Pure & Appl. Chem., Vol. 70, No. 8, pp. 1507–1512, 1998.
Printed in Great Britain.

Designer Lewis acids for selective organic synthesis *

Hisashi Yamamoto, Akira Yanagisawa, Kazuaki Ishihara, Susumu Saito

Graduate School of Engineering, Nagoya University, CRES

Abstract : A variety of Lewis acid reagents were utilized for Diels-Alder, aldol, and ene reactions with high enantioselectivities. The origin of the selectivity of these reactions is discussed.

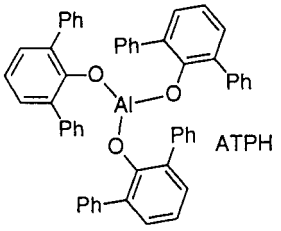
INTRODUCTION

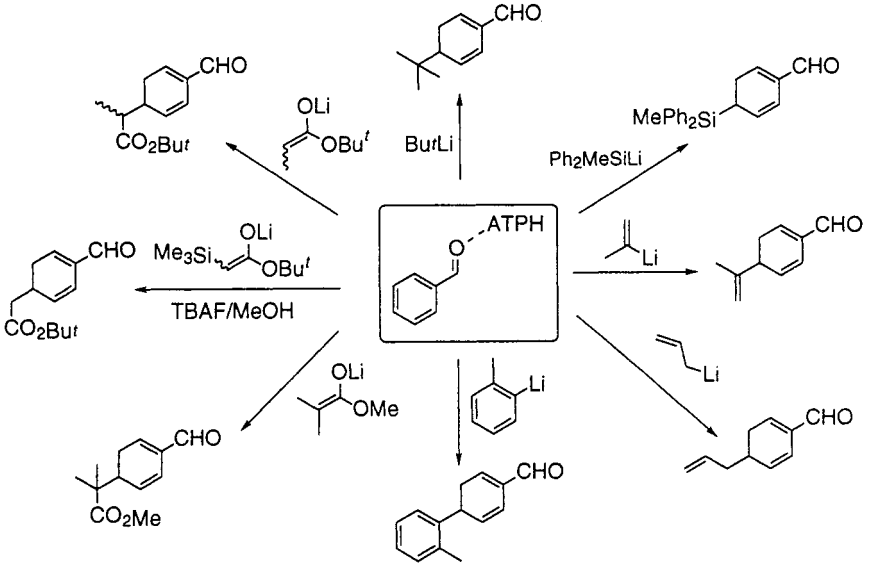
An excellent candidate as a proton substitute in man-made organic reactions is a Lewis acid. The goal of the research was to engineer an artificial proton of a special shape, which could be utilized as an effective tool for chemical reactions, by harnessing the high reactivity of the metal atom towards a variety of functional groups. Such a concept was initially researched by examining the influence of a specially designed organometallic reagent on a typical organic reaction. Michael addition of simple organolithium and magnesium reagent to aromatic aldehydes in the presence of a bulky organoaluminum reagent is described as an example of the concept. The successful discrimination observed led to examine the more intricate question of enantioface differentiation. A variety of Lewis acid reagents were utilized for Diels-Alder, aldol, and ene reactions with high enantioselectivities. The origins of the selectivity of these reactions are discussed. The review describes these points with a variety of designer Lewis acids selected to illustrate the utility of the concept.

SELECTIVE CARBON-CARBON BOND FORMATION USING ALUMINUM TRIS(2,6-DIPHENYLPHENOXIDE) (ATPH)

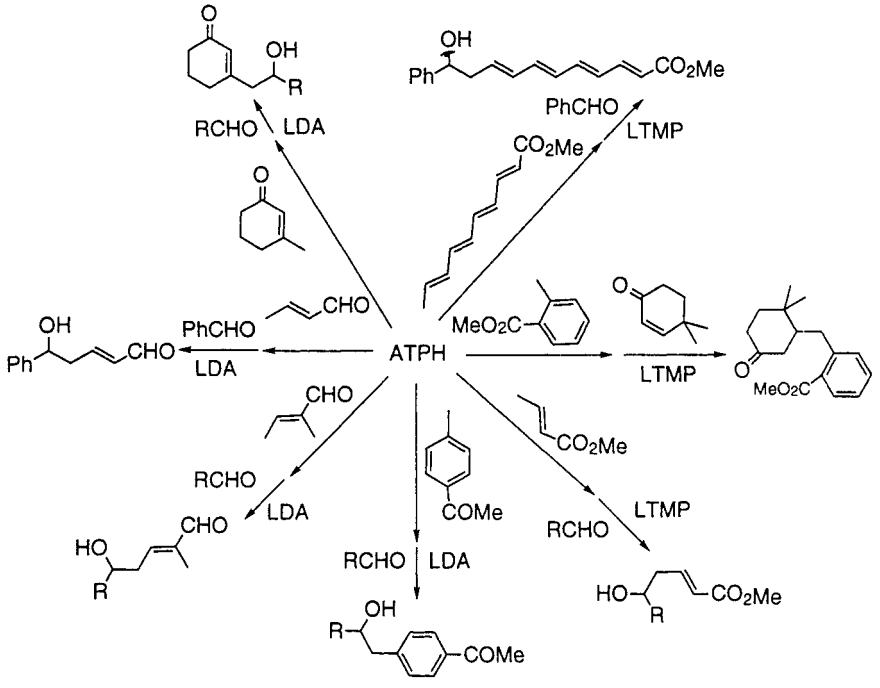
The selective functionalization of an aromatic nucleus has become increasingly important in synthetic organic chemistry. However, little is known about nucleophilic addition to aromatic nucleus covalently attached by a carbonyl functionality which serves as an electron-withdrawing group with weak activating capability. Accordingly, aromatic carbonyl compounds have long been believed as rather inactivated aromatics which do not allow the aromatic functonalization by the attack of nucleophiles but usually give addition at their carbonyl carbons. We recently discovered that organolithiums undergo conjugate addition to aromatic carbonyl compounds by complexation with aluminum tris(2,6-diphenylphenoxide) (ATPH) (ref. 1). This novel strategy represents a recent application to a number of nucleophiles including silyl- (ref. 2), aryl-, allyl- and vinyllithiums (ref. 3) as well as lithium enolates (ref. 4), leading to a powerful and general functionalization—dearomatization sequence for a wide range of aromatic carbonyl compounds (Scheme 1). Using ATPH as a key catalyst, a new directed aldol condensation was realized (ref. 5). Presented below is a new different strategy for combining two different carbonyl compounds using lithium diisopropyl amide (LDA), in which both of the substrates are complexed with ATPH (ref. 6). Several key issues have been documented here: (1) the two different carbonyl reactants and ATPH should be mixed together prior to treatment with a base to give effective cross-coupling, (2) conjugated carbonyl compounds including aldehydes, ketones, and esters (ref. 7) all demostrated to work as effective nucleophiles (Scheme 2), (3) neither the α-carbon of aromatic ketones nor the α'-carbon of α,β-unsaturated ketones were directed site for deprotonation. Thus, (4) deprotonation and ensuing alkylation are quite regioselective at an allylic terminus of given nucleophiles which serve as extended dienolates. Of particular note is the regioselective aldolization of highly conjugated esters which have several possible site for functionalization, (5) this transformation displayed high *E*-selectivity with respect to the γ-aldolization.

*Plenary lecture presented at the 12th International Conference on Organic Synthesis, Venice, 28 June–2 July 1998. Other presentations are published in this issue, pp. 1449–1512.





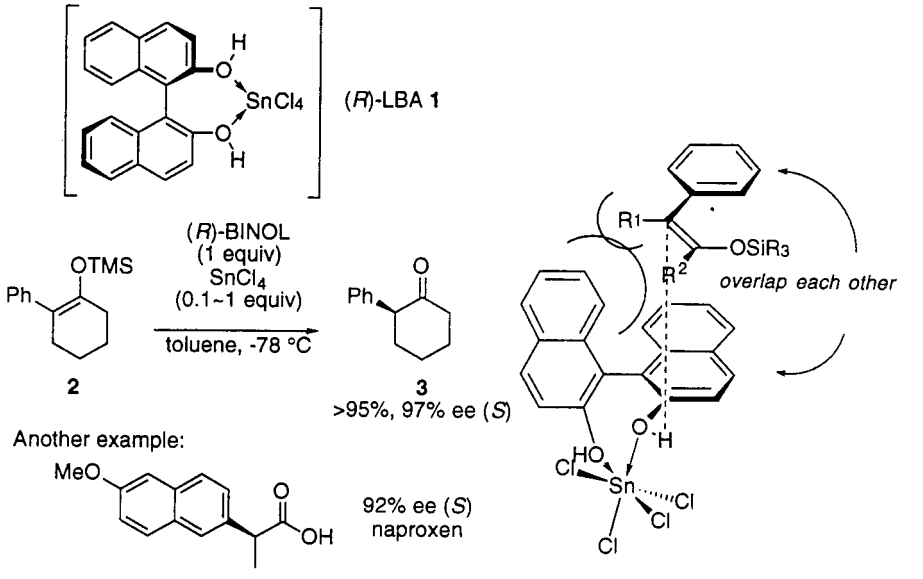
Scheme 1



Scheme 2

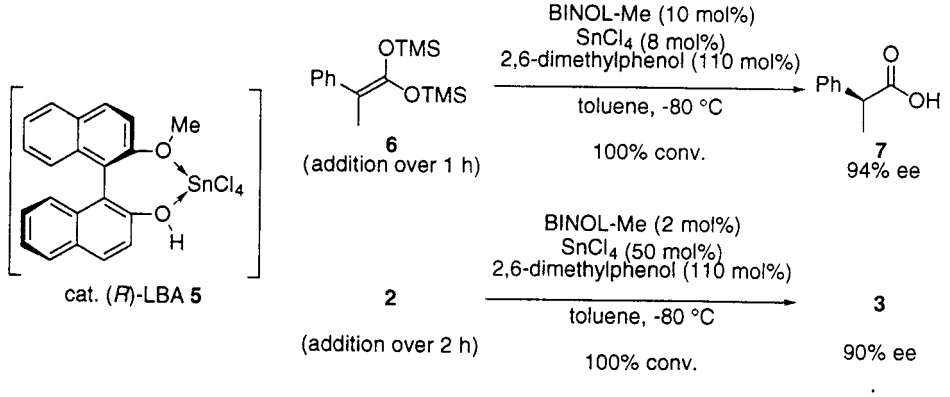
LEWIS ACID ASSISTED CHIRAL BRØNSTED ACID (LBA)

Enantioselective protonation of prochiral silyl enol ethers is a very simple and attractive route for preparing optically active carbonyl compounds (ref. 8). However, it is difficult to achieve high enantioselectivity using simple chiral Brønsted acids because of the conformational flexibility in the neighborhood of the proton. We expected that the coordination of a Lewis acid to a Brønsted acid would restrict the direction of the proton and increase its acidity. In 1994, we found that the Lewis acid assisted chiral Brønsted acid (LBA) is a highly effective chiral proton donor for the enantioselective protonation (ref. 9). LBA **1** is generated in situ from optically pure BINOL and tin tetrachloride in toluene, and is stable in the solution even at room temperature. In the presence of a stoichiometric amount of (*R*)-**1**, the protonation of the TMS enol ether **2** derived from 2-phenylcyclohexanone (**3**) proceeded at -78 °C to give the (*S*)-**3** with 97% ee. The observed absolute stereopreference can be understood in terms of the proposed transition state assembly. The trialkylsiloxy group is directed opposite to the binaphthyl moiety in order to avoid any steric interaction, and the aryl group stacks on this naphthyl group (Scheme 3).



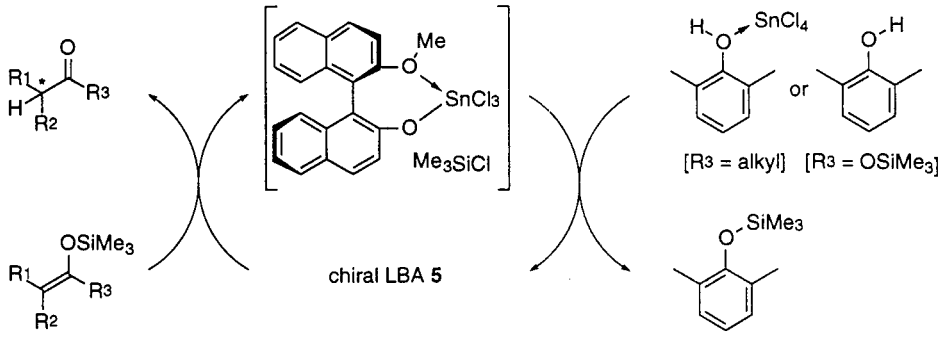
Scheme 3

In further studies, we succeeded in the enantioselective protonation using a stoichiometric amount of an achiral proton source and a catalytic amount of LBA **5** in place of LBA **1** (ref. 10). In the presence of 8 mol% of tin tetrachloride, 10 mol% of the monomethyl ether of (*R*)-BINOL, and stoichiometric amounts of 2,6-dimethylphenol as an achiral proton source, the protonation of the ketene bis(trimethylsilyl)acetal **6** derived from 2-phenylpropanoic acid (**7**) proceeded at –80 °C to give the (*S*)-**7** with 94% ee (Schema 4). The catalytic system was applied to the enantioselective synthesis of various α-arylcarbonyl compounds such as 2-phenylcycloheptanone, 2-(naphthyl)cyclohexanone and ibuprofen.



Scheme 4

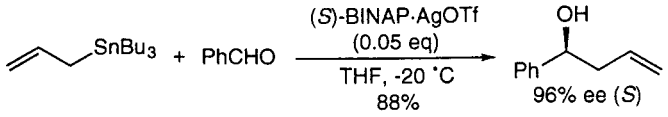
The mechanism of the catalytic cycle was investigated by ^{1}H NMR analysis of the 1 to 1 reaction mixtures of the silyl enol ether and chiral LBAs **1** and **5** at –78 °C. In this case, two singlets for the TMS groups of TMSCl and the mono TMS ether of (*R*)-BINOL were observed at a molar ratio of 15 to 85. In another case, only one singlet for TMSCl was observed. The presence of TMSCl leads us to anticipate the generation of these tin aryloxide intermediates. The catalytic cycle can be reasonably explained by assuming that the tin aryloxide intermediate is reconverted to the chiral LBA by receiving a proton and a chloride from 2,6-dimethylphenol and TMSCl or tin tetrachloride, respectively (Scheme 5).



Scheme 5

BINAP·SILVER(I)-CATALYZED ASYMMETRIC REACTIONS

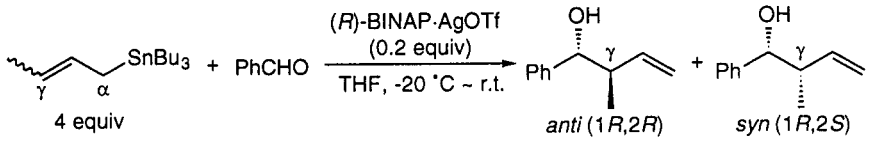
Enantioselective addition of an allyl group to carbonyl compounds to provide optically active secondary homoallylic alcohols is a valuable synthetic method since the products are readily transformed into β-hydroxy carbonyl compounds and various other chiral compounds (ref. 11). Although numerous important works on the reaction using a stoichiometric amount of chiral Lewis acids have been reported, there are few methods available for a catalytic process including a chiral (acyloxy)borane (CAB) complex (ref. 12) or a binaphthol-derived chiral titanium complex (ref. 13) as a catalyst. In contrast, we found that a BINAP·silver(I) complex also catalyzes the asymmetric allylation of aldehydes with allylic stannanes, and high γ-, anti-, and enantioselectivities are obtained by this method. The chiral phosphine-silver(I) catalyst can be prepared simply by stirring an equimolar mixture of chiral phosphine and silver(I) compound in THF at room temperature. Treatment of benzaldehyde with allyltributyltin under the influence of 5 mol % of (S)-BINAP·silver(I) triflate in THF at -20 °C provides the corresponding (S)-enriched homoallylic alcohol in 88% yield with 96% ee (ref. 14) (Scheme 6). The reaction furnishes high yields and remarkable enantioselectivities not only with aromatic aldehydes but also with α,β-unsaturated aldehydes and aliphatic aldehydes. Enantioselective addition of methallyltributylstannane to aldehydes can also be achieved using this method (ref. 15).



Scheme 6

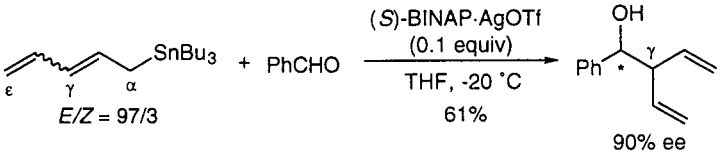
Condensation of γ-substituted allylmetals with aldehydes is a fascinating subject with respect to regioselectivity (α/γ) and stereoselectivity (E/Z or anti/syn). Addition of (E)-crotyltributyltin (E/Z = 95/5) to benzaldehyde in the presence of 20 mol % of (R)-BINAP·AgOTf in THF at -20 °C ~ r.t. exclusively gives the γ-adducts with an anti/syn ratio of 85/15 (ref. 15). The anti-isomer indicates 94% ee with a 1R,2R configuration. Use of (Z)-crotyltributyltin (E/Z = 2/98) or a nearly 1:1 mixture of the (E)- and (Z)-crotyltributyltin also results in a similar anti/syn ratio and enantioselectivity (Scheme 7).

Reaction of aldehydes with 2,4-pentadienylstannanes is also catalyzed by BINAP·silver(I) complex, and the corresponding γ-pentadienylated optically active alcohols are obtained with high enantioselectivity (ref. 16). When benzaldehyde is reacted with 1 equiv of pentadienyltributyltin (E/Z = 97/3) and 0.1 equiv of (S)-BINAP·AgOTf at -20 °C, the γ-product is obtained in 61% yield with 90% ee (Scheme 8). Pentadienyltrimethyltin offers a chemical yield and enantioselectivity comparable to those of pentadienyltributyltin. Ketones are inert under the standard reaction conditions.



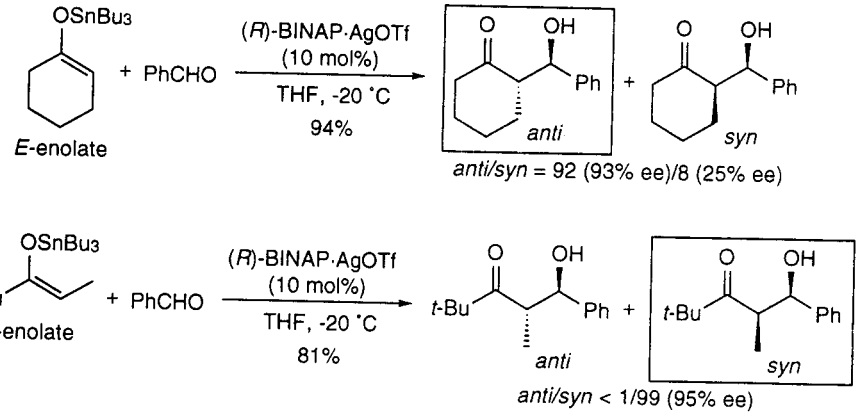
E/Z ratio of crotyltin	yield, %	anti (% ee)/syn (% ee)
95/5	56	85 (94)/15 (64)
2/98	72	85 (91)/15 (50)
53/47	45	85 (94)/15 (57)

Scheme 7

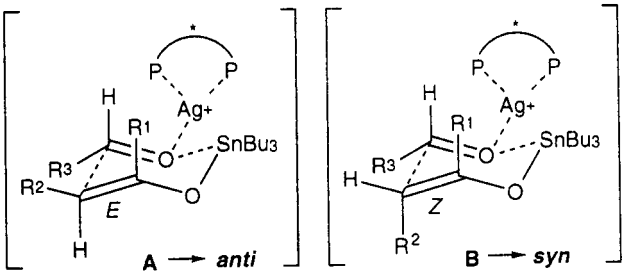


Scheme 8

The asymmetric Mukaiyama aldol reaction is a popular method for preparing optically active β-hydroxy carbonyl compounds, and has been widely applied to the synthesis of natural products. A variety of chiral Lewis acid catalysts have been developed for the enantioselective reaction of silyl enol ethers or ketene silyl acetals with carbonyl compounds (ref. 11c and 17). In contrast, the use of organotin(IV) enolates for aldol reactions has so far received little attention. Recently, we found that the aldol reaction of tributyltin enolates with aldehydes is catalyzed by a BINAP·silver(I) complex with high diastereo- and enantioselectivities (ref. 18). The tributyltin enolate is easily prepared from the corresponding enol acetate and tributyltin methoxide in the absence of solvent. The tin enolate thus obtained exists in O–Sn form and/or C–Sn form; however, both species can be used for the aldol reaction of the present system. Several different solvents were tested for the reaction and THF was found to provide the best result. The catalytic aldol reaction of a variety of tributyltin enolates with typical aromatic, α,β-unsaturated, and aliphatic aldehydes was investigated and the highest ee (95% ee) was obtained when the tin enolate prepared from pinacolone was added to benzaldehyde. Addition of substituted enol stannanes to aldehydes also proceeds to furnish high diastereo- and enantioselectivities using this chiral catalyst. For example, treatment of the tributyltin enolate of cyclohexanone (1 equiv) with benzaldehyde (1 equiv) under the influence of 10 mol % of (R)-BINAP·AgOTf complex in dry THF at -20 °C gives the optically active anti aldol product preferentially with an anti/syn ratio of 92/8. The anti-isomer indicates 93% ee with a 2S,1'R configuration. In contrast, the Z-enolate derived from tert-butyl ethyl ketone provides the syn aldol adduct nearly exclusively with 95% ee (Scheme 9). These results show that the diastereoselectivity depends on the geometry of enol stannane and that six-membered cyclic transition-state structures A and B are probable models (Scheme 10).



Scheme 9



Probable cyclic transition-state structures.

Scheme 10

REFERENCES

1. K. Maruoka, M. Ito and H. Yamamoto. *J. Am. Chem. Soc.* **117**, 9091 (1995).
2. S. Saito, K. Shimada, H. Yamamoto, E. Martínez de Marigorta and I. Fleming. *Chem Commun.* 1299 (1997).
3. S. Saito, K. Shimada, M. Ito, K. Maruoka and H. Yamamoto. in preparation.
4. S. Saito, T. Sone, K. Shimada and H. Yamamoto. in preparation.
5. S. Saito, M. Shiozawa, M. Ito and H. Yamamoto. *J. Am. Chem. Soc.* **120**, 813 (1998).
6. T. Mukaiyama. In Organic Reaction Vol. 28 (G. A. Boswell, Jr, R. F. Hirshmann, S. Danishefsky, A. S. Kende, H. W. Gschwend, L. A. Paquette, R. F. Heck, G. H. Posner, B. M. Trost and B. Weinstein, (eds.), pp. 203. John Wiley & Sons, New York (1982).
7. S. Saito, M. Shiozawa and H. Yamamoto. in preparation.
8. C. Fehr, *Angew. Chem. Int. Ed. Engl., 35*, 2566 (1996).
9. (a) K. Ishihara, M. Kaneeda and H. Yamamoto, *J. Am. Chem. Soc.*, **116**, 11179 (1994). (b) K. Ishihara, S. Nakamura and H. Yamamoto, *Croat. Chem. Acta*, **69**, 513 (1996). (c) For the enantioselective protonation of prochiral allyltrimethyltins, see: K. Ishihara, Y. Ishida, S. Nakamura and H. Yamamoto, *Synlett*, 758 (1997).
10. (a) K. Ishihara, S. Nakamura, M. Kaneeda and H. Yamamoto, *J. Am. Chem. Soc.*, **118**, 12854 (1996). (b) A. Yanagisawa, K. Ishihara and H. Yamamoto, Synlett, 411 (1997).
11. Reviews: (a) W. R. Roush. In Comprehensive Organic Synthesis (B. M. Trost, I. Fleming and C. H. Heathcock, eds.), vol. 2, pp. 1-53. Pergamon Press, Oxford (1991). (b) Y. Yamamoto and N. Asao. *Chem. Rev.* **93**, 2207 (1993). (c) T. Bach. *Angew. Chem. Int. Ed. Engl.* **33**, 417 (1994). (d) A. H. Hoveyda and J. P. Morken. *Angew. Chem. Int. Ed. Engl.* **35**, 1262 (1996).
12. (a) K. Furuta, M. Mouri and H. Yamamoto. *Synlett*, 561 (1991). (b) K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta and H. Yamamoto. *J. Am. Chem. Soc.* **115**, 11490 (1993).
13. (a) S. Aoki, K. Mikami, M. Terada and T. Nakai. *Tetrahedron* **49**, 1783 (1993). (b) A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi. *J. Am. Chem. Soc.* **115**, 7001 (1993). (c) G. E. Keck, K. H. Tarbet, L. S. Geraci. *J. Am. Chem. Soc.* **115**, 8467 (1993).
14. A. Yanagisawa, H. Nakashima, A. Ishiba and H. Yamamoto. *J. Am. Chem. Soc.* **118**, 4723 (1996).
15. A. Yanagisawa, A. Ishiba, H. Nakashima and H. Yamamoto. *Synlett*, 88 (1997).
16. A. Yanagisawa, Y. Nakatsuka, H. Nakashima and H. Yamamoto. *Synlett*, 933 (1997).
17. Reviews: (a) T. K. Hollis and B. Bosnich. J. Am. Chem. Soc. **117**, 4570 (1995). (b) M. Braun. In Houben-Weyl: Methods of Organic Chemistry (G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, eds.), vol. E 21, pp. 1730-1735. Georg Thieme Verlag, Stuttgart (1995). (c) S. G. Nelson. *Tetrahedron: Asymmetry* **9**, 357 (1998).
18. A. Yanagisawa, Y. Matsumoto, H. Nakashima, K. Asakawa and H. Yamamoto. *J. Am. Chem. Soc.* **119**, 9319 (1997).