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Design of Sophisticated Bidentate Lewis Acids and Organocatalysts for Fine Organic Synthesis

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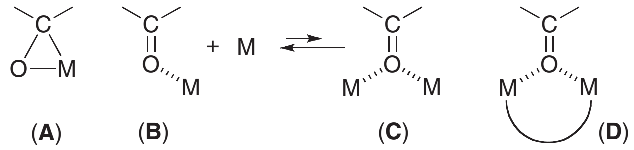
Apart from enzymes as biocatalysts, a broad repertoire of chiral reagents, auxiliaries, and catalysts have been developed in recent years. In this respect, the design of new catalysts and new reactions in an efficient manner is increasingly important in this century for the construction of new and useful molecules. Accordingly, by designing and synthesizing sophisticated metal and non-metal catalysts, hitherto unattainable, unusual reactivity and selectivity is pursued in synthetic organic reactions. For example, the rational design of designer Lewis acids, particularly bidentate Lewis acid catalysts and their application to selective organic synthesis is carried out. In addition, the design of chiral phase transfer catalysts, chiral bifunctional organocatalysts, and chiral Brønsted acid catalysts as promising organocatalysts is realized for their application to practical asymmetric synthesis.

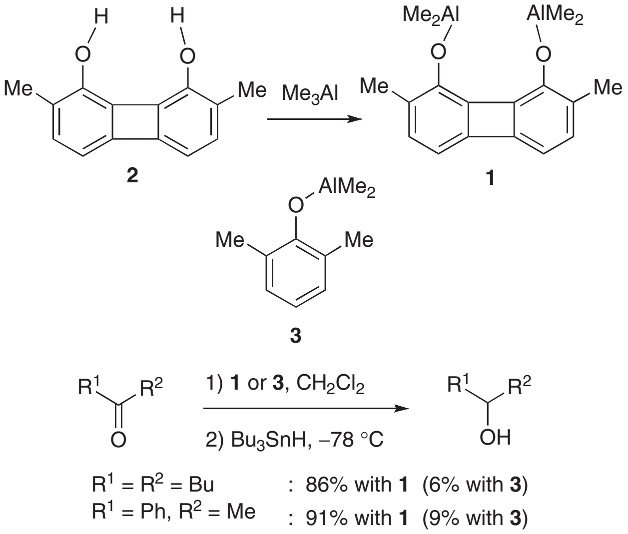
1. Chemistry of Bidentate Lewis Acid Catalysts

Electrophilic activation of carbonyl groups with certain Lewis acids is a well-established method for enhancing their reactivity and selectivity toward nucleophilic addition. The two principal modes of coordination of carbonyls to metals are π-bonding (**A**) and σ-bonding (**B**) as shown in Scheme 1.[1] The latter mode is generally preferred with main-group and early-transition metal Lewis acids. In addition, simultaneous coordination to carbonyl groups with two metals of type (**C**) would alter the reactivity and selectivity of the carbonyl substrates. Examples of such double coordination with two metals are rare despite its potential importance, simply because of the high preference for the single coordination mode (**B**) even in the presence of excess Lewis acids, and hence the nature of such di-σ-bonding (**C**) remains elusive. In this context, we have been interested in the possibility of designing bidentate Lewis acids that are capable of preferable di-σ-bonding (**D**) with two metals. Among various main-group and early-transition metal elements, aluminum and titanium seem to be the metals of choice in view of their high affinity toward oxygen. In the first part of this account, I wish to introduce our recent study on this subject by using modified bis(organoaluminum) and bis(titanium) reagents for the efficient simultaneous coordination toward carbonyls, thereby elucidating the characteristics of the double electrophilic activation of carbonyl substrates.



Scheme 1. The coordination mode of carbonyls to metals.

1.1 Bidentate Aluminum Lewis Acids. The requisite bidentate ligand, 2,7-dimethyl-1,8-biphenylenediol (**2**) was synthesized according to a literature procedure,[2] and the bidentate organoaluminum reagent, (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**1**) was prepared by treatment of the biphenylenediol **2** with Me_3Al (2 equiv) in CH_2Cl_2 at room temperature (Scheme 2).[3,4] Initial complexation of 5-nonanone with the in situ generated **1** (1.1 equiv) in CH_2Cl_2



Scheme 2. Preparation and evaluation of bidentate aluminum reagent.

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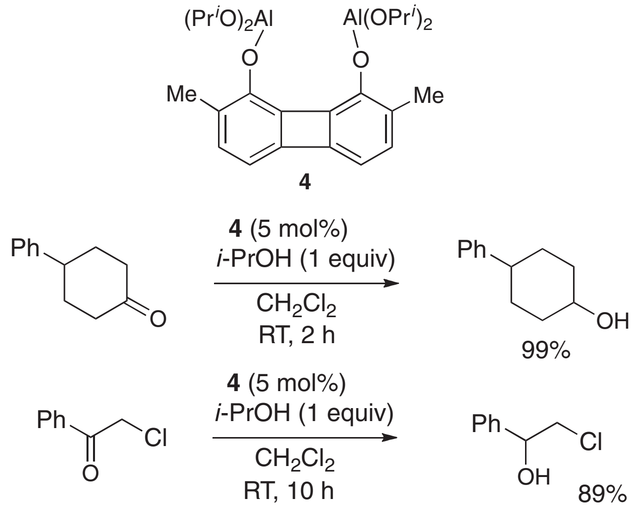
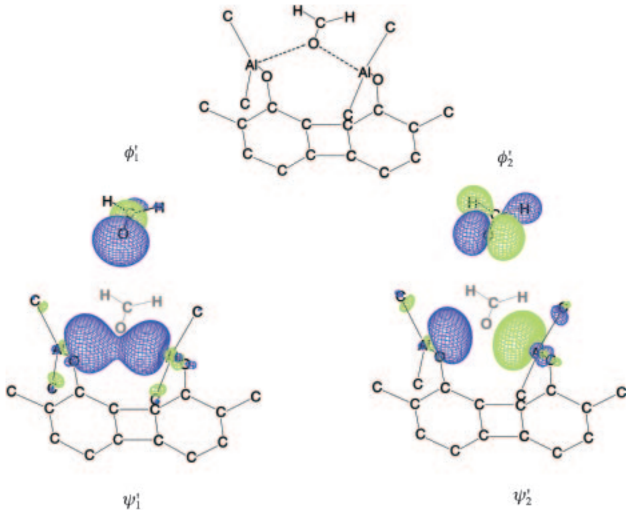
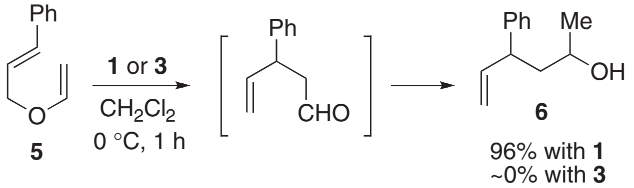


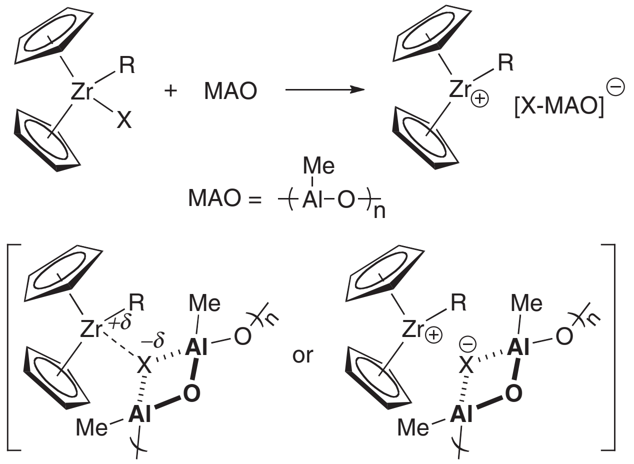
Scheme 3. Modern Meerwein–Ponndorf–Verley (MPV) reaction.



Scheme 4. Theoretical calculation of bidentate **1**/carbonyl complex.



Scheme 5. Bidentate Lewis acid-promoted Claisen rearrangement.



Scheme 6. Activation mode of metallocene catalysts with MAO.

and subsequent reaction of Bu_3SnH (1.2 equiv) at −78 °C for 20 min gave rise to the corresponding 5-nonanol in 86% yield. In marked contrast, however, reduction of 5-nonanone with Bu_3SnH in the presence of monodentate organoaluminum reagent **3** (prepared from 2,6-xylenol and Me_3Al (1:1 molar ratio)) under similar reaction conditions afforded 5-nonanol in only 6% yield. These results clearly demonstrate that the bidentate Lewis acid **1** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of carbonyl moiety. It should be noted that reduction of excess 5-nonanone (2 equiv) with bidentate **1** (1.1 equiv)/Bu_3SnH (2.4 equiv) in CH_2Cl_2 at −78 °C for 20 min gave 5-nonanol in 47% yield, suggesting the intervention of the 1:1 ketone/Lewis acid complex even in the presence of excess ketone. Furthermore, use of excess **3** (2 equiv) resulted in formation of 5-nonanol in 10% yield, implying the favorable monocoordination complex (**B**) with excess Lewis acids. A similar tendency is observed in the acetophenone carbonyl reduction.

Later, this finding was successfully utilized for the development of a modern Meerwein–Ponndorf–Verley (MPV) reaction by designing bidentate Lewis acid, (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum) (**4**) (Scheme 3).^{5}

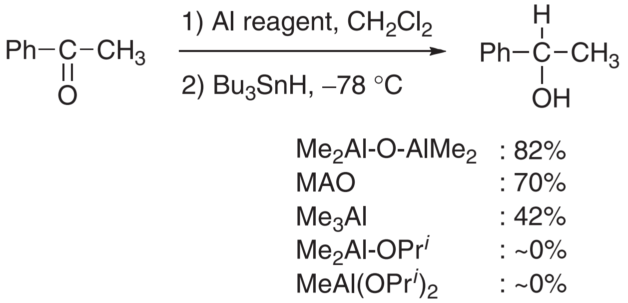
Although the simultaneous coordination and activation of carbonyl moiety to two aluminum atoms are supported by the above experiments, the formation of bidentate Lewis acid **1**/carbonyl complex is also verified by theoretical calculation using Gaussian 98 (Scheme 4). Namely, formaldehyde was chosen as a model substrate, and the structural optimization of the complex with **1** was carried out at the B3LYP/6-31G* level.^{6}

The high double coordination ability of bidentate Lewis acid **1** is, in principle, applicable to the activation of the ethereal substrates as exemplified by the Lewis acid-promoted Claisen rearrangement of allyl vinyl ethers. Indeed, treatment of *trans*-cinnamyl vinyl ether (**5**) with bidentate **1** in CH_2Cl_2 at 0 °C produced the rearrangement–methylation product **6** in 96% yield (Scheme 5).^{4a} With monodentate Lewis acid **3**, however, the reaction is very sluggish, resulting in almost total recovery of the starting material under comparable reaction conditions.

In addition to biphenylenediol, water is also assumed to be an appropriate spacer for preparing bidentate Al Lewis acids. In the olefin polymerization reactions, metallocene catalysts can be utilized as catalyst by combining use of MAO as cocatalyst, where we assume that a metallocene cationic catalyst might be generated by ligand abstraction using MAO with the Al–O–Al unit as shown in Scheme 6.

In order to verify our hypothesis, the electrophilic reduction of ketone was carried out with various modified aluminum reagents. Thus, reduction of acetophenone with Bu_3SnH in the presence of MAO furnished phenethyl alcohol in 70% yield. Here, which unit, O–Al–O or Al–O–Al in MAO is more important ? $MeAl(OPr^i)_2$, which has the O–Al–O unit, gave none of the reduction product. However, bis(dimethylaluminoxane) possessing an Al–O–Al unit shows high reactivity, which is even better than the parent Me_3Al. These results indicate the importance of the Al–O–Al unit for the activation of carbonyl by the double coordination (Scheme 7).[7]

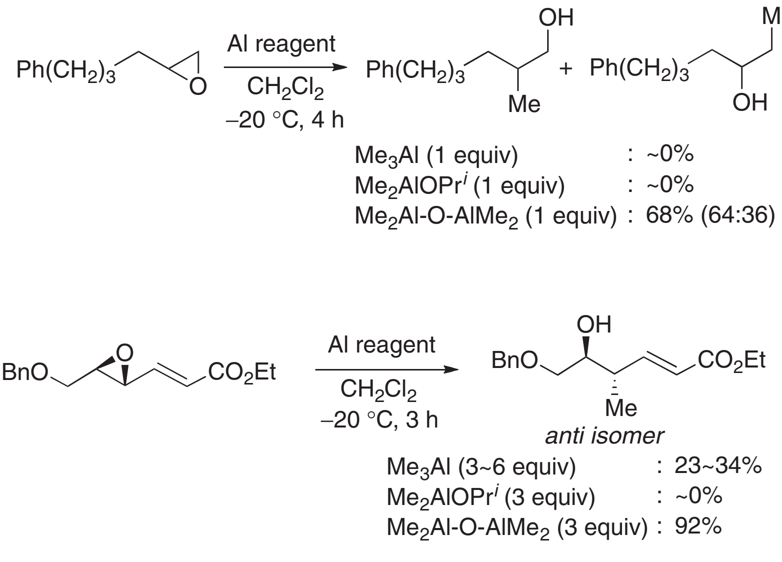
Such double activation can be also observed for epoxy substrates (Scheme 8). For example, functionalized epoxide reacted slowly with Me_3Al or Me_2AlOPr^i, but bis(dimethylaluminoxane) afforded epoxide cleavage products very cleanly in high yield by way of the double coordination intermediates.[7]



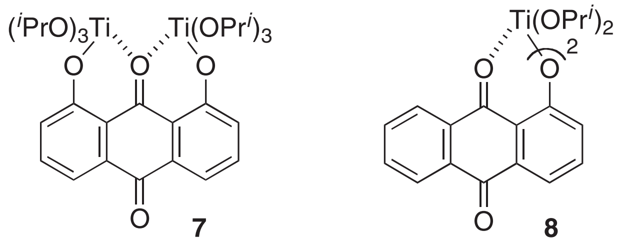
Scheme 7. Reduction of acetophenone with various aluminum reagents.

1.2 Bidentate Titanium Lewis Acids. In view of the wide applicability and versatility of titanium-based Lewis acids in selective organic synthesis including asymmetric synthesis,[8] we set out to design a new, bidentate bis-titanium catalyst of type **7** derived from a feeble Lewis acid, $Ti(OPr^i)_4$, and elucidated the double coordination phenomena toward carbonyl substrates by several synthetic examples.[9]

The bis-titanium catalyst **7** can be readily prepared by mixing commercially available 1,8-dihydroxyanthraquinone with $Ti(OPr^i)_4$ (2 equiv) in CH_2Cl_2 at 25 °C (Scheme 9). The simultaneous coordination of two titanium atoms to one anthraquinone carbonyl is verified by ^{13}C NMR analysis of the bis-titanium catalyst **7** [δ 207.38 and 183.89 (activated and non-activated C=O of **7**): cf. δ 184.03 and 182.60 (activated and non-activated C=O of **8**); δ 183.34 (C=O of anthraquinone)]. Similarly, the corresponding mono-titanium catalyst **8** was obtained from 1-hydroxyanthraquinone and $Ti(OPr^i)_4$, though 2 equiv of 1-hydroxyanthraquinone is replaced by isopropoxy ligands in this particular case. Complexation of 4-*tert*-butylcyclohexanone with the in situ generated bis-titanium catalyst **7** (10–20 mol %) in CH_2Cl_2 and subsequent treatment with Bu_3SnH (1.1 equiv) at −20 °C and at 20 °C for 6 h afforded 4-*tert*-butylcyclohexanol in 74–99% yield (Scheme 10).[9a] The *i*-PrOH-free catalyst **7**, which was also prepared from 1,8-dihydroxyanthraquinone and $Ti(OPr^i)_4$ (2 equiv) in CH_2Cl_2 by azeotropic removal of *i*-PrOH, gave similar results (97–99% with 20 mol % catalyst) in the reduction of 4-*tert*-butylcyclohexanone with Bu_3SnH. In

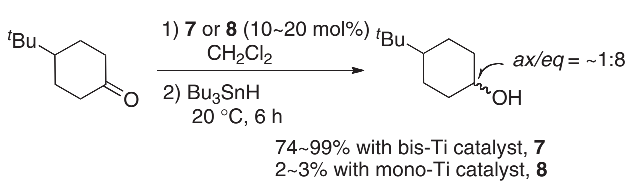


Scheme 8. Selective cleavage of epoxy substrates with bis(dimethylaluminoxane).

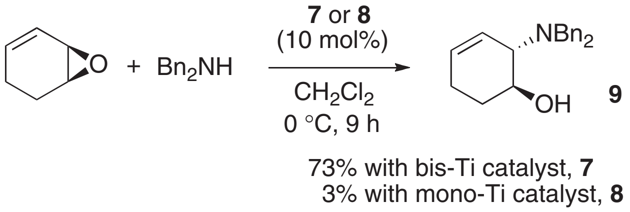


7 **8**

Scheme 9. Bidentate and monodentate titanium catalysts.



Scheme 10. Reduction of 4-*tert*-butylcyclohexanone with bis-Ti and mono-Ti catalysts.

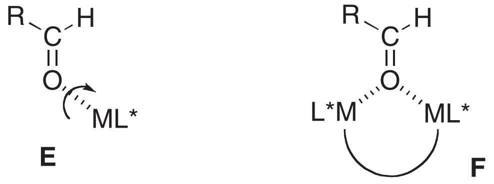


Scheme 11. Selective cleavage of epoxide with Ti catalysts.

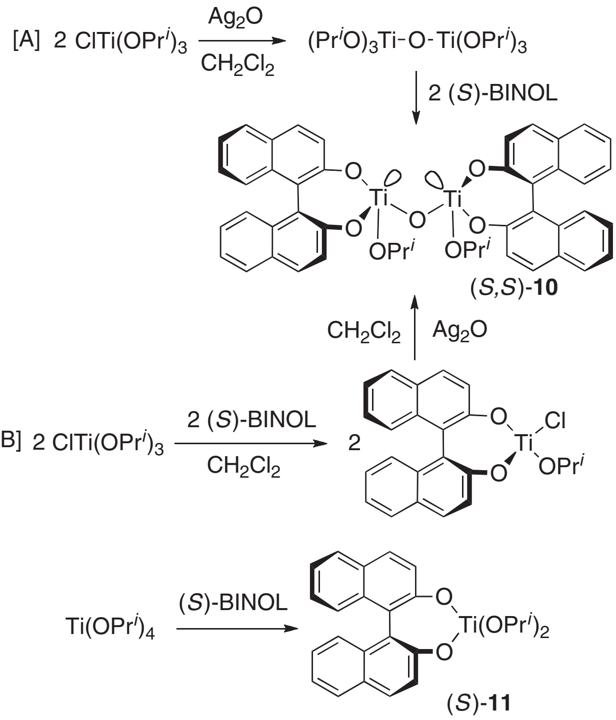
marked contrast, however, reduction of 4-*tert*-butylcyclohexanone with mono-titanium catalyst **8** (10–20 mol %) under otherwise similar reduction conditions gave 4-*tert*-butylcyclohexanol in only 2–3% yield. Further, use of $Ti(OPr^i)_4$ resulted in total recovery of the starting ketone. These results clearly demonstrate that the bidentate Ti catalyst **7** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of carbonyl moiety. It should be noted that attempted use of catalytic $ClTi(OPr^i)_3$ and $Cl_2Ti(OPr^i)_2$ (10 mol %) for this reduction afforded 4-*tert*-butylcyclohexanol (ax/eq = ca. 1:2) in low yields (10 and 16%, respectively, at 20 °C for 6 h).

In addition to the double activation of carbonyl moiety, the synthetic application of bidentate Ti catalyst is further illustrated by the regio- and stereoselective ring-opening of epoxides with amine bases (Scheme 11).[9a] For example, treatment of cyclohexadiene monoepoxide with dibenzylamine (1.1 equiv) in CH_2Cl_2 under the influence of catalytic bis-titanium **7** (10 mol %) at 0 °C gave amino alcohol **9** (73% yield) with rigorous regio- and stereoselectivity, while replacement of bis-titanium **7** by mono-titanium **8** under otherwise identical reaction conditions afforded **9** in only 3% yield.

1.3 Chiral Bidentate Titanium Lewis Acids. Our attention has now been focused on asymmetric catalytic synthesis with chiral, bidentate Ti Lewis acid catalysts. As a fundamental yet powerful C–C bond-forming reaction, enantioselective allylation of aldehydes attracts considerable attention in asymmetric synthesis.[10] Given the versatile chemistry of the resulting homoallylic alcohols,[11] this asymmetric transformation constitutes a valuable process. Despite considerable recent progress in this area using a stoichiometric amount of chiral Lewis acids, only a few types of reagents have been reported for catalytic versions, and continuing improvements in the efficiency of these acids have been made within the field of asymmetric catalysis. For instance, in the case of cinnamaldehyde, previously reported catalytic processes generally exhibited less satisfactory enantioselectivity (ca. 90% ee). This is mainly because previous strategies utilize a single coordination complex **E** between aldehyde and chiral monodentate Lewis acids which inevitably causes free rotation at the M–O bond, and it seems difficult to overcome this intrinsic problem by the approaches currently known (Scheme 12). In this context, we are interested in the possiblity of forming double coordination complex **F** with chiral bidentate Lewis acids, thereby allowing more precise enantioface discrimination of aldehyde carbonyl. Accordingly, we have developed a new catalytic, practical enantioselective allylation of aldehydes with allyltributyltin using a newly designed, chiral bidentate Ti^{IV} complex of type **10**.



Scheme 12. Coordination mode of carbonyls to monodentate vs. bidentate Lewis acids.

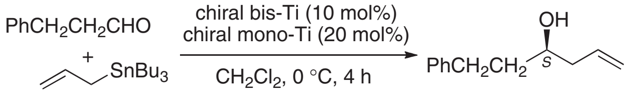


Scheme 13. Preparation of chiral bis-Ti and mono-Ti catalysts.

The requisite bis-Ti^{IV} oxide (*S*,*S*)-**10** was synthesized by two different routes [A] and [B] starting from triisopropoxytitanium chloride, $ClTi(OPr^i)_3$ as shown in Scheme 13.[12] Positive ESI-MS clearly showed an m/z peak at 943 ($M{\cdot}2THF + H^+$), indicating the formation of (*S*,*S*)-**10**•2THF coordination complex by comparison with the theoretical molecular ion peak.

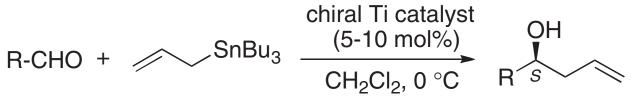
Reaction of hydrocinnamaldehyde with allyltributyltin (1.1 equiv) under the influence of in situ generated chiral bis-Ti^{IV} oxide (*S*,*S*)-**10** (10 mol %) [prepared by method A] in CH_2Cl_2 at 0 °C for 4 h afforded (*S*)-1-phenyl-5-hexen-3-ol in 84% yield with 99% ee (Scheme 14).[12] Notably, both the reaction rate and the enantioselectivity of the allylation are much lowered (e.g., 10% yield and 72% ee for hydrocinnamaldehyde) under similar reaction conditions with a chiral mono-Ti^{IV} catalyst **11** (20 mol %).[12] Alternatively, chiral bis-Ti^{IV} oxide (*S*,*S*)-**10**, prepared by method B, exhibited similar reactivity and enantioselectivity (81% yield with 98% ee) compared to the same catalyst by method A.

Other selected examples are listed in Scheme 15. Several characteristic features of the present allylation follow: (1) The chiral bis-Ti^{IV} oxide (*S*,*S*)-**10** exhibits uniformly high asymmetric induction as well as high chemical yield. (2) The use of



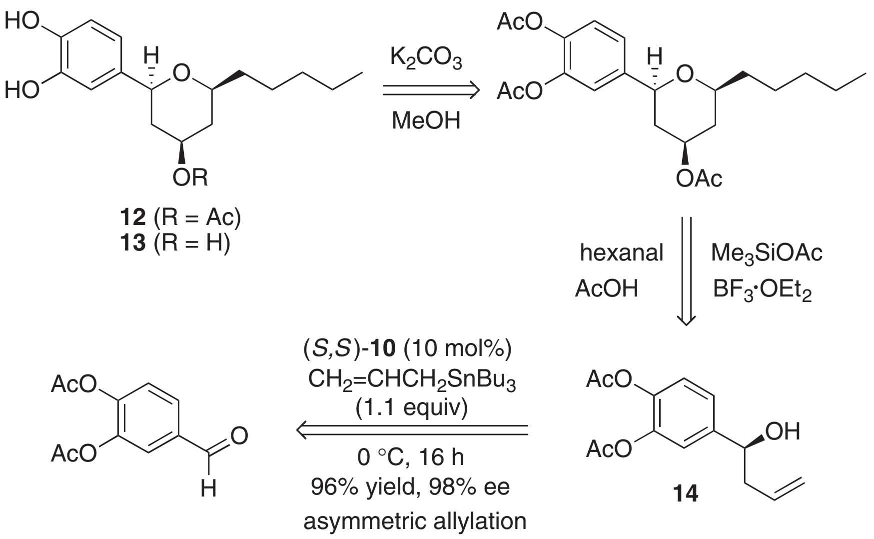
10% (72% ee) with mono-Ti
84% (99% ee) with bis-Ti [A]
81% (98% ee) with bis-Ti [B]

Scheme 14. Asymmetric allylation with chiral bis-Ti and mono-Ti catalysts.



R = $(CH_2)_6CH_3$: 99% ee (85%)
R = CH_2CH_2Ph : 99% ee (84%)
R = $CH(CH_3)_2$: >99% ee (71%)
R = CH=CHPh : 97% ee (77%)
R = *p*-Br-C_6H_4 : 98% ee (85%)
R = 2-Furyl : 97% ee (96%)

Scheme 15. Asymmetric allylation of various aldehydes with bis-Ti^{IV} catalyst (*S*,*S*)-**10**.



12 (R = Ac)
13 (R = H)

14

Scheme 16. Synthesis of tetrahydropyrans **12** and **13** via asymmetric allylation.

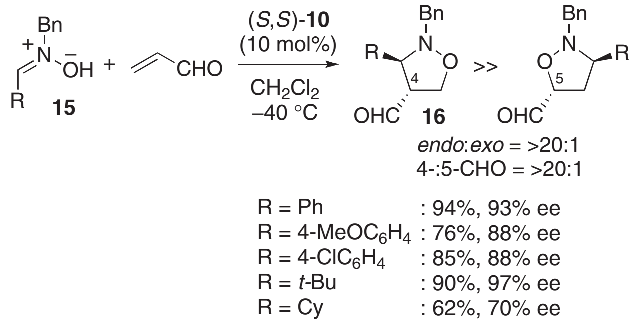
Ti–O–Ti unit in the chiral bis-Ti^{IV} catalyst (*S*,*S*)-**10** toward aldehyde carbonyls strongly accelerates the rate of allylation compared to the corresponding mono-Ti^{IV} catalyst **11**. (3) The enantioselectivity of the present allylation is not very sensitive to the reaction temperature.

The allylation products of aldehydes are useful intermediates for natural product syntheses.[13] For example, quite recently Willis reported the syntheses of tetrahydropyrans **12** and **13**,[14] starting from 3,4-diacetoxybenzaldehyde. These compounds, isolated from extracts of *Plectranthus sylvestris* (*Labiatae*), are in vitro potent antioxidants, inhibiting the Fe^{2+}-catalyzed autooxidation of linoleic acid, and possess anti-inflammatory properties. The crucial asymmetric allylation step was originally realized by Brown's method.[15] This procedure required stoichiometric amount of chiral boron reagent (1.39 equiv (−)-DIPCl) and gave a less satisfactory result (76% yield and 90% ee). In contrast, treatment of 3,4-diacetoxybenzaldehyde with allyltributyltin in the presence of catalytic (*S*,*S*)-**10** (10 mol %) at 0 °C for 16 h afforded the desired homoallylic alcohol **14** in 96% yield and 98% ee (Scheme 16). Hence, our method was apparently far superior in terms of catalyst loading, chemical yield, and enantioselectivity.

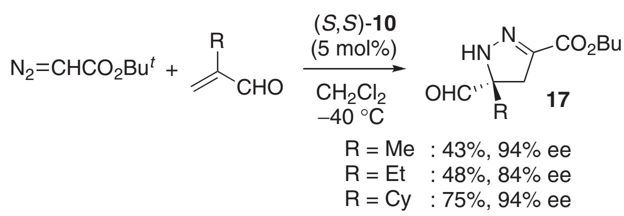
Despite the steady progress of chiral Lewis acid-catalyzed 1,3-dipolar cycloaddition of nitrones and α,β-unsaturated aldehydes, ordinary synthetic approaches suffered from the generation of two regioisomeric products, especially in the reaction of acyclic nitrones, although the endo selectivity was uniformly high with almost no exception. In addition, use of *N*-phenyl nitrones hampered the elaboration of the cycloadducts due to the difficulty to remove the phenyl functionality by a conventional deprotection method. In this context, the chiral bis-Ti^{IV} catalyst (*S*,*S*)-**10** was found to act as suitable promoter of the highly regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition of *N*-benzyl nitrones **15** and α,β-unsaturated aldehydes, which have been unattainable by the use of other chiral Lewis acids (Scheme 17).[16] For example, acrolein was utilized as a reactive α,β-unsaturated aldehyde under the influence of chiral bis-Ti^{IV} catalyst (*S*,*S*)-**10** to give the enantioenriched cycloadducts with the exclusive formation of the 4-CHO-*endo* adduct **16**. As for the C-substituent of nitrones, both electron-rich and electron-withdrawing groups were tolerated, as well as bulky alkyl group such as *t*-butyl.

Asymmetric 1,3-dipolar cycloaddition reaction of α-alkyl-α,β-unsaturated aldehydes and alkyl diazoacetates has been also developed by using the chiral bis-Ti^{IV} catalyst (*S*,*S*)-**10**.[17] With this methodology in hand, various chiral 2-pyrazolines **17** containing a quaternary stereogenic center were obtained in high to excellent enantioselectivities (up to 95% ee) (Scheme 18).

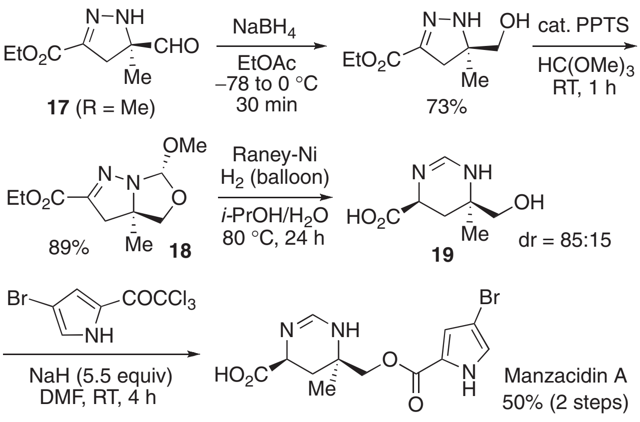
The synthetic utility of the optically enriched 2-pyrazoline thus obtained was demonstrated in the short synthesis of Manzacidin A (Scheme 19).[17] The synthesis of Manzacidin A



Scheme 17. Selective 1,3-dipolar cycloaddition of *N*-benzylnitrone **15** with (*S*,*S*)-**10**.



Scheme 18. Asymmetric 1,3-dipolar cycloaddition of diazoacetates.

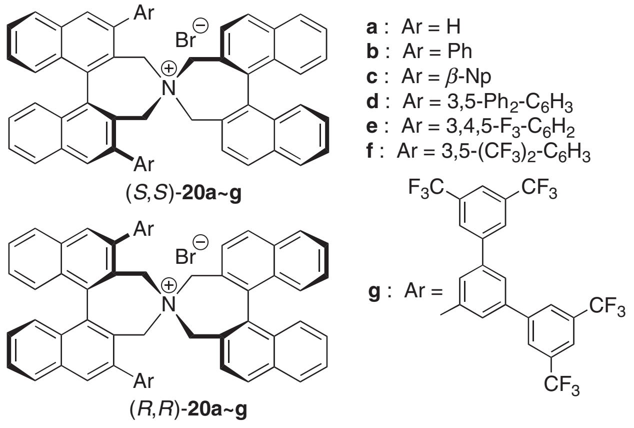


Scheme 19. Short synthesis of Manzacidin A.

began with reduction of the formyl group of 2-pyrazoline **17** (R = Me), followed by treatment with methyl orthoformate, which can be incorporated into the tetrahydropyrimidine ring as the amidine carbon in the following step. The resulting bicyclic compound **18** was then treated with Raney-nickel to give tetrahydropyrimidine **19** as a result of several reactions involving hydrolysis of the formamide acetal, reduction of the CN double bond, the reductive cleavage of the N–N bond, formation of the cyclic amidine, and hydrolysis of the ester. Finally, esterification of tetrahydropyrimidine **19** gave Manzacidin A.

2. Design of Spiro-Type Chiral Phase-Transfer Catalysts

The chemical community has witnessed the exponential growth of phase-transfer catalysis as a practical methodology for organic synthesis, featuring simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and possibility to conduct large-scale preparations.[18] Nowadays, it appears to be a prime synthetic tool being appreciated in various fields of organic chemistry, and also find widespread industrial applications. On the other hand, the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, non-racemic catalysts has progressed rather slowly, despite the great importance to create a new domain in modern asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetraalkylonium cations. However, recent enormous efforts toward this direction have resulted in notable achievements, making it feasible to perform various bond formation reactions under mild phase-transfer-catalyzed conditions.[19] The subsequent section illustrates our recent development on the design of various types of chiral phase-transfer catalysts, which are highly environmentally benign and apply them to practical asymmetric synthesis of useful organic molecules, mainly amino acid derivatives.

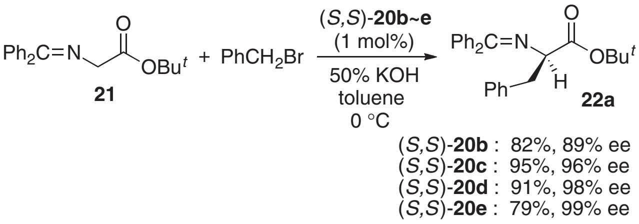


Scheme 20. Binaphthyl-modified C_2-symmetric chiral phase-transfer catalysts.

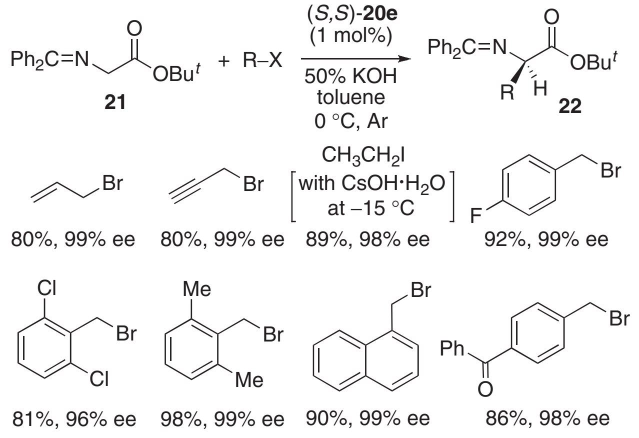
2.1 Asymmetric Synthesis of α-Alkyl-α-amino Acids.

Since the initial work of O'Donnell et al. in 1989,[20] asymmetric synthesis of α-alkyl-α-amino acids by asymmetric phase-transfer alkylation of a prochiral protected glycine derivative using a chiral catalyst has become an attractive method for the preparation of both natural and unnatural amino acids.[19] However, when we started asymmetric phase transfer chemistry in 1998, almost all the elaborated chiral phase-transfer catalysts had been restricted to *cinchona* alkaloid derivatives, which unfortunately constituted a major difficulty in rationally designing and fine-tuning of catalysts to attain sufficient reactivity and selectivity. In this context, the structurally rigid, chiral spiro ammonium salts of type **20** derived from commercially available (*S*)- or (*R*)-1,1′-bi-2-naphthol have been designed as new C_2-symmetric chiral phase-transfer catalysts and successfully applied to the highly efficient, catalytic asymmetric synthesis of various α-alkyl-α-amino acids under mild phase-transfer conditions (Scheme 20).[21]

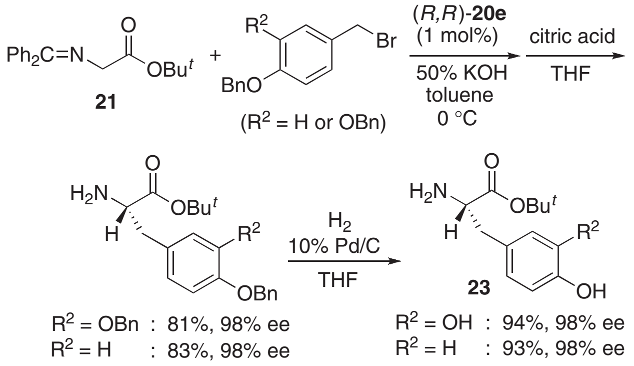
Attempted benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **21** with 1 mol % of symmetric (*S*,*S*)-**20a** in 50% aqueous NaOH–benzene (volume ratio = 1:3) at room temperature afforded the corresponding benzylation product **22a** in 76% yield and 73% ee. Introduction of aromatic substituents (Ar) on the 3,3′-position of one binaphthyl subunit of the catalyst afforded a beneficial effect on the enantiofacial discrimination, and a similar reaction in toluene under the



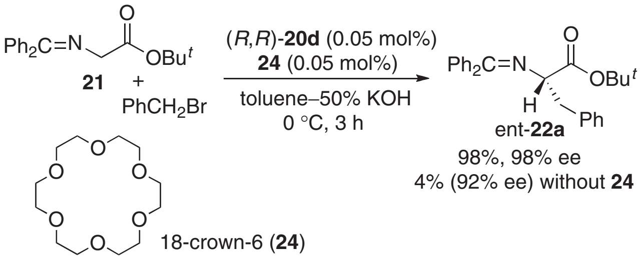
Scheme 21. Asymmetric alkylation of glycine derivative with catalysts (*S*,*S*)-**20**.



Scheme 22. Generality in the asymmetric alkylation of glycine derivative with (*S*,*S*)-**20e**.



Scheme 23. Asymmetric synthesis of L-Dopa and its analog.



Scheme 24. Acceleration effect of 18-crown-6 in the asymmetric alkylation of glycine derivative.

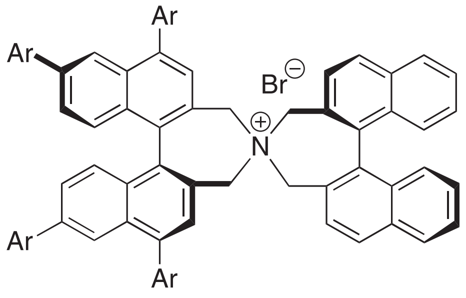
influence of (*S*,*S*)-**20b** gave the product **22a** in 82% yield and 89% ee (Scheme 21). Switching the catalyst to (*S*,*S*)-**20c** and sterically more hindered (*S*,*S*)-**20d** further increased the enantioselectivity to 96% ee and 98% ee, respectively, and virtually complete stereochemical control was achieved using (*S*,*S*)-**20e** as catalyst.[21,22] The lower chemical yield (79%) with (*S*,*S*)-**20e** was ascribed to the intervention of enolate oxidation by aerobic oxygen and was improved to 90% by simply performing the reaction under argon atmosphere. In the case of a reactive alkyl halide, the catalyst loading can be reduced to 0.2 mol % without loss of enantiomeric excess.[22]

(*S*,*S*)-**20e** is the catalyst of choice for the preparation of a variety of essentially enantiopure α-alkyl-α-amino acids by this transformation (Scheme 22). Facile asymmetric synthesis of α-alkyl-α-amino acids, which is usually inaccessible by enzymatic processes, becomes feasible by employing appropriate electrophiles such as ortho-disubstituted benzyl bromides. In the reaction with the simple alkyl halides such as ethyl iodide, use of aqueous cesium hydroxide (CsOH) as a basic phase at lower reaction temperature is generally recommended.[22] Since both enantiomers of the catalyst of type **20** can be readily available from either (*R*)- or (*S*)-1,1′-bi-2-naphthol, a wide variety of natural and unnatural α-alkyl-α-amino acids can be synthesized in an enantiomerically pure form by the catalytic phase transfer alkylation of **21**.

The synthetic utility of chiral phase-transfer catalysis by **20** was highlighted by the facile synthesis of L-Dopa ester **23** ($R^2 = OH$) and its analog, which have usually been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease (Scheme 23). The successful asymmetric synthesis of natural tyrosine *tert*-butyl ester **23** ($R^2 = H$) in a similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogs.[23]

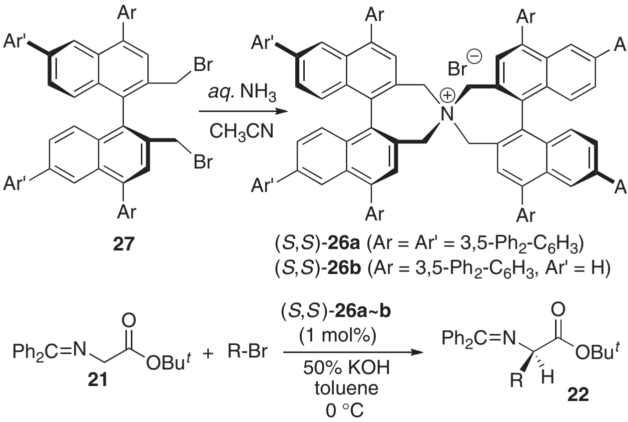
In order to fully induce the potential catalytic activity of *N*-spiro chiral ammonium salts such as **20d**, we have developed binary phase transfer catalysis using an appropriate achiral co-catalyst. For instance, the phase-transfer-catalyzed alkylation of **21** with benzyl bromide under the influence of (*R*,*R*)-**20d** (0.05 mol %) turned out to be sluggish to give **22a** in only 4% yield (92% ee), while benzylation of **21** in the presence of 18-crown-6 (**24**) (0.05 mol %) under similar conditions proceeded smoothly to furnish **22a** in 98% yield and 98% ee (Scheme 24).[24] The origin of this dramatic rate enhancement would be the ability of the crown ether to extract KOH into the toluene phase, thereby accelerating the otherwise slow deprotonation. Interestingly, achiral tetrabutyl- and tetraoctylammonium bromides are also employable for this purpose.

In this series of this work, introduction of 3,3′-diaryl substituents to the parent symmetric ammonium bromide **20a** is found to be crucially important for obtaining high enantioselectivity. In this regard, we have been interested in the possibility of examining the effect of adjacent 4,4′-substituents of the catalyst rather than 3,3′-substituents in the asymmetric phase-transfer alkylations.[25] Interestingly, even 4,4′-diaryl substituents on type **25** catalysts exhibited unexpectedly high asymmetric induction in such asymmetric phase-transfer alkylations. For example, asymmetric alkylation of **21** with benzyl bromide in toluene–50% aqueous KOH under the influence of 1 mol % of catalyst (*S*,*S*)-**25a** gave rise to benzylation product **22a** in 90% yield with 91% ee (Scheme 25). The observed enantioselectivity is rather surprising compared to



(*S*,*S*)-**25a** (Ar = Ph)
(*S*,*S*)-**25b** (Ar = 3,5-Ph_2-C_6H_3)

Scheme 25. 4,4′-Diaryl-substituted phase-transfer catalyst.

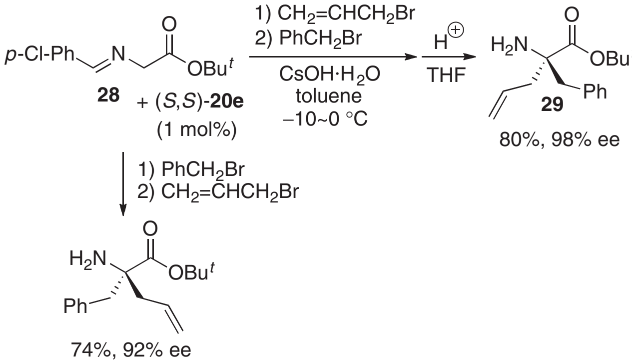


R = CH_2Ph with (*S*,*S*)-**26a**: 87%, 97% ee
with (*S*,*S*)-**26b**: 86%, 96% ee
R = $CH_2CH{=}CH_2$ with (*S*,*S*)-**26a**: 76%, 93% ee
with (*S*,*S*)-**26b**: 91%, 92% ee

Scheme 26. Binaphthyl-modified symmetric phase-transfer catalysts.

that (89% ee) using 3,3′-diphenyl-substituted **20b** under similar reaction conditions. Sterically more hindered 4,4′,6,6′-tetrakis(3,5-diphenylphenyl)binaphthyl analog (*S*,*S*)-**25b** was also prepared and applied to the asymmetric alkylation of **21** to furnish the alkylation product **22** with slightly higher enantioselectivity (96% ee) and shorter reaction time (cf., 98% ee in the asymmetric benzylation of **21** with **20d** under similar phase-transfer conditions).

On the other hand, we were intrigued with the preparation of symmetric *N*-spiro type catalyst to avoid the independent synthesis of two different binaphthyl-modified subunits required for **20**. Along this line, 4,4′,6,6′-tetraarylbinaphthyl-substituted ammonium bromide **26** was assembled through the reaction of aqueous ammonia with bis-bromide **27** on the basis of our study of the substituent effect of this type of salt (Scheme 26). Evaluation of **26** as a chiral phase-transfer catalyst in the alkylation of **21** uncovered its high catalytic and chiral efficiency.[26]

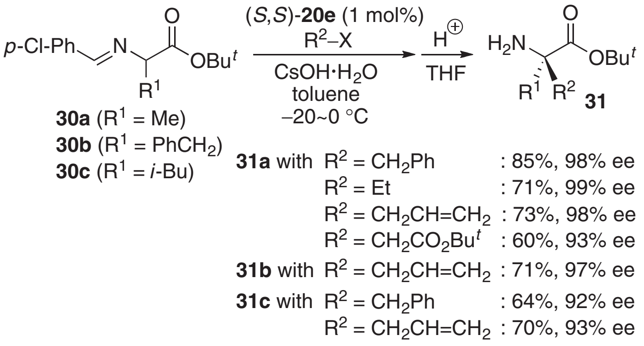


Scheme 27. Synthesis of both enantiomeric α,α-dialkyl-α-amino acids.

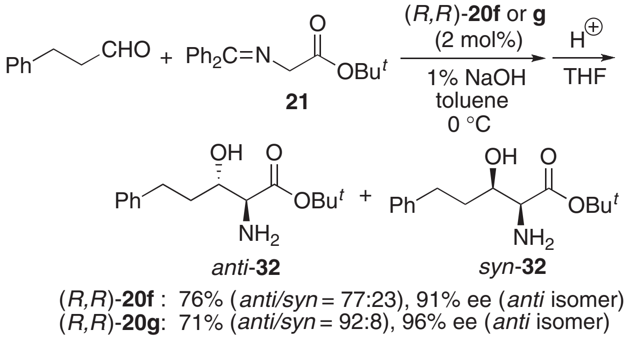
2.2 Asymmetric Synthesis of α,α-Dialkyl-α-amino Acids. With this basic information at hand, our attention has been focused on the α,α-dialkyl-α-amino acid synthesis. We envisioned that two different side chains could be introduced directly to the aldimine Schiff base **28** derived from glycine in a highly enantioselective manner by appropriate chiral phase-transfer catalysis. This possibility of one-pot asymmetric double alkylation has been realized by using C_2-symmetric chiral quaternary ammonium bromide (*S*,*S*)-**20** (Scheme 27).[27] Initial treatment of the toluene solution of **28** and (*S*,*S*)-**20c** (1 mol %) with allyl bromide and $CsOH{\cdot}H_2O$ and the subsequent reaction with benzyl bromide resulted in formation of the double alkylation product **29** in 61% yield and 87% ee after hydrolysis. It is of interest that the use of (*S*,*S*)-**20e** as catalyst under similar conditions enhanced both the chemical yield and the enantioselectivity to 80% and 98% ee, respectively.[27] The distinct feature of this procedure is that it enables straightforward asymmetric synthesis of various α,α-dialkyl-α-amino acids including those otherwise inaccessible from the naturally occurring amino acids. Notably, in the double alkylation of **28** by the addition of the halides in a reverse order, the absolute configuration of the product was confirmed to be opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation stage. This double alkylation procedure works well only for reactive alkyl halides.

Since the stereochemistry of the newly created quaternary carbon center was apparently determined in the second alkylation process, the core of this method should be applicable to the asymmetric alkylation of aldimine Schiff base **30** derived from the corresponding α-amino acids. Indeed, rapid benzylation of DL-alanine-derived imine **30a** occurred in toluene with benzyl bromide and $CsOH{\cdot}H_2O$ using (*S*,*S*)-**20e** (1 mol %) as a catalyst, giving the alkylation product **31** (R^1 = Me, R^2 = CH_2Ph; 85%) in an almost enantiomerically pure form (98% ee). Other selected results demonstrate the remarkable efficiency and generality of this method (Scheme 28).[27] Use of *tert*-butyl α-bromoacetate as an alkylating agent allows facile enantioselective access to α-methyl aspartic acid and asymmetric synthesis of α-methyl tryptophan, an important amino acid for the design of dipeptoid with high affinity for the central cholecystokinin receptor, can also be realized. In addition, the phase-transfer catalytic alkylation of aldimine Schiff base derived from other α-alkyl-α-amino acids such as DL-phenylalanine (**30b**) and DL-leucine (**30c**) also appeared to be feasible with high efficiency, providing the desired non-coded amino acid esters **31** with excellent asymmetric induction.

2.3 Asymmetric Synthesis of β-Hydroxy-α-amino Acids. Although phase-transfer catalytic enantioselective direct aldol reactions of glycine donor with aldehyde acceptors could



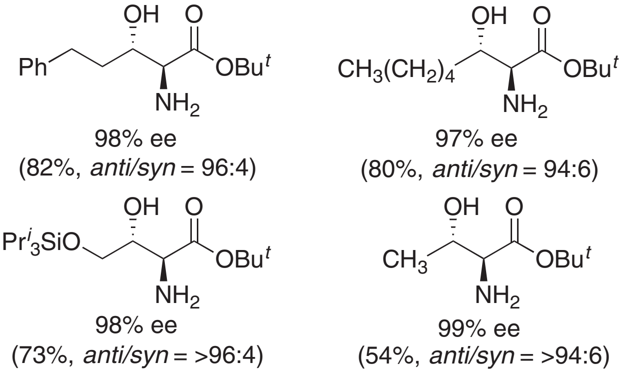
Scheme 28. Asymmetric synthesis of α,α-dialkyl-α-amino acids.



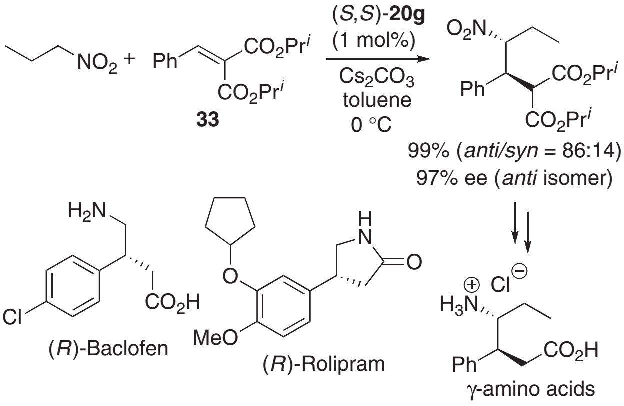
Scheme 29. Asymmetric aldol reaction of glycine derivative under phase-transfer conditions.

provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids, extremely important chiral units, especially from a pharmaceutical viewpoint, the examples reported to date are very limited. In this context, we were successfully able to realize an efficient, highly enantioselective direct aldol reaction of glycine Schiff base with aldehydes under phase-transfer conditions using C_2-symmetric chiral quaternary ammonium salt **20**. Treatment of **21** with 3-phenylpropanal in toluene–1% NaOH aqueous solution in the presence of (*R*,*R*)-**20f** (2 mol %) and subsequent hydrolysis with 1 M HCl in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **32** in 76% isolated yield with the anti/syn ratio of 77:23, and the enantiomeric excess of the major anti isomer was determined to be 91% ee (Scheme 29). Interestingly, use of (*R*,*R*)-**20g** possessing 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent as a catalyst enhanced both diastereo- and enantioselectivities (anti/syn = 92:8, 96% ee for anti isomer).[28]

The initially developed reaction conditions using 2 equiv of aqueous base (1% NaOH aq) exhibited inexplicably limited general applicability in terms of aldehyde acceptors. For example, reaction of glycine derivative **21** with 4-benzyloxybutanal gave aldol product with low diastereoselectivity (anti/syn = 58:42; 82% ee for anti isomer). The mechanistic investigation revealed the intervention of an unfavorable yet inevitable retro aldol process involving chiral catalyst **20**. Based on this information, a reliable procedure has been established by use of the catalyst **20g** (2 mol %) with a catalytic amount of 1% NaOH (15 mol %) and ammonium chloride (10 mol %), which tolerates a wide range of aldehydes to afford the corresponding *anti*-β-hydroxy-α-amino esters almost exclusively in an essentially optically pure form (Scheme 30).[29]



Scheme 30. Asymmetric aldol reaction of glycine derivative under modified phase-transfer conditions.

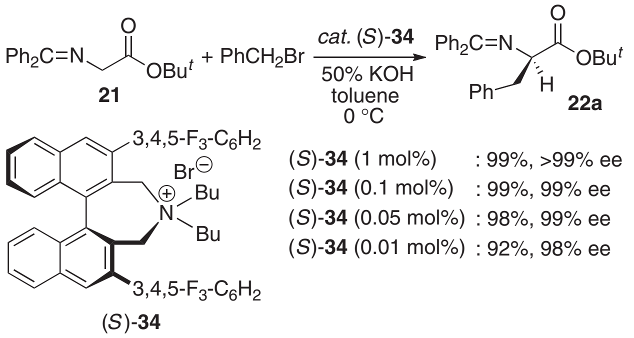


Scheme 31. Asymmetric conjugate addition of nitroalkanes to alkylidenemalonates.

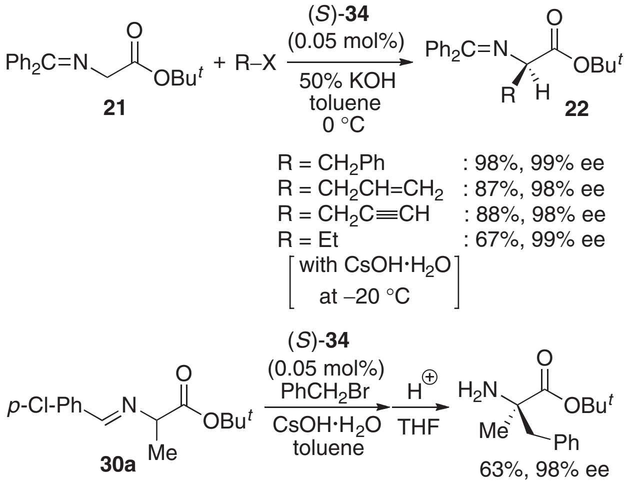
2.4 Asymmetric Conjugate Addition of Nitroalkanes. Asymmetric conjugate addition of α-anions of nitroalkanes to α,β-unsaturated esters is not an easy task due to the low reactivity of α,β-unsaturated esters as Michael acceptor. Accordingly, we developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates **33** under mild phase-transfer conditions by using chiral quaternary ammonium bromide **20g** as an efficient catalyst (Scheme 31).[30] This new protocol offers a practical entry to the facile synthesis of optically active γ-amino acid derivatives such as (*R*)-Baclofen and (*R*)-Rolipram.

3. Design of Simplified, Yet Very Efficient Chiral Phase-Transfer Catalysts

Our further efforts toward the design of very efficient, chiral phase-transfer catalyst have led to the discovery that chiral quaternary ammonium bromide **34** possessing flexible straight-chain alkyl groups instead of a rigid binaphthyl moiety functions as an efficient chiral phase-transfer catalyst. Most notably, the asymmetric alkylation of **21** with various alkyl halides proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01–0.05 mol % of (*S*)-**34** to afford the corresponding alkylation products with excellent



Scheme 32. Asymmetric alkylation of glycine derivative with simplified Maruoka catalyst®.



Scheme 33. Practical synthesis of α-alkyl- and α,α-dialkyl-α-amino acids.

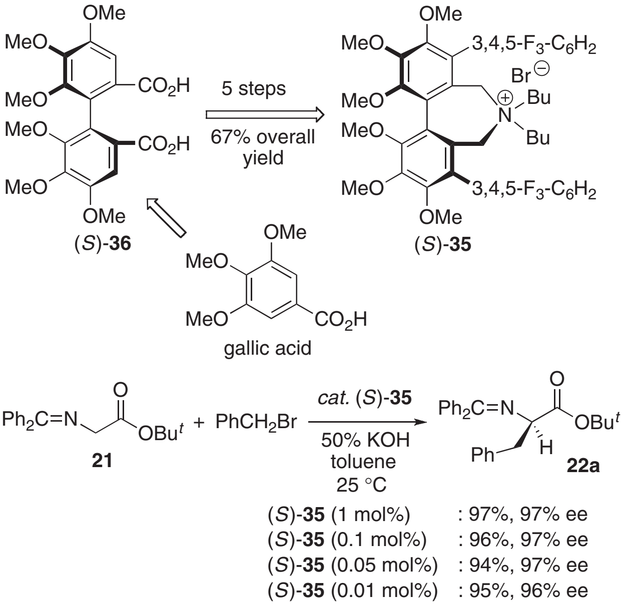
enantioselectivities (Scheme 32).[31] Both (*R*)-**34** and (*S*)-**34** are commercially available as simplified Maruoka catalyst®.

Various alkyl halides are employable for the practical synthesis of α-alkyl- and α,α-dialkyl-α-amino acids (Scheme 33).[31]

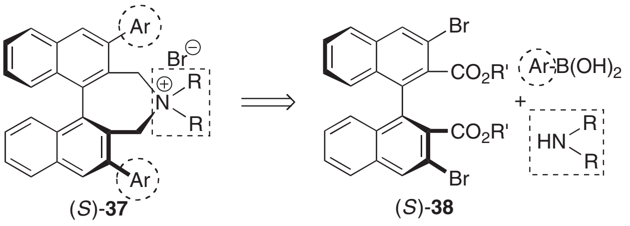
In designing practical phase-transfer catalysts, the ready availability of starting chiral sources is crucial. Accordingly, chiral phase-transfer catalyst **35** was conveniently prepared from the known, readily available (*S*)-4,4′,5,5′,6,6′-hexamethoxybiphenyldicarboxylic acid (**36**) derived from gallic acid (Scheme 34). The catalyst (*S*)-**35** exhibited high catalytic performance (0.01–1 mol %) in the asymmetric alkylation of **21** compared to the existing chiral phase-transfer catalysts, thereby providing a general and useful procedure for highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids.[32]

4. Design of New, Chiral Phase-Transfer Catalysts

4.1 Asymmetric Strecker Reaction for Sterically Hindered α-Alkyl-α-amino Acids Synthesis. One disadvantage of the asymmetric phase-transfer alkylation of glycine derivative **21** for the synthesis of α-alkyl-α-amino acids is the difficulty of preparaing sterically hindered α-alkyl-α-amino acids. In this context, we are intrigued by the development of asymmetric Strecker reactions under phase-transfer conditions.



Scheme 34. Asymmetric alkylation of glycine derivative with another high-performance phase-transfer catalyst.



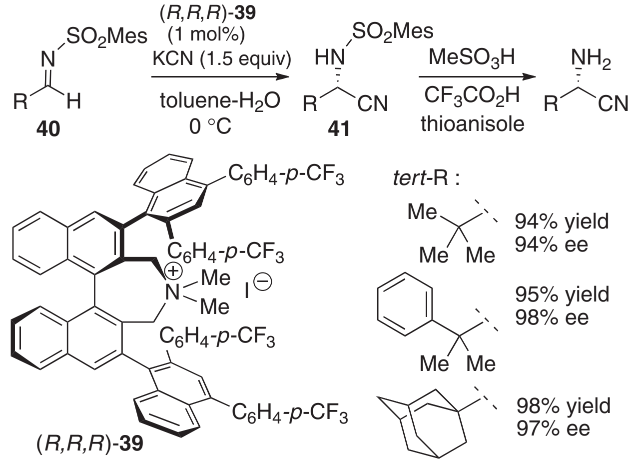
Scheme 35. Combinatorial design approach of chiral phase-transfer catalyst.

The Strecker reaction, catalytic asymmetric cyanation of imines represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. However, there is no example of asymmetric Strecker reaction under phase transfer conditions.

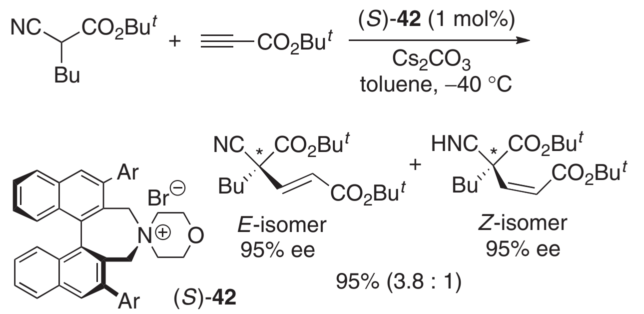
Our strategy is based on our recent finding of a very active, chiral phase-transfer catalyst of type (*S*)-**37** (Ar = 3,4,5-F_3-C_6H_2; R = Bu) for the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.[31a] Since the catalyst (*S*)-**37** can be readily prepared from three components, i.e., a chiral binaphthyl (*S*)-**38**, an arylboronic acid ($ArB(OH)_2$), and a secondary amine (R_2NH),[31b,31c,33] the appropriate modification of $ArB(OH)_2$ and R_2NH should give a newly designed catalyst for the development of a novel asymmetric transformation (Scheme 35).

Accordingly, by designing helical chiral-phase transfer catalysts of type **39**, asymmetric phase-transfer-catalyzed cyanation of sulfonyl imines **40** can be realized under phase-transfer conditions to furnish protected amino nitriles **41** with excellent enantioselectivity (Scheme 36).[34] Deprotection of sulfonamide moiety is effected under acidic conditions with $MeSO_3H$ and CF_3CO_2H without any racemization of the resultant α-amino nitriles.

N-Arylsulfonyl α-amido sulfones can be used directly as a starting substrate, thus obviating the preformation of the



Scheme 36. Asymmetric Strecker reaction under phase-transfer conditions.



(Ar = 3,5-bis[3,5-$(CF_3)_2$-C_6H_3]C_6H_3)

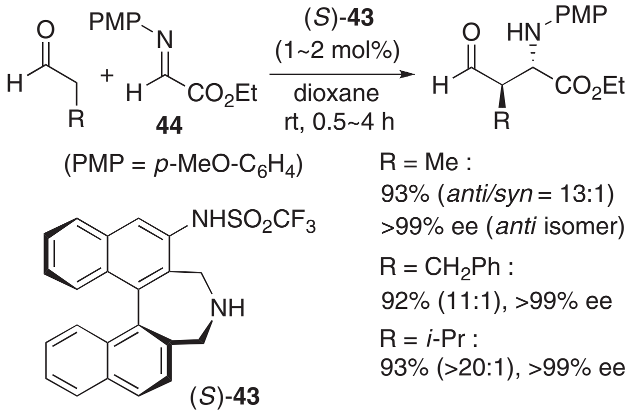
Scheme 37. Asymmetric conjugate addition of α-cyanoacetates under phase-transfer conditions.

reactive *N*-arylsulfonyl aldimines with primary or secondary alkyl α-substituents. Here, only 1.05 equivalents of KCN is sufficient for the smooth cyanation reaction (within 2 h at 0 °C) with excellent levels of chemical yield and enantioselectivity.[35]

4.2 Asymmetric Conjugate Additions of α-Substituted-α-cyanoacetates to Acetylenic Esters. Our second example of the design of a new phase-transfer catalyst is illustrated by the development of a hitherto unknown asymmetric conjugate addition of α-substituted-α-cyanoacetates to acetylenic esters. The combination of these substrates is quite appealing, because both α-substituted-α-cyanoacetates and acetylenic esters have been a difficult class of nucleophiles and electrophiles, respectively, in current asymmetric stereochemical control. Accordingly, we succeeded in designing a new, chiral phase transfer catalyst of type (*S*)-**42** to realize a general and useful procedure for the asymmetric conjugate addition of various *t*-butyl α-substituted-α-cyanoacetates to *t*-butyl propiolate with high enantioselectivity (Scheme 37).[36]

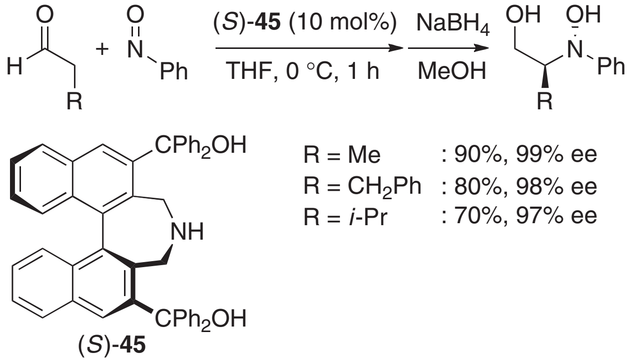
5. Design of Binaphthyl-Based Chiral Secondary Amine Catalysts

In addition to such promising chiral phase-transfer catalysts, we also developed several types of new bifunctional aminocatalysts for the synthesis of α-amino and β-amino acid derivatives.



(PMP = *p*-MeO-C_6H_4)

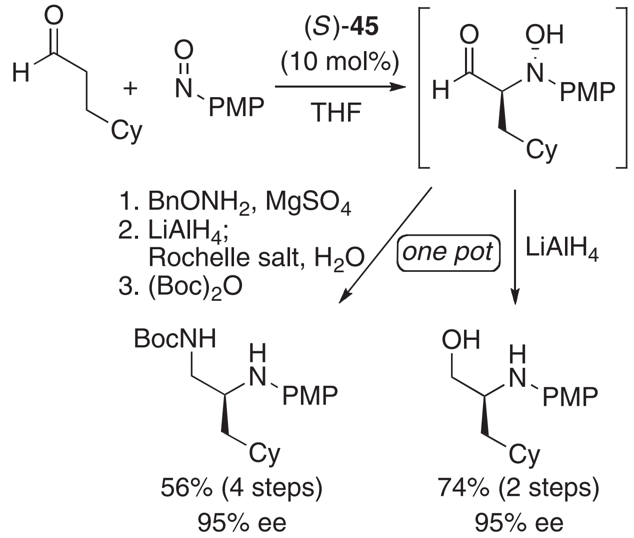
Scheme 38. Asymmetric Mannich reaction with chiral bifunctional catalyst.



Scheme 39. Asymmetric hydroxyamination with chiral bifunctional catalyst.

5.1 Asymmetric Synthesis of β-Formyl-α-amino Acids and β-Amino Acids. The asymmetric direct Mannich reaction was developed to prepare optically enriched β-formyl-α-amino acids.[37] Proline and its derivatives are known to catalyze the asymmetric direct Mannich reaction between α-imino esters and aldehydes through the enamine intermediate to give the syn product predominantly. Thus, we designed a novel axially chiral amino sulfonamide (*S*)-**43**, which is structurally different from the proline derivatives and has a chemically stable binaphthyl backbone, to obtain the anti product. The reaction between propanal and α-imino ester **44** with the catalyst (*S*)-**43** (1 mol %) in dioxane was found to proceed smoothly at room temperature to give the corresponding Mannich product in 93% isolated yield with excellent stereoselectivities (anti/syn = 13:1, >99% ee for anti isomer) (Scheme 38). Additionally, other aldehydes with a primary or secondary alkyl group at the α-position proved to be suitable substrates in the anti selective direct asymmetric Mannich reaction. Of course, this asymmetric Mannich reaction is also employable for the asymmetric synthesis of β-amino acids by simple oxidation of the aldehyde moiety of the Mannich product.

5.2 Asymmetric Synthesis of α-Amino Aldehyde Derivatives. The asymmetric direct hydroxyamination reaction of aldehydes, which would give the α-amino aldehyde derivative, was realized by a related axially chiral secondary amine catalyst (*S*)-**45** (Scheme 39).[38] Thus, treatment of propanal with



Scheme 40. One-pot synthesis of in situ generated hydroxyamination products.

nitrosobenzene in the presence of 10 mol % (*S*)-**45** in THF at 0 °C and subsequent reduction with $NaBH_4$ in THF/MeOH furnished the corresponding *N*-hydroxy-β-amino alcohol in 90% yield and 99% ee. The reaction with other aldehydes such as 3-phenylpropanal and 3-methylbutanal also proceeded to completion in 1 h at 0 °C to give *N*-hydroxy-β-amino alcohols in good yield with excellent enantioselectivity.

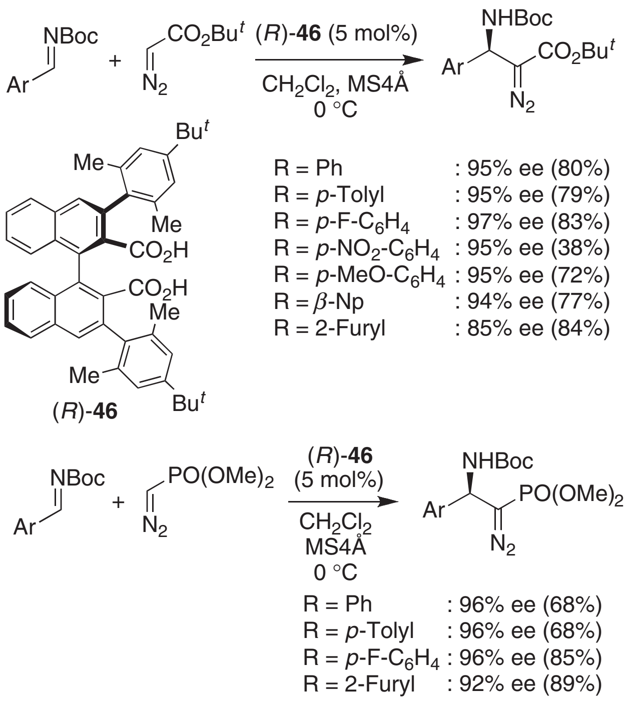
In order to enhance the synthetic utility of this methodology, *p*-methoxynitrosobenzene was employed instead of nitrosobenzene, and by using the resulting hydroxyamination product, one-pot procedures to prepare the β-amino alcohol or the 1,2-diamine were also developed (Scheme 40).[38]

6. Design of Binaphthyl-Based Chiral Brønsted Acid Catalysts

Despite the use of thiourea, diol, and phosphoric acid in asymmetric organocatalysis, the important class of moderate Brønsted acids, carboxylic acids, has rarely been employed in these catalyses. This is quite surprising because carboxylic acids are often utilized as one of the most promising acid catalysts in various organic transformations. We assumed that the difficulty in building an effective chiral recognition site around the carboxylic acid might be the main reason for this deficiency. In an effort to address this issue, we successfully designed new, chiral bis-carboxylic acid catalysts, which consist of two carboxylic acids and an axially chiral binaphthyl moiety, and applied them to highly enantioselective Mannich reaction of *N*-Boc imines and *tert*-butyl diazoacetate (Scheme 41).[39]

7. Conclusion

This account overviews our recent development of the practical asymmetric synthesis of various useful organic molecules by using both metal and non-metal synthetic catalysts. Such achievements certainly provide valuable tools for the production of a wide variety of pharmaceutical intermediates. We believe that continuous efforts should be devoted to the rational design of various chiral metal and organocatalysts including chiral phase-transfer catalysts and their applications to synthetically useful transformations. These would make great contributions to establish genuinely sustainable chemical processes within the context of the forthcoming paradigm shift in worldwide production of highly valuable pharmaceutical substances in this century.



Scheme 41. Asymmetric Mannich reaction of *N*-Boc imines and *tert*-butyl diazoacetate.

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