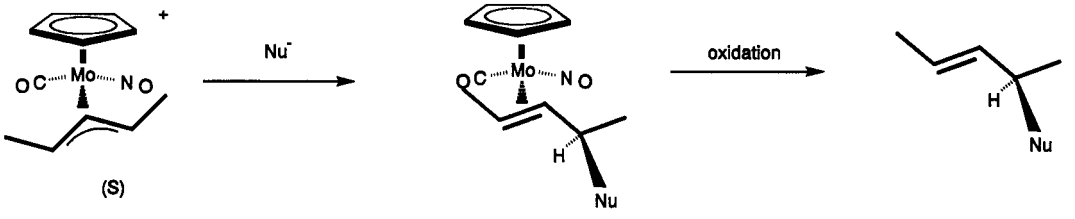
J.W. Faller, Maria R. Mazzieri, Jenna Thu Nguyen, Jonathan Parr, Makoto Tokunaga

Department of Chemistry, Yale University, New Haven, Connecticut, 06511, U.S.A.

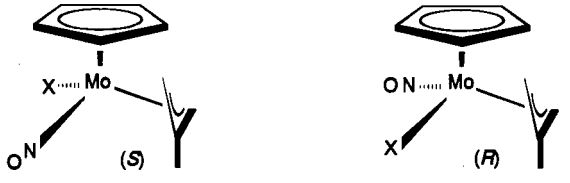
Abstract. Air stable (cyclopentadienyl)Mo(NO)(halide)(η^3-allyl) complexes add to aldehydes to yield homoallylic alcohols in high enantioselectivity and diastereoselectivity. A new strategy, chiral poisoning, is applied to asymmetric hydrogenation and the kinetic resolution of allylic alcohols using transition metal catalysts prepared from *racemic* bis-phosphine ligands.

The activation afforded an organic moiety by complexation led to the extensive development of transition metal reagents for organic synthesis. The increased reactivity is influenced by differences in the steric and electronic nature of the metal and its ligands. Ultimately the environment at the metal can induce high stereoselectivity in reactions involving the coordinated ligands. Our aim has been the improvement of our understanding of the origins of selectivity in these reactions and the application of these principles to the rational design of reagents and catalysts. Our approach modifies the conventional emphasis on steric effects in catalyst design and focuses attention on electronically controlled selectivity.

Our initial work emphasized the control which could be obtained with nucleophilic additions to chiral [CpMo(allyl)(NO)(CO)]$^+$ cations, wherein the difference in electronic influences of the carbonyl and



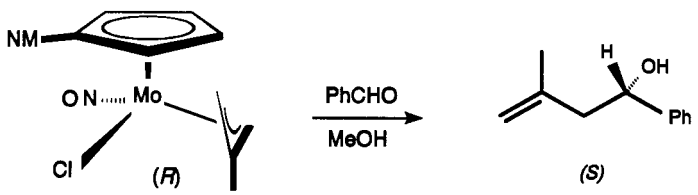
nitrosyl ligands directs attack of the nucleophile to the terminus of the allyl that is cis to NO. Using enantiomerically pure metal centers, this regio- and stereocontrol allows the enantioselective preparation of olefins with stereogenic centers at the α position. These reagents have also been used successfully by others in more elaborate organic syntheses (ref. 3-4). In our earlier work, resolution of the stereogenic metal center was accomplished using neomenthyl-substituted cyclopentadienyl ligands (ref. 2, 5-7).



Nucleophilic attack also occurs on the neutral CpMo(allyl)(NO)(halide) complexes. Although these halide complexes are somewhat more stable, they do not offer exceptional advantages over the carbonyl nitrosyl compounds in reactions with nucleophiles. We recently discovered that the reactions of aldehydes with the neomenthyl analogues of CpMo(allyl)(NO)(halide) complexes provide extraordinarily effective asymmetric syntheses of homoallylic alcohols. The metal center, functioning as a Lewis acid, serves to orient and *rationally control allylic addition to a specific face of an aldehyde.* This system has allowed the preparation of homoallylic alcohols in >99% ee (ref. 8-11) and we have now found alternative routes to resolving the stereogenic metal center.

ALLYLIC ADDITIONS TO ALDEHYDES

Reactions of allyl metal compounds with aldehydes yielding chiral homoallylic alcohols have been widely investigated owing to their application in stereoselective synthesis of acyclic compounds. Allylboronates derived from camphor glycols and tartrate and allylboranes derived from α-pinene have provided syntheses of homoallylic alcohols with 71-96 % *ee* (ref. 11-14). Titanium allyls with ligands derived from sugar derivatives and chiral diols have been shown to yield homoallylic alcohols in very high enantiomeric purity (ref. 15-16).

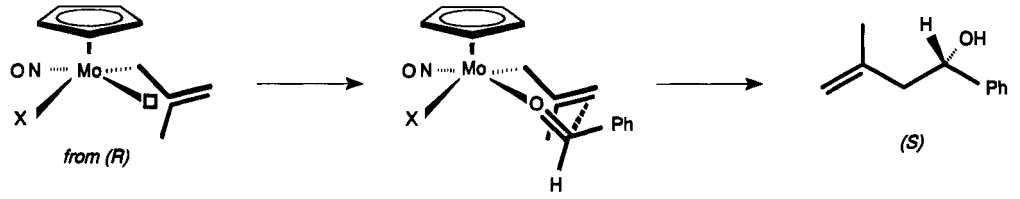


We have shown that the reaction of PhCHO with NMCpMo(NO)(η^3-methallyl)Cl (NMCp = neomenthylcyclopentadienyl) proceeds with >98% enantioselectivity (ref. 8). These allylmolybdenum systems are air stable and require no special precautions for their manipulation at room temperature. This has a clear advantage over the allylboron and allyltitanium systems since some of these reagents decompose readily and the reactions must be conducted at very low temperature. We have separated the diastereomers of CpMo(NO)(η^3-methallyl)(1*S*-(10)-camphorsulfonate), **1**, and conversions to the halides have allowed the isolation of enantiomerically pure CpMo(NO)(η^3-methallyl)X (X= Cl, Br, and I) complexes which also react with aldehydes with high enantioselectivity.

The stereogenic metal centers in CpMo(NO)(η^3-methallyl)X complexes have previously been resolved by replacing the Cp ligand by a NMCp group, which yields diastereomeric complexes. Fractional crystallization yields diastereomerically pure complexes. The diastereomeric camphorsulfonate CpMo complexes can also be separated by crystallization. The major advantage of this method is that the enantiomerically pure camphorsulfonate complexes can be subsequently converted back to halide compounds. This allows recovery of the resolving agent and provides enantiomerically pure molybdenum reagents with the chirality at the molybdenum and not in the X ligand or on the Cp ring. These Cp reagents are more reactive and avoid possible adverse diastereomeric differentiation arising from interactions with chiral groups other than those at the metal center, as might be found with the NMCp reagents. The isolation of product from the reagent is also more readily effected with the Cp reagents than with the NMCp reagents.

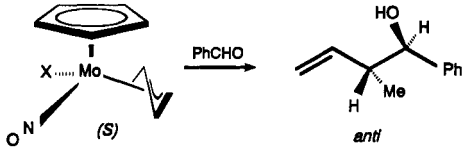
The selectivity in this system arises from the electronic asymmetry originating from the nitrosyl and halide ligands. X-ray diffraction studies show that the allyl is distorted toward a σ,π-type binding with the double bond trans to NO. NMR evidence indicates that there is a low energy barrier of ~18 kcal/mol in CpMo(NO)(η^3-allyl)X complexes for syn-anti substituent averaging *cis* to NO, which indicates a π-σ-π interconversion mechanism in which the Mo-C bond cis to NO is retained. This interconversion produces a vacant Lewis acid site *trans* to NO to which an aldehyde could bind. In the complexed aldehyde one expects an antiperiplanar arrangement of the R group in RCHO relative to the Cp in order to minimize steric interactions with the Cp ring (ref. 17-18). The metal thus serves to orient the aldehyde as well as

activate it to attack by the allyl. Since only one face of the aldehyde is accessible to the allyl, the stereochemical outcome of the reaction at the carboxaldehyde carbon is predetermined.



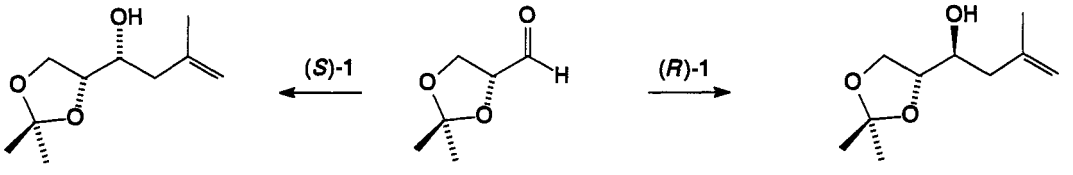
As shown for the methallylmolybdenum complex with the *R* configuration at the metal center, attack on the *si* face of the aldehyde occurs to yield the (*S*)-alcohol. This allows a confident prediction of the absolute stereochemistry of the product. Assuming a chair-like transition state also allows one to account for the high diastereoselectivity observed with crotyl reagents.

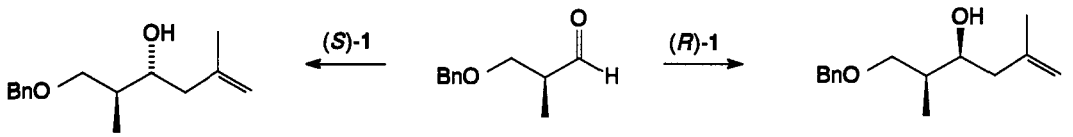
The racemic complex, (±)-CpMo(NO)(η^3-crotyl)I, can be prepared in large quantity from $CpMo(CO)_2(\eta^3$-crotyl) by treatment with NO^+, and I^-. The reaction is highly stereoselective and yields the product with the nitrosyl trans to the methyl group of the crotyl. A mixture of the (+)- and (–)-CpMo(NO)(O_3Scam^S)(η^3-crotyl) diastereomers were produced by treatment of the iodide with silver (1*S*)-(+)-10-camphorsulfonate. The (*S*)-(–) isomer is less soluble and can be separated in high diastereomeric purity after several crystallizations. (*S*)-(–)-CpMo(NO)(O_3Scam^S)(η^3-crotyl) can be converted to the (*S*)-(–)-halides with effectively complete retention of configuration by treatment with sodium halide.



(*S*)-(–)-NMCpMo(NO)(Cl)(η^3-crotyl) reacts with benzaldehyde to yield the (*R,R*)-1-phenyl-2-methylbut-2-en-1-ol in >98% ee and 92% de, but the reaction is rather slow. Under the same conditions (*S*)-(–)-CpMo(NO)(O_3Scam^S)(η^3-crotyl) gave the same product in >98% ee and 94% de in less than a third of the time. The enantiomeric purities of the products from these organomolybdenum reagents compare favorably to those of most other reagents. For example, the crotylboronate formed from diisopropyl tartrate yields the product in 67% ee (ref. 12). We have generally observed that the Cp complexes react somewhat faster than the NMCp complexes and that the camphorsulfonate complexes react faster than the chlorides. The reaction times can be shortened by using methylene chloride as solvent, using more concentrated solutions, and using excess aldehyde. The separation of the organometallics and minimization of side reactions can generally be improved by using water instead of methanol as a proton source. During reactions with the iodide complex the $[CpMo(NO)(I)(OH)]_2$ dimer, with bridging hydroxyls, precipitates as large crystals from the methylene chloride solvent as the reaction proceeds.

The reactions with aldehydes are effective for aryl, alkyl and unsaturated aldehydes. With aldehydes that are highly substituted in the α-position the reactions can be slow, so that the faster-reacting camphorsulfonates or chlorides are preferred reagents. In additions to α-chiral aldehydes, it appears that there is generally a high degree of reagent control, which can overcome inherent Cram selectivity. The de is >96% with *D*-glyceraldehyde acetonide and >90% with (*S*)-3-benzyloxy-2-methylpropanal for either (*S*)-**1** or (*R*)-**1**.

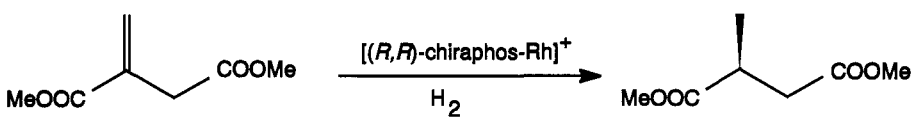




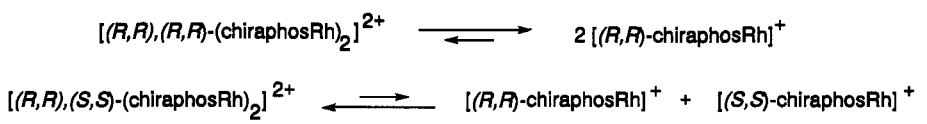
CHIRAL AMPLIFICATION

The CpMo reactions are very effective enantioselective reagents; nevertheless they are stoichiometric reactions. Catalytic reactions offer the potential of yielding products in high enantiomeric purity using a small quantity of asymmetric material. Generally, new asymmetric catalysts are generated by taking a known catalytic reaction and developing an asymmetric analogue of the catalyst. An obvious approach would be the use of enantiomerically pure catalysts. Nevertheless, nonlinear effects are sometimes observed and a catalyst of modest enantiomeric purity can yield a product of high ee. This type of non-linear effect was originally investigated by Kagan (ref. 19) and recently shown to be important in chiral amino alcohol-assisted R_2Zn addition to carbonyls by Oguni, Noyori and their coworkers (ref. 20).

[(Chiraphos)Rh(norbornadiene)]BF_4 was developed as an asymmetric hydrogenation catalyst and extensively studied in the enantiomerically pure form by Bosnich (ref. 21). Under the reaction conditions the catalytically active species is presumably a solvated [(*R,R*)-chiraphosRh]$^+$ complex. The enantioselective hydrogenation of dimethyl itaconate using the pure (*R,R*)-chiraphos-rhodium complex yields the (*S*)-methylsuccinate in greater than 98% ee.



For example, if we consider a case of [(*R,R*)-chiraphosRh]$^+$ of 33% ee, where there is a 1:2 ratio of (*S,S*) to (*R,R*), one would generally presume that a product of 33% ee would be produced. We, however, have observed a *chiral amplification* effect in this catalytic reaction. The use of a catalyst prepared from a 1:2 mixture of (*S,S*)-chiraphos:(*R,R*)-chiraphos yields a 1:4 mixture of (*R*)-methylsuccinate to (*S*)-methylsuccinate.



This non-linear effect can be attributed to the formation of dimers and their relative stabilities. Hydrogenation of [(*S,S*)-chiraphos-Rh(norbornadiene)]BF_4, yields a stable [(*S,S*)-chiraphosRh]$_2^{2+}$ dimer (ref. 22). This dimer is an excellent catalyst precursor and presumably produces the same active species as the norbornadiene complex. The [(*S,S*)-chiraphosRh]$_2^{2+}$ dimers tend to dissociate significantly, particularly in donor solvents, to yield the active [(*S,S*)-chiraphosRh]$^+$. In a mixture of dimers prepared with 33% ee (*R,R*)-chiraphos there would be two diastereomeric types of dimers: the chiral homodimers [(*R,R*)-chiraphosRh]$_2^{2+}$ and [(*S,S*)-chiraphosRh]$_2^{2+}$; and the heterodimer [(*R,R*)-chiraphosRh-(*S,S*)-chiraphosRh]$^{2+}$. It appears from ^{31}P NMR studies in nonpolar solvents that the mixed dimer is more stable. If the dissociation constant of the homodimer were much greater than that of the heterodimer under the reaction conditions, most of the (*S,S*)-(*S,S*)-dimer would be dissociated. This would also imply that

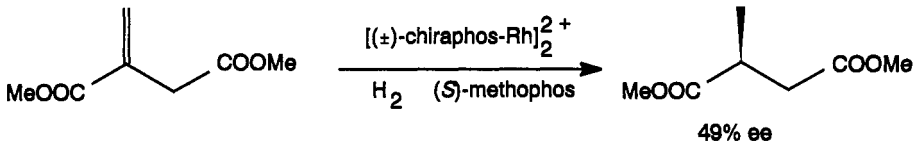
much of the (*R,R*)-(*S,S*)-dimer would remain associated; whereas, the (*R,R*)-(*R,R*) would mostly be dissociated. In effect some of the (*R,R*)-monomer sequesters the (*S,S*)-monomer leaving the remaining pure (*R,R*) monomer available for catalysis. This example illustrates how a catalyst of low enantiomeric purity can yield a product of higher *ee.*

CHIRAL POISONING

In the case above, one monomer effectively deactivated the other by tying it up in a the form of a mixed dimer. We have investigated a racemic version of the reaction with the notion that an enantiomerically pure *poison* might be added which would preferentially sequester one enantiomer of the [(chiraphos)Rh]$^+$ monomer. Hopefully this poison would be even more effective in this role than the other hand of the monomer in the example of *chiral amplification.* If racemic chiraphos is used to prepare the dimers, dissociation should provide equal amounts of [(*S,S*)-chiraphosRh]$^+$ and [(*R,R*)-chiraphosRh]$^+$. If a poison selectively deactivated all of one enantiomer, then the hydrogenation due to the remaining active catalyst would yield a product of high *ee.* In the ideal case one half an equivalent of poison per equivalent of racemic catalyst would leave a half of an equivalent of active enantiomerically pure catalyst.

Asymmetric hydrogenation

A fairly effective poison, which we call (*S*)-methophos, (*S*)-[Ph_2P-O-$CH_2CH(NMe_2)CH_2CH_2SMe$] can be readily prepared from methionine. The [(*S*)-methophos]rhodium complex is a very poor catalyst for the asymmetric hydrogenation of dimethyl itaconate and yields dimethyl methylsuccinate in <2% *ee.* However, *the racemic chiraphos/(S)-methophos system gives a product in 49% ee*, illustrating that the poisoning has

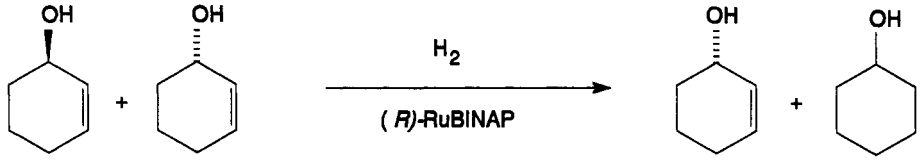


dramatically enhanced the enantioselectivity of the catalysis (ref. 23). This implies that the primary role of the (*S*)-methophos is to bind to [(*S,S*)-chiraphosRh]$^+$ and so reduce its equilibrium concentration. Naturally one anticipates a large number of equilibria in this system and the poison functions by forming several complexes which have reduced rates of catalytic activity. The poison would be expected in practice to deactivate both enantiomers of the active species to some extent.

These studies demonstrated that the *chiral poisoning* strategy had the potential of guiding the development of practically useful systems for asymmetric syntheses of products of high enantiomeric purity. Other workers have considered *in situ* resolutions as an alternate approach. We sought a system where there would be a significant advantage in reducing the cost or the synthetic effort required by using the racemic catalyst and an inexpensive enantiomerically pure poison.

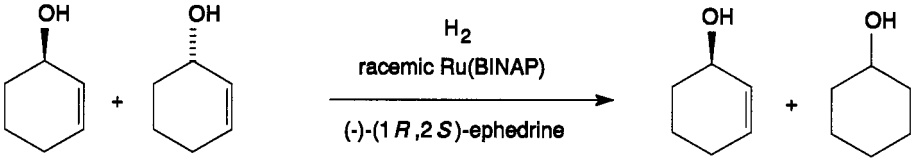
Kinetic resolution of allylic alcohols.

We turned our attention to the use of catalysts based on racemic BINAP, 2,2'-bis(diphenylphosphino)-1-1'-binapthyl. This ligand is not based on a naturally occurring chiral source and involves a resolution step. The kinetic resolution of cyclic allylic alcohols has been developed by Noyori and his coworkers (ref. 24), who have shown that hydrogenation of allylic alcohols using ruthenium catalysts with enantiomerically



pure phosphines, such as (*R*)-BINAP have proven effective. This provides a method complementary to Sharpless epoxidation, which is effective for flexible acyclic substrates, but does not always work well with cis olefins, particularly cyclic allylic alcohols (ref. 25-26). Using a *racemic* BINAP-ruthenium catalyst with (-)-(1*R*,2*S*)-ephedrine as a poison we have been able to prepare (*R*)-2-cyclohexenol in >95% ee (ref. 27).

We have used (BINAP)-$RuCl_2(dmf)_x$, **2**, (ref. 28) as the catalyst in our studies. Poisoning of racemic **2**, with (1*R*,2*S*)-ephedrine yielded (*R*)-2-cyclohexenol in 93% ee at 72% conversion and is >95% at 77% conversion. Naturally, poisoning of (±)-(BINAP)-$RuCl_2(dmf)_x$ with (1*S*,2*R*)-ephedrine provided (*S*)-2-cyclohexenol in comparable enantiomeric purity.



The analogue of **2** prepared from pure (*R*)-BINAP is effective for the kinetic resolution of 2-cyclohexenol. Since the remaining (*S*)-2-cyclohexenol is obtained in >95% ee, this indicates that the (*R*)-BINAP-Ru catalyst hydrogenates (*R*)-2-cyclohexenol much faster than (*S*)-2-cyclohexenol. Addition of amine noticeably slows the reaction. The amine presumably interacts with and partially deactivates both the (*R*)- and (*S*)-BINAP-Ru catalysts, but it does so more selectively with one hand of the catalyst. A survey of a number of amines and amino alcohols showed that ephedrine was the most effective. Since the (*R*)-2-cyclohexenol is obtained in high ee with (1*R*,2*S*)-ephedrine, the poison is selectively deactivating the (*R*)-BINAP-Ru component of the racemic catalyst.

We anticipate that the chiral poisoning strategy will be useful with a number of known catalytic systems. In the future this approach may be lead to new catalysts which were previously untested owing to the impracticality of separating the enantiomers of the chiral catalyst.

Acknowledgement: We thank the National Science Foundation and National Institute of General Medical Sciences for support of this research.

REFERENCES

1. A.F. Noels, M. Graziani, A.J. Hubert, eds, "Metal Promoted Selectivity in Organic Synthesis," Kluwer, Boston, (1991).
2. J.W. Faller and K. Chao, *J. Am. Chem. Soc, 105*, 3893-3898 (1983)
3. W.-J. Vong, S.-M. Peng, and R.-S. Liu, *Organometallics, 9*, 2187-2189 (1990).
4. S. Hansson, J.F. Miller, L.S. Liebeskind, *J. Am. Chem. Soc., 112*, 9660-9661 (1990).
5. J.W. Faller, Y. Shvo, K. Chao, H.H. Murray, *J. Organometal. Chem., 226*, 251-275 (1982).
6. J.W. Faller and K. Chao, *Organometallics, 3*, 927-932 (1984).
7. J.W. Faller, C. Lambert, and M.R. Mazzieri, *J. Organometal. Chem., 383*, 161-178 (1990).
8. J.W. Faller and D.L. Linebarrier, *J. Am. Chem. Soc., 111*, 1937-1939 (1989).
9. J.W. Faller, J.A. John, and M. R. Mazzieri, *Tetrahedron Letters, 30*, 1769-1772 (1989).
10. J.W. Faller, M.J. DiVerdi, and J.A. John, *Tetrahedron Letters, 33*, 1271-1274 (1991).
11. J.W. Faller, J.T. Nguyen, W. Ellis, and M.R. Mazzieri, *Organometallics, 12*, 1434-1438 (1993).
12. W.T. Roush, K. Ando, D.B. Powers, R.L. Halterman, and A.D. Palkowitz, *Tetrahedron Lett.*, 29, 5579-5582 (1988).
13. R.W. Hoffman, *Pure and Appl. Chem., 60*, 123-130 (1988).
14. H.C. Brown, S.B. Krishna, and R.S. Randad, *J. Org. Chem., 52*, 319-320 (1987).
15. (a) D. Seebach, A.K. Beck, S. Roggo, and A. Wonnacot, *Helv. Chim. Acta, 70*, 954 (1987). b) R. Imwinkelried and D. Seebach, *Angew. Chem. Int. Ed. Engl., 24*, 765-6 (1985). (b) J.L. Von dem Bussche-Huennefeld and D. Seebach, *Tetrahedron*, 5719-5730 (1992).

16. (a) M. Riediker and R.O. Duthaler, *Angew. Chem. Int. Ed. Engl., 28*, 494-5 (1989). (b) R.O. Duthaler, A. Hafner, M. Riediker in K.H. Dötz and R.W. Hoffmann, (eds), *Organic Synthesis via Organometallics*, pp 285-309 Vieweg, Braunschweig (1991).
17. J.W. Faller, Y. Ma, C.J. Smart, M.J. Diverdi, *J. Organometal. Chem., 420*, 237-252 (1991).
18. (a) Y.-H. Huang and J.A. Gladysz, *J. Chem. Ed., 65*, 298-303 (1988). (b) S. Shambayati, W.E. Crowe and S.L. Schreiber, *Angew. Chem. Int. Ed. Engl., 29*, 256-272 (1990).
19. C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami and H.B. Kagan, *J. Am. Chem. Soc., 108*, 2353-2357 (1986).
20. (a) R. Noyori and M. Kitamura, *Angew. Chem. Int. Ed. Engl., 30*, 49-69 (1991). (b) R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, *Pure and Appl. Chem., 60*, 1597-1606 (1988). (c) R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, N. Oguni, M. Hayashi, T. Kaneko, and Y. Matsuda, *J. Organometal. Chem., 382*, 19-37 (1990).
21. M.D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc., 99*, 6262-6267 (1977).
22. (a) D.P. Fairlie and B. Bosnich, *Organometallics, 7*, 936-945, 946-954 (1988). (b) S.H. Bergens, P. Noheda, J. Whelan and B. Bosnich, *J. Am. Chem. Soc., 114*, 2121-2128 (1992).
23. J.W. Faller and J. Parr, *J. Am. Chem. Soc., 115*, 804-805 (1993).
24. M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem., 53*, 708-710 (1988).
25. V.S. Martin, S.S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K.B. Sharpless, *J. Am. Chem. Soc., 103,* 6237-6240 (1981).
26. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune, K.B. Sharpless, *J. Am. Chem. Soc., 109,* 5765-5780 (1987).
27. J.W. Faller and M. Tokunaga, *Tetrahedron Letters, 35*, (1993) submitted.
28. (a) M. Kitamura, M. Tokunaga, T. Ohkuma and R. Noyori, *Tetrahedron Lett., 32*, 4163-4166 (1991). (b) M. Kitamura, M. Tokunaga, T. Ohkuma and R. Noyori, *Organic Syntheses, 71*, 1-11 (1992).