Award Accounts

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Development of Highly Selective Organic Reactions Catalyzed by Designed Amine Organocatalysts

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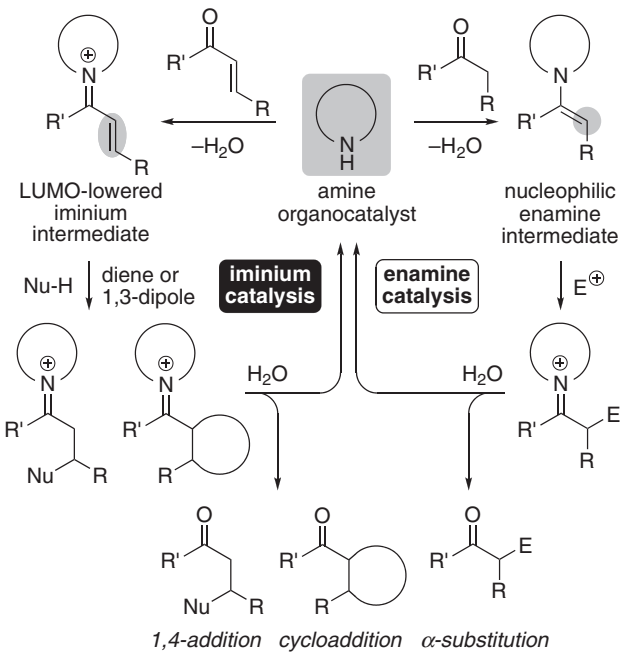
A series of chiral amines with conceptually new design have been developed as chiral organocatalysts. These chiral amine organocatalysts have been successfully applied to several asymmetric reactions via iminium and enamine intermediates and exhibited unique reactivity and selectivity in comparison with previous amine organocatalysts derived from naturally occurring amino acids. The synthetic utility of these asymmetric organocatalytic reactions has also been demonstrated in their application to the synthesis of versatile chiral building blocks.

1. Introduction

Development of organocatalytic reactions is one of the most exciting topics in practical organic synthesis because of its operational simplicity, mild reaction conditions, and environmental consciousness.[1] In this area, chiral amines are widely employed as organocatalysts in various asymmetric reactions.[1–3] The in situ generation of an iminium intermediate from an α,β-unsaturated aldehyde or ketone and an amine catalyst lowers the LUMO energy of the conjugated π system, and consequently, 1,4-nucleophilic additions as well as cycloadditions such as Diels–Alder reaction are facilitated. Hydrolysis of the resulting iminium intermediate affords the product and the amine catalyst (*iminium catalysis*) (Scheme 1).[1f,2,4] After the highly enantioselective catalytic Diels–Alder reaction via iminium intermediates was reported by MacMillan et al. in 2000,[4] a wide variety of highly enantioselective 1,4-additions and cycloadditions have been developed by using chiral amine catalysts.[1f,2] The amine catalyst also reacts with an aldehyde or ketone to form a nucleophilic enamine intermediate, which then reacts with various electrophiles.[1f,3] The following hydrolysis gives the α-substituted product and the amine catalyst (*enamine catalysis*) (Scheme 1). The first asymmetric enamine catalysis was developed in the 1970s by Wiechert and co-workers, and Hajos and Parrish for the intramolecular aldol reaction catalyzed by L-proline.[5] After their work and the first example of a direct asymmetric aldol reaction catalyzed by heterobimetallic complexes,[6] List, Barbas, et al. reported pioneering studies in 2000 on the intermolecular aldol reaction catalyzed by L-proline.[7] Enamine catalysis was then found to be applicable to a wide range of electrophiles, and became one of the most active areas in asymmetric catalysis for the last decade.[1f,3]

In most organocatalytic reactions through iminium and enamine intermediates, naturally occurring amino acids and their derivatives are utilized as catalyst (Scheme 2).[1–3] To date a large number of such amine catalysts have been developed.[8] Although they are ideal catalysts owing to their availability and cost, most amine catalysts share a similar scaffold. In this context, we have been interested in developing amine catalysts with conceptually new design to extend the possibility of iminium and enamine catalysis. In this article, we wish to review our recent achievements on the development of organo-



Scheme 1. Iminium catalysis and enamine catalysis by amine organocatalysts.

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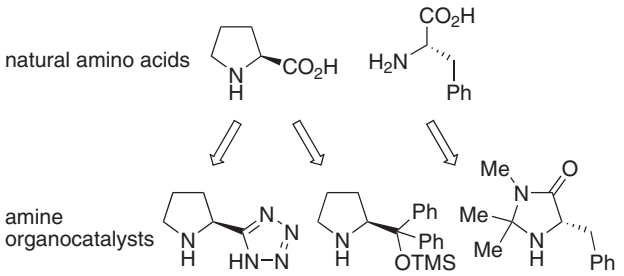
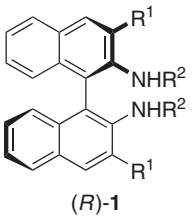


Scheme 2. Representative amine organocatalysts derived from natural amino acids.

catalytic asymmetric reactions with newly designed amine catalysts.

2. Iminium Catalysis

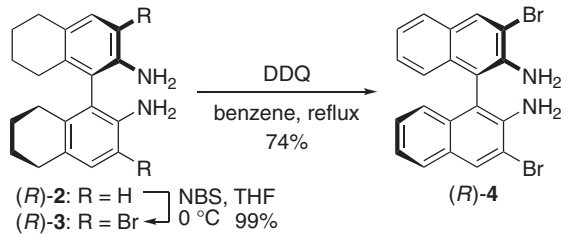
2.1 Design and Synthesis of Binaphthyl-Based Diamine Catalysts. In our initial study to find a novel amine catalyst for iminium catalysis, we chose aromatic amines due to their having enough nucleophilicity to form the iminium salts of α,β-unsaturated aldehydes as a reactive intermediate, in addition to the ease of structural and electronic modification. Thus, axially chiral catalysts of type (*R*)-**1** having 2,2′-diamino-1,1′-binaphthyl (BINAM) core structure were designed for asymmetric organocatalytic reactions (Figure 1). However, a limited number of 3,3′-substituted BINAMs were available due to the difficulty in their synthesis.[9,10]



(*R*)-**1**

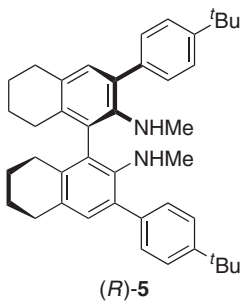
Figure 1. Binaphthyl-based diamine catalyst (*R*)-**1**.

To our surprise, a general method to prepare 3,3′-dihalo BINAMs, which are expected to be key intermediates for further derivatization of BINAM, has not been reported. Since the direct halogenation of 3,3′-positions of BINAM is known to be difficult because of the high reactivity of the 6,6′-positions of BINAM,[11] we decided to employ the partially hydrogenated H_8-BINAM (*R*)-**2** as a starting material, whose 6,6′-positions were temporally masked.[12] In addition, (*R*)-**2** would be expected to act as a simple aniline in aromatic substitution reactions. Indeed, when (*R*)-**2** was treated with *N*-bromosuccinimide in THF at 0 °C for 1 min, the desired 3,3′-dibromo H_8-BINAM (*R*)-**3** was obtained in quantitative yield (Scheme 3). Rearomatization of dibromo H_8-BINAM (*R*)-**3** with 5 equiv of DDQ in benzene proceeded smoothly under reflux conditions to give the desired dibromo BINAM (*R*)-**4** in good yield without loss of the enantiopurity.[13] Using this methodology, synthesis of various binaphthyl-based diamine catalysts has been accomplished.



Scheme 3. Synthetic route to 3,3′-dibromo BINAM (*R*)-**4**.

2.2 *exo*-Selective Asymmetric Diels–Alder Reaction. Diels–Alder reaction is one of the most important carbon–carbon bond forming reactions in synthetic organic chemistry, and a number of asymmetric Diels–Alder reactions have been developed using chiral Lewis acids.[14] Among them, the enantioselection is controlled with chiral Lewis acid catalysts, while the degree of diastereoselectivity depends mainly on the structure of substrates. For instance, the reaction of cyclopentadiene with α,β-unsaturated aldehydes catalyzed by such Lewis acid catalysts generally proceeds with *endo*-selectivity. In this area, small chiral organic compounds were found to catalyze asymmetric Diels–Alder reactions to give the cycloadduct with high enantioselectivity; however, a general method to obtain the cycloadduct with *exo*-selectivity is still of great interest.[4,15] In the course of our studies on the amine-catalyzed Diels–Alder reaction, the combination of 2,2′-bis(methylamino)-1,1′-binaphthyl (12 mol %) and trifluoromethanesulfonic acid (10 mol %) was found to be a highly *exo*-selective catalyst for the reaction of cinnamaldehyde with cyclopentadiene.[16] Thus, the novel axially chiral diamine (*R*)-**5** was designed for the hitherto difficult *exo*-selective asymmetric Diels–Alder reaction (Figure 2).

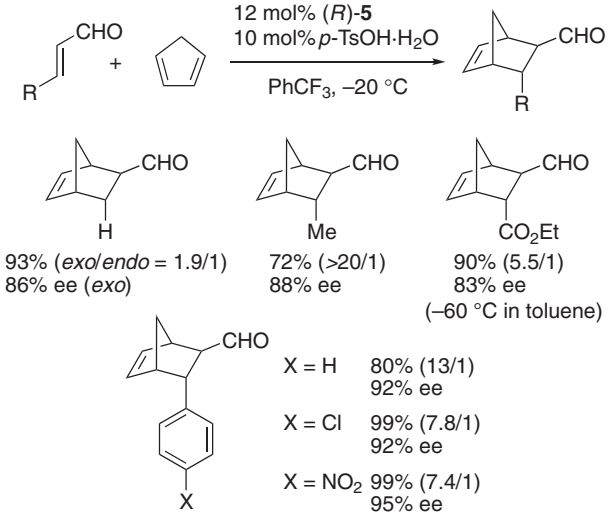


(*R*)-**5**

Figure 2. Axially chiral diamine catalyst (*R*)-**5**.

In the presence of (*R*)-**5** (12 mol %) and *p*-toluenesulfonic acid (10 mol %), the reaction of α,β-unsaturated aldehydes with cyclopentadiene proceeded to give the corresponding cycloadducts with good to excellent *exo*- and enantioselectivity (Scheme 4).[16] Unfortunately, however, this reaction system was only suitable for a combination of α,β-unsaturated aldehydes and cyclopentadiene. For example, the reactions of α,β-unsaturated aldehydes with the other dienes 1,3-cyclohexadiene and 1,3-pentadiene gave only traces of cycloadducts.

The observed stereochemistry in the asymmetric reaction using (*R*)-**5** could be explained by two possible transition state models (Figure 3). In both cases, one face of iminium intermediates was blocked by a 4-*t*-butylphenyl substituent, and the other face is cleanly open for approach of cyclopentadiene in accordance with the experimental results. In



Scheme 4. *exo*-Selective asymmetric Diels–Alder reaction catalyzed by (*R*)-**5**.

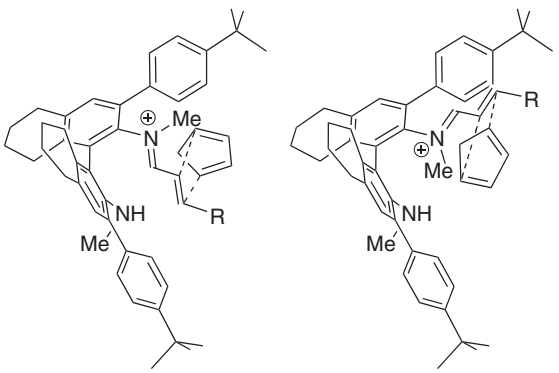


Figure 3. Possible transition state models for the *exo*-selective asymmetric Diels–Alder reaction catalyzed by (*R*)-**5**.

addition, the *exo*-selectivity might be attributed to the influence of the sterically hindered biaryl moiety.

2.3 Asymmetric Diels–Alder Reaction of Methacroleins. Asymmetric Diels–Alder reactions of α-substituted α,β-unsaturated aldehydes such as methacrolein are utilized to construct a chiral quaternary carbon center. However, only methacrolein has been employed as an α,β-unsaturated aldehyde having an α-alkyl substituent in most catalytic asymmetric Diels–Alder reactions.[14,17] Thus, the axially chiral diamine (*R*)-**6** having primary amine moieties was designed for the organocatalytic asymmetric Diels–Alder reaction of acroleins with various α-alkyl substituents (Figure 4),[18] since the secondary amine is known not to catalyze such reactions due to serious steric repulsion between the α-substituent of aldehyde and the amine catalyst.[17]

A combination of (*R*)-**6** (20 mol %) and trifluoromethanesulfonic acid (10 mol %) effectively catalyzed the asymmetric Diels–Alder reaction of acroleins having various α-alkyl substituents with cyclopentadiene to give the cycloadducts in good to excellent enantioselectivity (Scheme 5).[18] This reaction system catalyzed by (*R*)-**6**–TfOH was also applicable to an α,β-disubstituted acrolein, tiglaldehyde and acyclic dienes such as 2-methylbutadiene and 2,3-dimethylbutadiene, giving

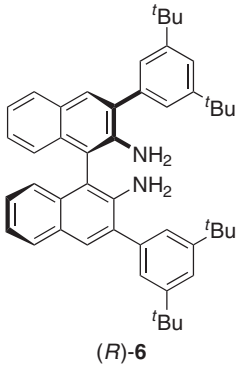
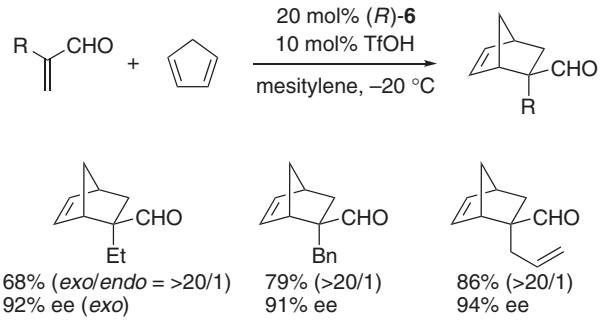


Figure 4. Axially chiral diamine catalyst (*R*)-**6**.



Scheme 5. Asymmetric Diels–Alder reaction of methacroleins catalyzed by (*R*)-**6**.

the corresponding Diels–Alder adducts with moderate to good enantioselectivity.

The observed stereochemistry in the asymmetric reaction using (*R*)-**6** could be explained by a possible transition state model shown in Figure 5. In this model, a 3,5-di-*t*-butylphenyl group of (*R*)-**6** effectively blocks one face of *s*-*cis*-aldimine, which is activated by an internal hydrogen bonding with the ammonium proton.

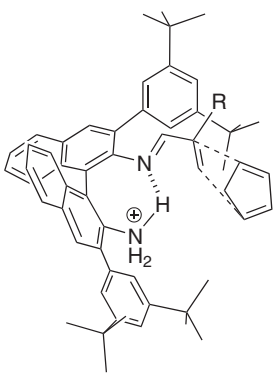


Figure 5. Possible transition state model for the asymmetric Diels–Alder reaction of methacroleins catalyzed by (*R*)-**6**.

2.4 Oxa-Michael Addition. In the field of organocatalysis, 1,4-addition reactions of heteroatom nucleophiles such as thiols,[19] amides,[20] carbamates,[21] and triazoles[22] to α,β-unsaturated aldehydes have been realized by iminium catalysis. However, only a few reports have been made on organocatalytic conjugate addition of oxygen nucleophiles to α,β-unsaturated aldehydes despite its potential application in

organic synthesis,[23] and the oxa-Michael addition of alcohols to α,β-unsaturated aldehydes remains a challenge, mainly because of the competitive acetal formation. During a study directed toward finding new catalytic methods for such oxa-Michael addition, we discovered that *N*-methylaniline (**7**)·HCl salt was somewhat effective as catalyst in the reaction between 2-heptenal and methanol, although a substantial amount of acetal by-product **11** was formed (Scheme 6). Use of a weaker acid such as TFA led to an increased ratio of oxa-Michael adduct **10** to acetal **11**. Moreover, in the case of the weakly acidic additive **8**, the oxa-Michael addition occurred exclusively to give **10** in moderate yield. Based on these observations, we then prepared the biphenyldiamine-based catalyst **9**, which has both secondary amine and acidic moieties in the molecule (Figure 6), and consequently, it was found that the reaction using **9** proceeded smoothly to give oxa-Michael adduct **10** in good yield.[24]

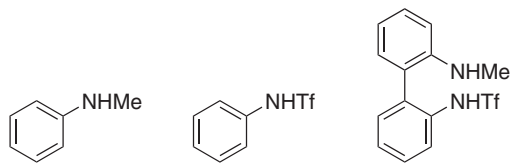
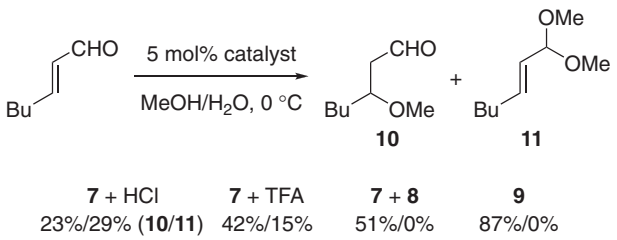
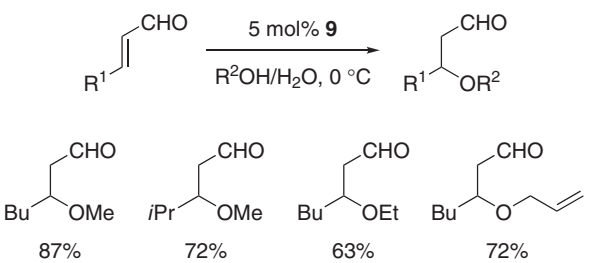


Figure 6. Amine catalysts **7**–**9** for the oxa-Michael addition.



Scheme 6. Catalyst screening for the oxa-Michael addition.

The oxa-Michael addition of methanol to α,β-unsaturated aldehydes, which have a primary alkyl or a secondary alkyl group at the β-position, gave the corresponding oxa-Michael adducts in moderate to good yields (Scheme 7), while the reaction of sterically hindered *tert*-butyl-substituted analog resulted in a decrease in yield. In addition, catalyst **9** was also shown to be effective for the oxa-Michael addition of other alcohols such as ethanol and allyl alcohol, and the corresponding oxa-Michael adducts were obtained in moderate to good yields. In each case, the addition of a proper amount of H_2O to the alcohol solvent is necessary to attain good chemical yields.



Scheme 7. Oxa-Michael addition of alcohols to α,β-unsaturated aldehydes catalyzed by **9**.

Based on the structure of catalyst **9**, some axially chiral biaryl-type catalysts including (*R*)-**12** were designed and applied to the asymmetric variant of oxa-Michael addition (Figure 7).

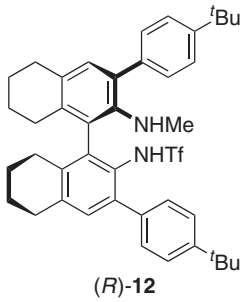
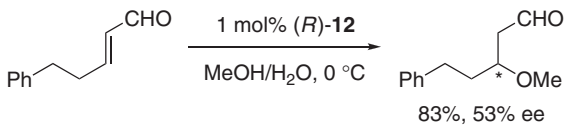


Figure 7. Axially chiral diamine-based catalyst (*R*)-**12**.

When 1 mol % of (*R*)-**12** was employed as catalyst in the oxa-Michael addition of methanol to 5-phenyl-2-pentenal, the oxa-Michael adduct was obtained with moderate enantioselectivity (Scheme 8).[24b]



Scheme 8. Asymmetric oxa-Michael addition of methanol catalyzed by (*R*)-**12**.

3. Enamine Catalysis

3.1 Design of Chiral Secondary Amine Catalysts. Chiral secondary amine catalysts have been frequently utilized in various asymmetric reactions via enamine intermediates.[3] Most such efficient chiral secondary amine catalysts were derived from proline, and a pyrrolidine core structure with at least one α-substituent seemed indispensable for the rational design of catalyst. In this context, we have developed several secondary amine catalysts having a binaphthyl scaffold and various functional groups at the 3-position (Figure 8). Our binaphthyl-based secondary amine catalysts are characterized by the following features: (1) larger space between the secondary-amino nitrogen and the functional group at the 3-position than that of proline derivatives, (2) chemical stability originating from such a distance between functional groups, (3) the absence of α-substituent, which decreases the steric repulsion in the enamine intermediate, (4) ease of introduction of various

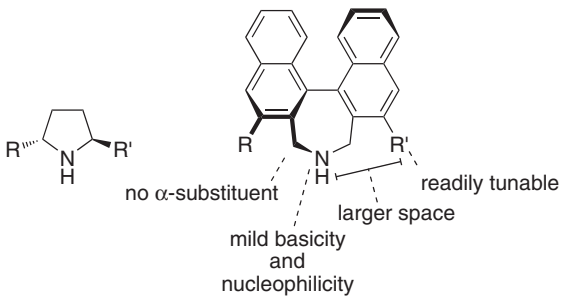
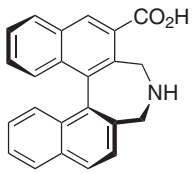


Figure 8. Binaphthyl-based secondary amine catalyst.

functional groups at the 3,3′-positions and C_2-symmetry (R = R′), and (5) their mild basicity and nucleophilicity. By utilizing these characteristic features of our catalysts, unique reactivity and selectivity were realized in some organocatalytic asymmetric reactions in the course of our study. In addition, some pyrrolidine-type catalysts, which are not derived from natural amino acids, have also been developed for novel asymmetric reactions via enamine intermediates.

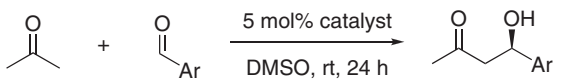
3.2 Direct Asymmetric Aldol Reaction of Ketones with Aldehydes. In the area of organocatalysis, proline has been utilized in various asymmetric reactions including direct asymmetric aldol reactions.[3,5,7] Some such proline-catalyzed aldol reactions, however, have serious limitations on the reactivity and selectivity. Although these problems were overcome through the development of new catalysts derived from proline, there is still an urgent need for structurally and electronically novel catalysts due to the difficulty in appropriate modification of proline. In this context, we were interested in the possibility of designing a certain artificial amino acid catalyst (*S*)-**13** having a binaphthyl backbone as a frequently utilized chiral unit in the asymmetric catalysts (Figure 9).[25]



(*S*)-**13**

Figure 9. Binaphthyl-based amino acid catalyst (*S*)-**13**.

We first examined the direct asymmetric aldol reaction of acetone with the newly synthesized binaphthyl-based amino acid catalyst (*S*)-**13**. In the presence of 5 mol % of (*S*)-**13**, the reaction of 4-nitrobenzaldehyde with acetone in DMSO at room temperature proceeded gradually to afford the aldol adduct in 70% yield with 93% ee (Scheme 9). In contrast, the reaction with L-proline under the same reaction conditions gave the aldol adduct in low yield with moderate enantioselectivity, together with 1,3-oxazolidine **14** (48% yield based on proline) derived from proline and two equivalents of 4-nitrobenzaldehyde (Figure 10). Kinetic study revealed that the reaction with proline catalyst proceeded more rapidly than that with (*S*)-**13**



Scheme 9. Asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde.

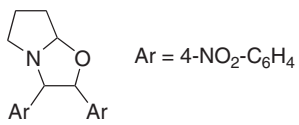


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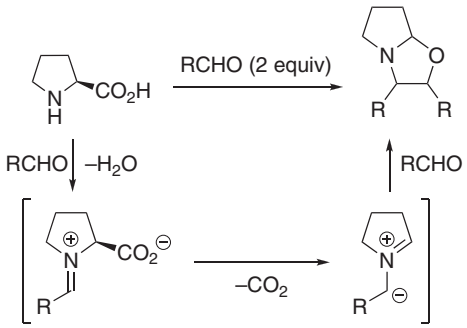
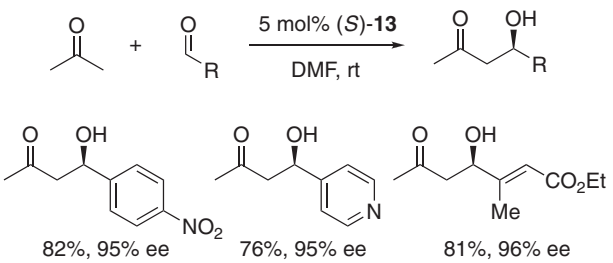
Figure 10. 1,3-Oxazolidine **14** derived from proline and 4-nitrobenzaldehyde.

for the first 30 min and then stopped at low conversion. These observations can be explained by the consumption of proline under the reaction conditions. As shown in Scheme 10, proline is known to decompose by decarboxylation of an iminium salt, which is formed in the presence of an electron-deficient aldehyde, followed by cycloaddition of the resulting azomethine ylide with another equivalent of aldehyde to give the corresponding 1,3-oxazolidine.[26] On the other hand, binaphthyl-based amino acid (*S*)-**13** is chemically stable, and hence the reaction promoted by (*S*)-**13** leads to a better yield despite the slower reaction rate owing to the moderate nucleophilicity of the benzylic amine moiety in (*S*)-**13**.



Scheme 10. Decomposition of proline and formation of 1,3-oxazolidine.

Under the optimized conditions, electron-deficient aromatic, heteroaromatic, and olefinic aldehydes were found to be suitable substrates, with the direct aldol reactions generally giving the corresponding aldol adducts in moderate to good yields with excellent enantioselectivities in most cases (>95% ee) (Scheme 11). Unfortunately, however, the reaction of a simple aldehyde benzaldehyde gave the aldol adduct in low yield (22%), albeit with excellent enantioselectivity (96% ee).

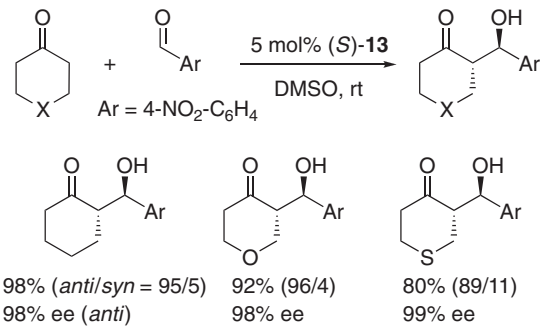


Scheme 11. Asymmetric aldol reaction of acetone with aldehydes catalyzed by (*S*)-**13**.

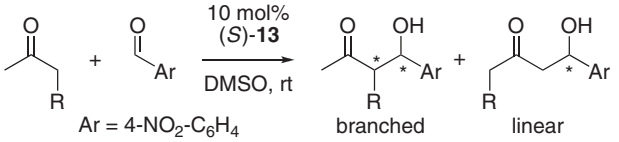
Binaphthyl-based amino acid catalyst (*S*)-**13** was also applicable to the direct asymmetric aldol reaction of cyclic ketones, and the reaction of cyclohexanone with various reactive aldehydes gave the *anti*-products predominantly in good yields with excellent enantioselectivities (>95% ee). When other six-membered cyclic ketones tetrahydropyran-4-one and tetrahydrothiopyran-4-one were employed, satisfactory yields and stereoselectivities were attained (Scheme 12).[25b]

We also investigated the use of a series of acyclic unsymmetrical ketones (Scheme 13). Surprisingly, the reaction of 2-butanone with 4-nitrobenzaldehyde took place mainly at the

methylene position to afford the branched *anti*-aldol adduct as a major regioisomer and diastereomer, with virtually complete enantioselectivity, while the use of proline as catalyst for this reaction exclusively gave the linear aldol adduct.[27] As the alkyl group R of the unsymmetrical ketones became larger, the linear aldol adduct became more dominant; thus the reaction of 4-methylpentan-2-one gave only the linear adduct.



Scheme 12. Asymmetric aldol reaction of cyclic ketones catalyzed by (*S*)-**13**.



R = Me	R = Pr	R = Bn	R = *i*-Pr
72% (b/l = 2.6/1)	57% (1/1.6)	50% (1/2.0)	26% (linear only)
99% ee (branched)	99% ee	99% ee	-
91% ee (linear)	87% ee	99% ee	89% ee

Scheme 13. Asymmetric aldol reaction of acyclic ketones catalyzed by (*S*)-**13**.

In the reaction catalyzed by (*S*)-**13**, both *s-trans*- and *s-cis*-enamines are possible as shown in Figure 11. The absolute stereochemistry of the *anti*-aldol adduct, which was obtained as a major isomer in the reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by (*S*)-**13**, was determined to be (2*S*,1′*R*) (Scheme 14). On the basis of the observed stereochemistry, a plausible transition state is proposed in which the *Re* face of an aldehyde approaches the *Re* face of the *s-trans*-enamine. Hence, the reaction of an aldehyde with other ketones in the presence of (*S*)-**13** presumably proceeds by way of *s-trans*-enamine structure, similar to the transition state involving the *s-trans*-enamine in the proline-catalyzed reaction.[27]

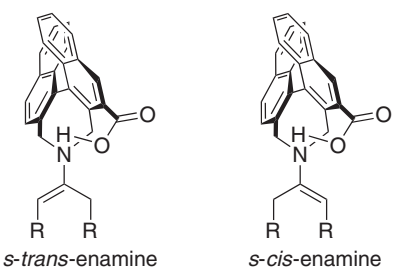
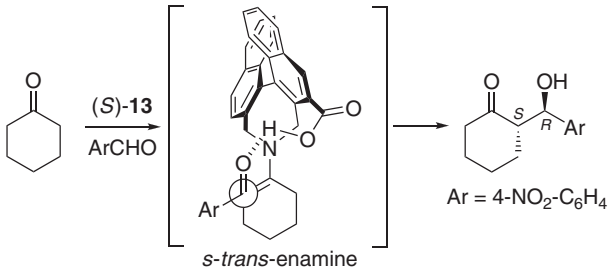


Figure 11. Possible enamine intermediates generated from (*S*)-**13**.



Scheme 14. Plausible transition state model for the asymmetric aldol reaction catalyzed by (*S*)-**13**.

Although a robust binaphthyl-based amino acid (*S*)-**13** gave a higher yield than the proline catalyst in the direct asymmetric aldol reaction with electron-deficient aldehydes, somewhat high catalyst loadings (5–10 mol %) were still necessary to achieve high yields, presumably due to the moderate nucleophilicity of the benzylic amine moiety in (*S*)-**13**. Accordingly, we designed a biphenyl-based amino acid of type (*S*)-**15**, which is highly substituted with electron-donating methoxy groups, with the expectation of the increasing nucleophilicity of the amine moiety (Figure 12).[28]

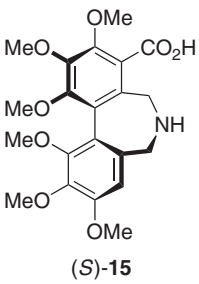
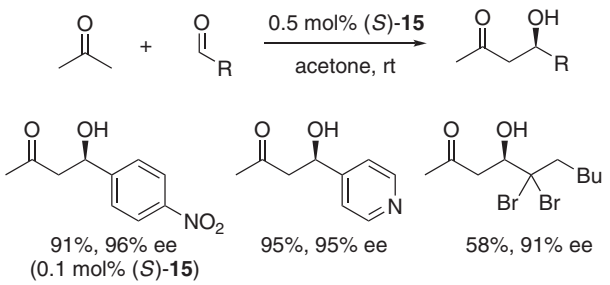


Figure 12. Biphenyl-based amino acid catalyst (*S*)-**15**.

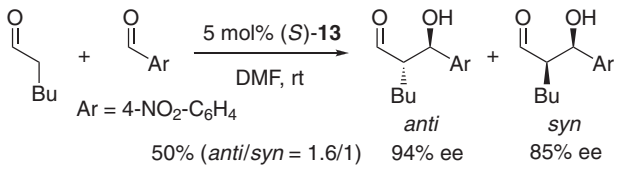
As expected, the aldol reaction of acetone with 4-nitrobenzaldehyde catalyzed by (*S*)-**15** was significantly accelerated in comparison with (*S*)-**13**, and only 0.5 mol % of (*S*)-**15** was sufficient to obtain the desired aldol adduct without loss of enantioselectivity. Upon further investigation of the catalyst loading, it was found that even 0.1 mol % of (*S*)-**15** was sufficient to achieve a high yield (91%) and an excellent enantioselectivity (96% ee) in the reaction of acetone with 4-nitrobenzaldehyde (Scheme 15). To prove the efficiency of this new catalyst, the aldol reaction of acetone with several other aldehydes was carried out in the presence of 0.5 mol % of (*S*)-**15**. Olefinic, heteroaromatic, and aromatic aldehydes with



Scheme 15. Asymmetric aldol reaction of acetone with aldehydes catalyzed by (*S*)-**15**.

electron-withdrawing groups were found to be suitable substrates (>68%, >94% ee). With 2 mol % of (*S*)-**15**, even simple aromatic aldehydes such as benzaldehyde and 2-naphthylaldehyde gave the corresponding aldol adducts in moderate yields (50%, 95% ee and 50%, 94% ee). Furthermore, the reaction of α,α-dibromoheptanal as an aliphatic aldehyde substitute was also found to proceed with high enantioselectivity (91% ee).

3.3 Direct Asymmetric Cross-Aldol Reaction between Aldehydes. The cross-aldol reaction between two different aldehydes is known to be often problematic because of undesired side reactions, including dehydration of products, self-aldol reaction, and multiple addition of enolates to aldol products. To date, however, several organocatalytic cross-aldol reactions between aldehydes, first reported by MacMillan and co-workers, have been developed,[29] and *anti*-aldol adducts are obtained in highly enantioselective fashion by using proline and related catalysts. We then examined the cross-aldol reaction between hexanal and 4-nitrobenzaldehyde using the binaphthyl-based amino acid (*S*)-**13** as catalyst.[30] The reaction proceeded to give the *anti*-aldol adduct as a major diastereomer with excellent enantioselectivity (Scheme 16), and the transition state seemed to involve the *s-trans*-enamine intermediate which is similar to that of the proline-catalyzed reaction (Figure 13). Interestingly, however, a substantial amount of the *syn*-aldol adduct was also obtained, suggesting the existence of *s-cis*-enamine intermediate, in which a steric repulsion between the enamine and the carboxylic acid group is much smaller than that of proline.



Scheme 16. Asymmetric cross-aldol reaction between aldehydes catalyzed by (*S*)-**13**.

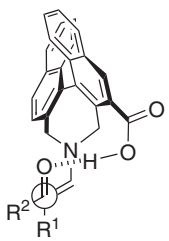


Figure 13. Plausible transition state model for the cross-aldol reaction catalyzed by (*S*)-**13**.

These observations prompted us to develop a hitherto difficult *syn*-selective direct cross-aldol reaction and design a new axially chiral amino sulfonamide (*S*)-**16** with a more remote acidic proton from the secondary amino group than the carboxy group in (*S*)-**13** (Figure 14).[30,31]

Since it would be difficult for the *s-trans*-enamine, which is generated from a donor aldehyde and (*S*)-**16**, to react with an acceptor aldehyde that is activated by the distal acidic proton of the triflamide of (*S*)-**16**, the cross-aldol reaction catalyzed by (*S*)-**16** would be expected to proceed through the *s-cis*-enamine,

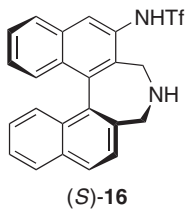
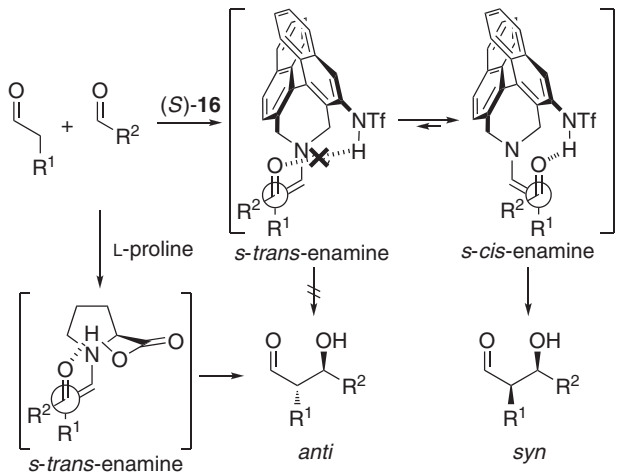


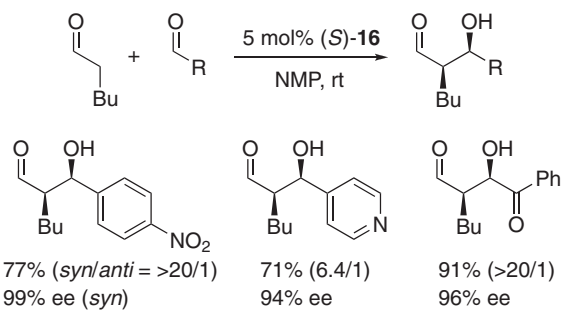
Figure 14. Binaphthyl-based amino sulfonamide catalyst (*S*)-**16**.



Scheme 17. Possible transition state models for the asymmetric cross-aldol reaction catalyzed by L-proline and (*S*)-**16**.

thus giving the desired unusual *syn*-product as shown in Scheme 17.

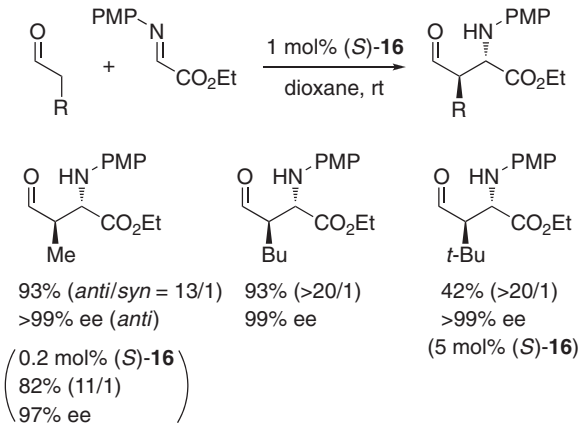
We first examined the reaction between hexanal and 4-nitrobenzaldehyde in the presence of 5 mol % (*S*)-**16** in various solvents at room temperature. Unfortunately, the reaction in less polar solvents such as toluene, CH_2Cl_2, and dioxane gave the corresponding cross-aldol product in poor yield with low stereoselectivities (<31%, *syn*/*anti* = <1/1.5, <25% ee). When amide solvents, DMF and NMP (*N*-methylpyrrolidone) were used, the desired *syn*-aldol adduct was obtained in moderate to good yield with excellent diastereo- and enantioselectivity (>60%, *syn*/*anti* = >13/1, >97% ee). The observed large solvent effect on selectivity might be attributed to the change in the pK_a value of the acidic proton of catalyst (*S*)-**16**, depending on the solvent used.[32] The reaction catalyzed by (*S*)-**16** was also applicable to 4-pyridinecarbaldehyde and phenylglyoxal as its monohydrate (Scheme 18). In all cases,



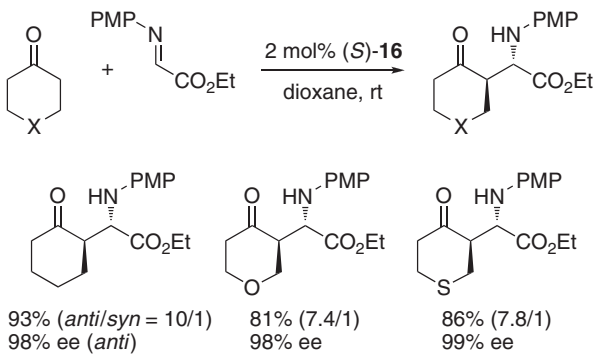
Scheme 18. Asymmetric cross-aldol reaction between aldehydes catalyzed by (*S*)-**16**.

the (*S*)-**16**-catalyzed method was complementary to the proline-catalyzed reactions in terms of the *syn*/*anti* selectivity. It should also be noted that more than 95% of (*S*)-**16** was recovered unchanged after column chromatography.

3.4 Direct Asymmetric Mannich Reaction. The axially-chiral amino sulfonamide (*S*)-**16** was also successfully applied to the direct asymmetric Mannich reaction of aldehydes with α-imino esters.[30,33,34] This catalyst (*S*)-**16** has the advantage of giving mainly *anti*-products, while proline shows the opposite *syn*-selectivity.[35] In the case of *primary*-alkyl aldehydes, 1 mol % of (*S*)-**16** was sufficient to produce the corresponding β-amino aldehydes in high yields (>92%) with virtually complete enantioselectivities (99% ee) and excellent *anti*-selectivities (>11/1) (Scheme 19). The catalyst loading can be reduced to less than 1 mol % of (*S*)-**16** with slightly decreased yield and stereoselectivities. Although the reaction of a sterically hindered aldehyde 3,3-dimethylbutanal required a higher catalyst loading (5 mol %) and proceeded in moderate yield (42%), optimal *anti*-selectivity and enantioselectivity were observed (*anti*/*syn* = >20/1, >99% ee). It should be noted that self-aldol products were not detected even in the presence of excess aldehydes. Additionally, (*S*)-**16** was also applicable to the direct asymmetric Mannich reaction of cyclic ketones (Scheme 20).



Scheme 19. Asymmetric Mannich reaction of aldehydes catalyzed by (*S*)-**16**.



Scheme 20. Asymmetric Mannich reaction of cyclic ketones catalyzed by (*S*)-**16**.

Based on the observed stereochemistry in the cross-aldol and Mannich reactions catalyzed by (*S*)-**16**, transition state models can be proposed as shown in Figure 15. In each case, the *Re* face of aldehydes or the *Si* face of imines approaches the enamine intermediate as directed by the distant acidic proton of triflamide group, and consequently, the C–C bond forming reaction takes place on the *Si* face of the *s*-*cis*-enamine in highly diastereo- and enantioselective fashion, giving *syn*-aldol adducts or *anti*-Mannich adducts, respectively.

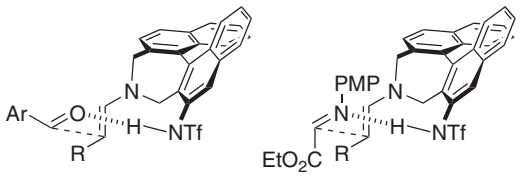


Figure 15. Plausible transition state models for the asymmetric cross-aldol and Mannich reactions catalyzed by (*S*)-**16**.

Moderate yield in the Mannich reaction of sterically hindered aldehydes can be explained by the moderate nucleophilicity of the binaphthyl-based amino sulfonamide (*S*)-**16**. Thus, we have designed and synthesized new chiral amino sulfonamide catalysts (*R*,*R*)-**17**,[36] (*S*)-**18**,[34b,37] and (*S*)-**19**[38] possessing a highly nucleophilic pyrrolidine core and one or two acidic sulfonamide groups (Figure 16).

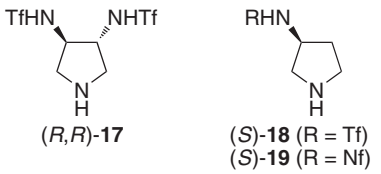
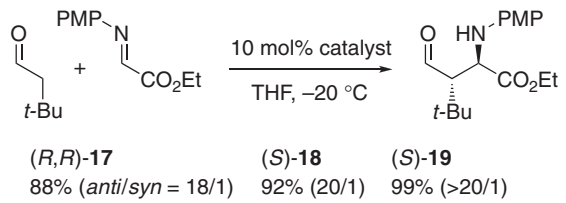
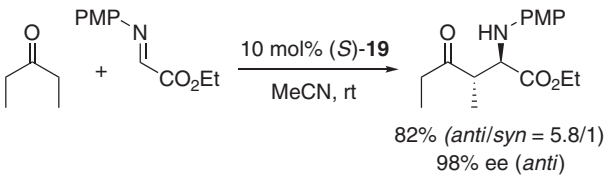


Figure 16. Pyrrolidine-based amino sulfonamides (*R*,*R*)-**17**, (*S*)-**18**, and (*S*)-**19**.

New pyrrolidine-based amino sulfonamides (*R*,*R*)-**17**, (*S*)-**18**, and (*S*)-**19** effectively catalyzed the Mannich reaction of a sterically demanding 3,3-dimethylbutanal and a less reactive acyclic ketone 3-pentanone to give the *anti*-adducts predominantly in good to excellent yields and enantioselectivities (Schemes 21 and 22).

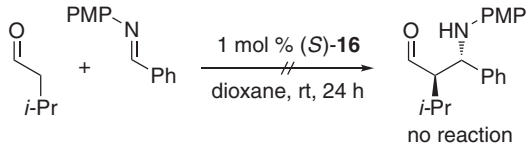


Scheme 21. Asymmetric Mannich reaction of 3,3-dimethylbutanal catalyzed by (*R*,*R*)-**17**, (*S*)-**18**, and (*S*)-**19**.



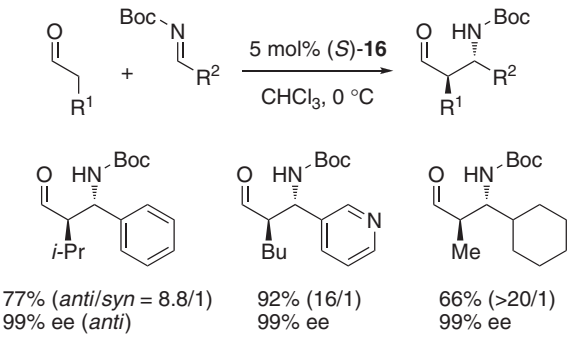
Scheme 22. Asymmetric Mannich reaction of 3-pentanone catalyzed by (*S*)-**19**.

We then turned our attention to the reaction of aromatic imines, and attempted to expand the substrate scope of the *anti*-selective Mannich reaction catalyzed by (*S*)-**16**. Unfortunately, however, the reaction between the *N*-PMP-protected aromatic imine and 3-methylbutanal did not proceed under the optimal conditions for the reaction of *N*-PMP-protected α-imino esters, probably due to the low reactivity of the aromatic imine (Scheme 23).[30] We then decided to explore the *anti*-selective Mannich reaction using more reactive *N*-Boc-protected aromatic imines,[30,39] which have been successfully utilized by the groups of List[40] and Córdova[41] in the *syn*-selective Mannich reaction catalyzed by proline.



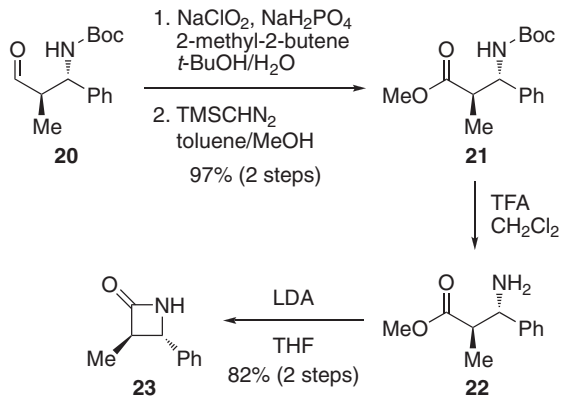
Scheme 23. Low reactivity of the *N*-PMP-protected aromatic imine.

The reaction between the benzaldehyde-derived *N*-Boc-imine and 3-methylbutanal in the presence of 5 mol % of (*S*)-**16** in chloroform gave the *anti*-adduct in low yield, albeit with good diastereo- and excellent enantioselectivity (31%, *anti*/*syn* = 11/1, 99% ee). Since a similar low yield (30%) of the *anti*-adduct was obtained even at a higher catalyst loading (10 mol %), we suspected that the low yield might be due to the catalyst deactivation by the *N*-Boc-imine. Indeed, when a solution of the *N*-Boc-imine was slowly added to the reaction mixture using a syringe pump, the *anti*-adduct was obtained in good yield with satisfactory *anti*- and enantioselectivity (77%, *anti*/*syn* = 8.8/1, 99% ee). This reaction system was also applicable to various imines including heteroaromatic and aliphatic imines (Scheme 24).



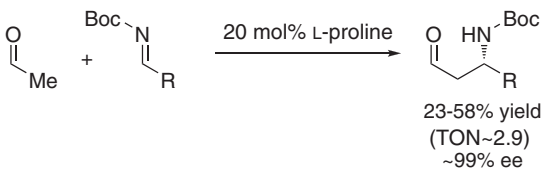
Scheme 24. Asymmetric Mannich reaction of aldehydes with *N*-Boc-protected imines catalyzed by (*S*)-**16**.

To extend the synthetic utility of this asymmetric transformation, an optically enriched *anti*-β-amino aldehyde was successfully converted to the corresponding β-lactam (Scheme 25). Thus, treatment of the *anti*-Mannich product **20** with $NaClO_2$, followed by addition of $TMSCHN_2$, resulted in clean formation of the corresponding methyl ester **21** (97% yield over two steps). Subsequent *N*-Boc deprotection and treatment of the resulting β-amino ester **22** with LDA gave the β-lactam **23** without loss of enantiopurity (82% yield over two steps).[42]



Scheme 25. Transformation of *anti*-Mannich product to β-lactam.

The reaction between acetaldehyde and *N*-Boc-protected imines gives the simplest Mannich products as versatile chiral building blocks, which are known to be obtained from the reaction catalyzed by proline, albeit in low to moderate yields (Scheme 26).[43,44] Since the enamine intermediate generated from pyrrolidine-type secondary amine catalysts such as proline is highly nucleophilic, it seems to be difficult to suppress undesired side reactions including aldol reactions and further reactions of the Mannich product (Figure 17). In contrast, catalyst (*S*)-**16** has a less nucleophilic dibenzylic secondary amine moiety compared to pyrrolidine-type catalysts, and was expected to suppress such undesired side reactions.



Scheme 26. Asymmetric Mannich reaction of acetaldehyde catalyzed by L-proline.

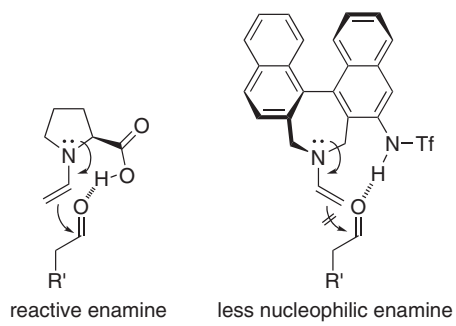
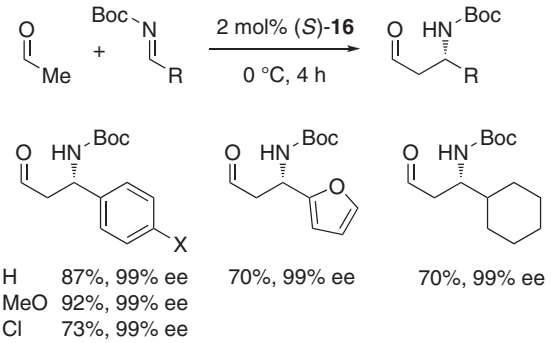


Figure 17. Undesired Aldol reaction of acetaldehyde with aldehydes.

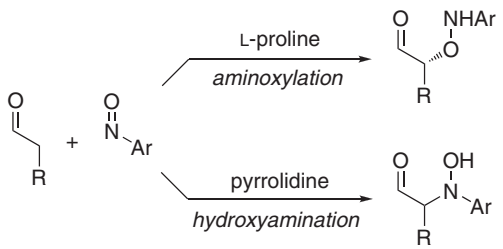
Under solvent-free condition, the reaction between an excess amount of acetaldehyde and various *N*-Boc-protected imines in the presence of 2 mol % (*S*)-**16** proceeded to give the desired Mannich products in good yield (>70%) with excellent enantioselectivity (>98% ee) (Scheme 27).[39] An *N*-Boc-protected aliphatic imine (R = cyclohexyl) was also applicable to

this reaction system, when the imine was added slowly by syringe pump.



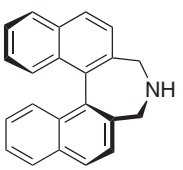
Scheme 27. Asymmetric Mannich reaction of acetaldehyde catalyzed by (*S*)-**16**.

3.5 Direct Asymmetric Hydroxyamination of Aldehydes with Nitrosobenzene. Nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry,[45] and various organocatalytic asymmetric reactions have recently been developed by exploiting their unique properties. The reactions between nitrosobenzene and enamines as activated carbonyl compounds are known to provide aminoxylation or hydroxyamination products, depending on the catalyst used. For example, while proline catalyzes the reaction of an aldehyde with nitrosobenzene to give the aminoxylation product with excellent enantioselectivity,[46] use of pyrrolidine as catalyst affords a hydroxyamination product exclusively (Scheme 28).



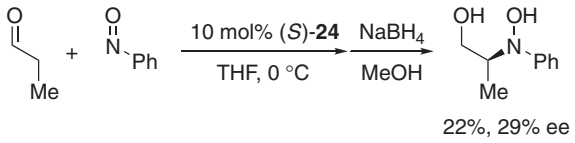
Scheme 28. Aminoxylation and hydroxyamination in enamine catalysis.

In the absence of relatively strong acids such as carboxylic acid, tetrazole, and sulfonamide, the organocatalytic reaction of aldehydes with nitrosobenzene gives hydroxyamination products exclusively. For instance, a binaphthyl-based secondary amine (*S*)-**24** having no acidic group catalyzed the reaction of propanal with nitrosobenzene to give the hydroxyamination product exclusively (Figure 18 and Scheme 29).[47]



(*S*)-**24**

Figure 18. Binaphthyl-based amine catalyst (*S*)-**24**.



Scheme 29. Asymmetric hydroxyamination of propanal with nitrosobenzene catalyzed by (*S*)-**24**.

The hydroxyamination reaction with nitrosobenzene is known to be accelerated by addition of alcohols, probably due to the activation of nitrosobenzene through the weak hydrogen bonding between the hydroxy group of alcohols and the nitroso group.[48] However, since the hydroxyamination of aldehydes proceeds with or without such activation, a binaphthyl-based amine catalyst with a mono activating group was not expected to be the optimal catalyst for a highly enantioselective hydroxyamination reaction, unlike the aminoxylation reaction (Figure 19). Thus we have designed a novel C_2-symmetric binaphthyl-based amino alcohol catalyst (*S*)-**25** with hydroxy groups at the appropriate positions to improve both reactivity and enantioselectivity (Figure 20).[47]

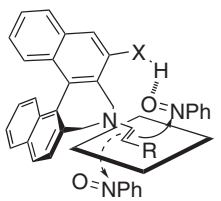
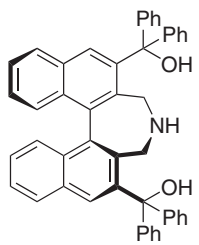


Figure 19. Undesired hydroxyamination of the enamine intermediate with unactivated nitrosobenzene.

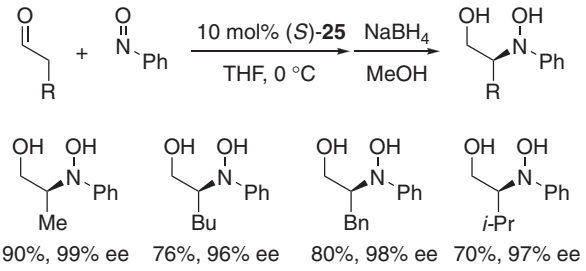


(*S*)-**25**

Figure 20. Binaphthyl-based amino alcohol catalyst (*S*)-**25**.

In the presence of 10 mol % of (*S*)-**25**, which has sterically congested *tert*-alcohol moieties at 3,3′-positions, the reaction of various aldehydes with nitrosobenzene in THF proceeded smoothly to give desired hydroxyamination products in good yields (>70%) with excellent enantioselectivities (>96% ee) without forming aminoxylation products (Scheme 30).

A plausible transition state model has been proposed to account for the high selectivity of the catalyst (*S*)-**25** (Figure 21). Each of the hydroxydiphenylmethyl groups on the catalyst (*S*)-**25** might play a different role in the present reaction. After formation of the enamine intermediate from aldehydes and (*S*)-**25**, one hydroxydiphenylmethyl group shields the *Re*-face of the enamine effectively, and the other directs and activates the nitrosobenzene by hydrogen bonding to give hydroxyamination products with the *S*-configuration.



Scheme 30. Asymmetric hydroxyamination of aldehydes with nitrosobenzene catalyzed by (*S*)-**25**.

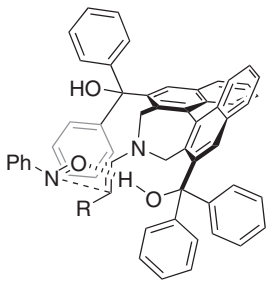
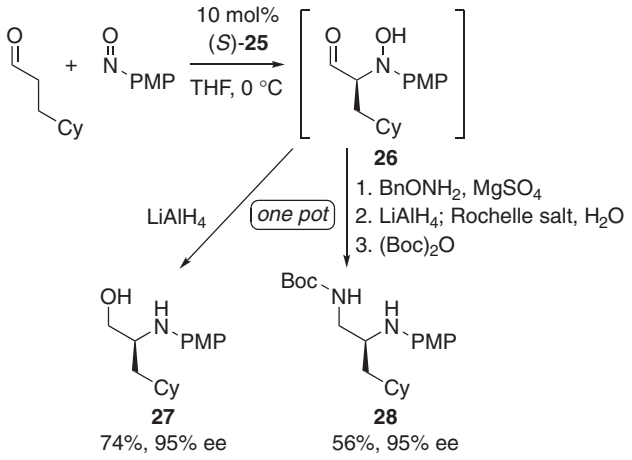


Figure 21. Plausible transition state model for the asymmetric hydroxyamination catalyzed by (*S*)-**25**.

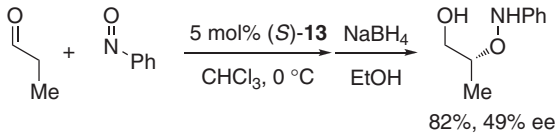
To enhance the synthetic utility of this methodology, *p*-methoxynitrosobenzene was employed instead of nitrosobenzene, and by using the resulting hydroxyamination product **26**, one-pot procedures to prepare the β-amino alcohol **27** or the 1,2-diamine **28** having cleavable protecting groups were also developed (Scheme 31).



Scheme 31. One-pot asymmetric synthesis of β-amino alcohol and 1,2-diamine.

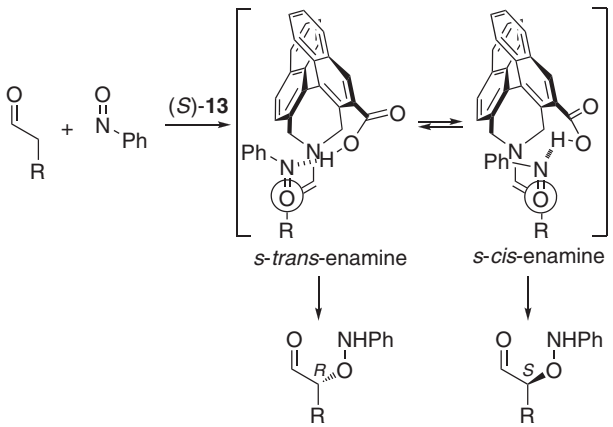
3.6 Direct Asymmetric Aminoxylation of Aldehydes with Nitroso Compounds. We then investigated the aminoxylation of aldehydes by using our binaphthyl-based amino acid (*S*)-**13** to understand the selectivity difference between proline and (*S*)-**13**.[49,50] As expected, the reaction of propanal with nitrosobenzene in the presence of 5 mol % of (*S*)-**13** gave the aminoxylation product with moderate enantioselectivity (49% ee) (Scheme 32).

Since activation of nitrosobenzene by strong acids such as carboxylic acid and tetrazole is necessary to obtain the



Scheme 32. Asymmetric aminoxylation of propanal catalyzed by (*S*)-**13**.

aminoxylation product,[45f] only the combination of the *s-cis*-enamine and nitrosobenzene activated on the *Si* face of the enamine could provide the (*S*)-isomer as shown in Scheme 33. The moderate enantioselectivity in the reaction catalyzed by (*S*)-**13** strongly suggests the existence of the *s-cis*-enamine intermediate, and that is consistent with the low diastereoselectivity observed in the cross-aldol reaction catalyzed by (*S*)-**13** (Scheme 16).



Scheme 33. Possible transition state models for the asymmetric aminoxylation catalyzed by (*S*)-**13**.

To increase the enantioselectivity through the preferential formation of the *s-cis*-enamine intermediate, various aromatic substituents were introduced on the 3-position of (*S*)-**13**. Contrary to our expectation, however, the reaction using new catalysts with aromatic substituents gave the (*R*)-isomer as a major enantiomer with higher enantioselectivity than that of (*S*)-**13**. For instance, the reaction using (*S*)-**29** provided the (*R*)-isomer with good enantioselectivity (91% ee) (Figure 22 and Scheme 34), and consequently, the preferential formation of the *s-trans*-enamine intermediate was suggested.[49,50] The reason the reaction catalyzed by (*S*)-**29** proceeds through the *s-trans*-enamine intermediate is not clear at this stage.

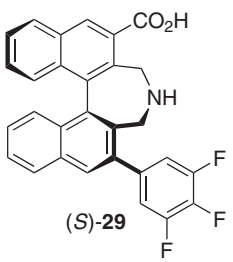
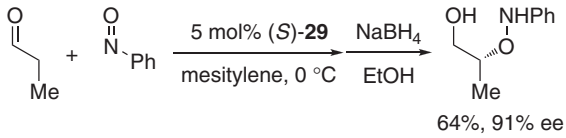
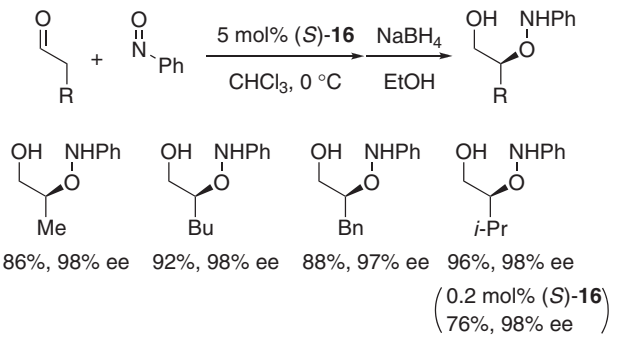


Figure 22. Binaphthyl-based amino acid catalyst (*S*)-**29**.



Scheme 34. Asymmetric aminoxylation of propanal catalyzed by (*S*)-**29**.

Since the direct asymmetric aldol reaction and Mannich reaction using the binaphthyl-based amino sulfonamide (*S*)-**16** gave a single stereoisomer predominantly through the *s-cis*-enamine intermediate, the direct asymmetric aminoxylation reaction with (*S*)-**16** was then examined.[50,51] In the presence of 5 mol % of (*S*)-**16**, the reaction of aldehydes with nitrosobenzene proceeded smoothly to give aminoxylation products in good yields (>86%) with excellent enantioselectivities (>97% ee) (Scheme 35). In addition, the catalyst loading could be reduced to 0.2 mol % without loss of enantioselectivity. No hydroxyamination product was observed in the reaction, and the triflamide group on (*S*)-**16** was found to have enough acidity for the aminoxylation reaction, similar to those of carboxylic acid and tetrazole groups.



Scheme 35. Asymmetric aminoxylation of aldehydes catalyzed by (*S*)-**16**.

In all cases examined in this study, the absolute configuration of the aminoxylated products was determined to be *S*. The observed stereochemistry was rationalized by the transition state model, in which nitrosobenzene approaches the *Si* face of the *s-cis*-enamine as directed by triflamide group (Figure 23). In addition, these results support the transition state models including the *s-cis*-enamine intermediate in the *syn*-selective cross-aldol reaction and the *anti*-selective Mannich reaction catalyzed by (*S*)-**16** (Figure 15).

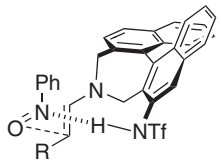
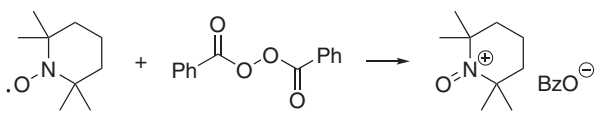


Figure 23. Plausible transition state model for the asymmetric aminoxylation reaction catalyzed by (*S*)-**16**.

3.7 Direct Asymmetric Aminoxylation of Aldehydes with TEMPO. The direct asymmetric aminoxylation of aldehydes with nitrosobenzene gives virtually optically pure α-oxygenated aldehydes as an important building block. However, the obtained α-aminoxy aldehydes are unstable because of instability of the N–O bond and the reactivity of the carbonyl group as well as the nucleophilic nitrogen atom, and are not isolable without reduction to the corresponding alcohols.[46] As another type of organocatalytic aminoxylation of aldehydes, a coupling reaction between stable radical TEMPO and the enamine intermediate, which is generated from a secondary amine catalyst and an aldehyde, in the presence of a metal single electron oxidant has been developed by Sibi and has been investigated by several groups in the past few years.[52,53] Although α-aminoxy aldehydes obtained from such reactions seemed to be stable and useful due to the bulky aminoxy group, there is some room for improvement. First, the substrate scope is still limited, and indeed, in the reaction of 3-methylbutanal, the racemic product was obtained under the Sibi's conditions. Second, a metal oxidant or a metal catalyst in the presence of a co-oxidant is necessary to promote this aminoxylation. In consideration of environmental consciousness, the development of a metal-free variant of this reaction is quite attractive and challenging. In an effort to address these issues, we found that oxoammonium salt **30**, which is in situ generated from TEMPO and benzoyl peroxide (BPO), could be used as an effective aminoxylating agent (Scheme 36).[54] In this metal-free aminoxylation, a newly designed binaphthyl-based amine (*S*)-**31** was found to be an efficient catalyst (Figure 24), and a highly enantioselective *metal-free* α-aminoxylation of alde-



Scheme 36. Generation of oxoammonium salt from TEMPO and BPO.

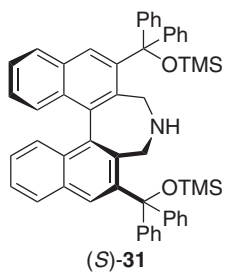
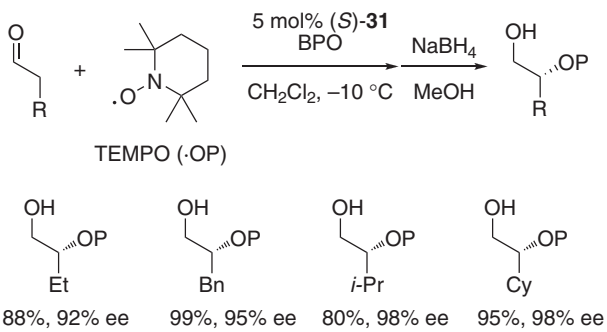


Figure 24. Binaphthyl-based amine catalyst (*S*)-**31**.



Scheme 37. Asymmetric aminoxylation of aldehydes by (*S*)-**31**.

hydes with broad substrate scope has successfully been achieved (Scheme 37). It should be noted that an α-aminoxy aldehyde could be isolated by column chromatography without reduction of the carbonyl group, and neither decomposition nor racemization was observed.

Based on the observed stereochemistry, transition state models can be proposed as shown in Figure 25. The present aminoxylation seems to proceed through the enamine intermediate or the enamine radical cation generated by the oxidation of the enamine intermediate with BPO or oxoammonium salt **30**. In either ionic or radical pathway, one face of the enamine intermediate or the enamine radical cation is effectively shielded by the bulky substituent of (*S*)-**31**.

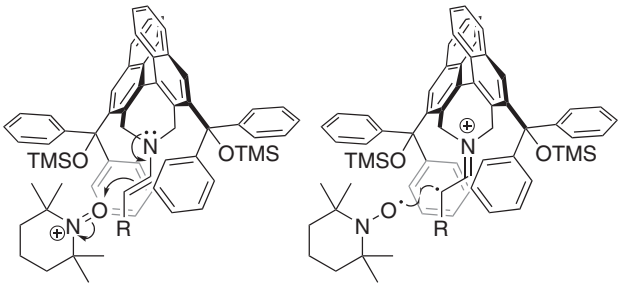
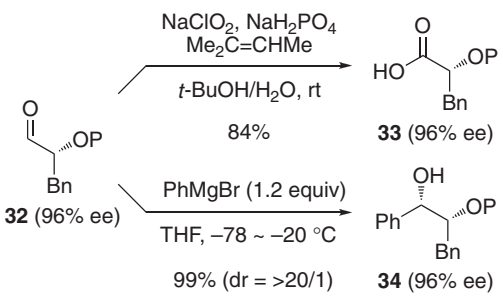


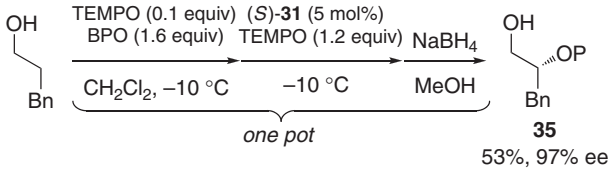
Figure 25. Plausible transition state models for the asymmetric aminoxylation reaction catalyzed by (*S*)-**31**.

The obtained optically enriched α-aminoxy aldehyde **32** was converted to the corresponding α-hydroxy acid derivative **33** without loss of optical purity (Scheme 38, upper path). In this transformation, the 2,2,6,6-tetramethylpiperidinyl group was not oxidized and acted as a protecting group. The reaction of **32** with PhMgBr in THF proceeded smoothly to give the corresponding half-protected 1,2-diol **34** in excellent diastereoselectivity (Scheme 38, lower path). The observed diastereoselectivity is well explained by non-chelation control, which might be attributable to the bulky and non-protic aminoxy group of **32**.



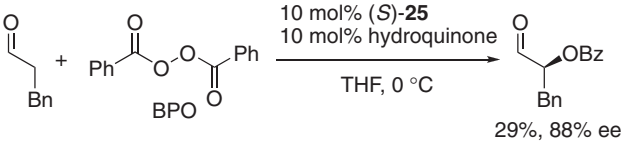
Scheme 38. Synthetic applications of α-aminoxy aldehyde.

Since TEMPO serves the dual roles of oxidation catalyst and aminoxylating agent, the one-pot oxidation–aminoxylation of an alcohol has also been realized (Scheme 39).[55] 3-Phenylpropanol was first treated with BPO (1.6 equiv) and a catalytic amount of TEMPO (0.1 equiv) in CH_2Cl_2 at $-10\,^{\circ}C$ for 10 h, and the resulting 3-phenylpropanal was then aminoxylated by (*S*)-**31** (5 mol %) and TEMPO (1.2 equiv). The obtained α-aminoxy aldehyde was reduced with $NaBH_4$ to determine the enantioselectivity, giving the corresponding β-aminoxy alcohol **35** in 53% yield with 97% ee.

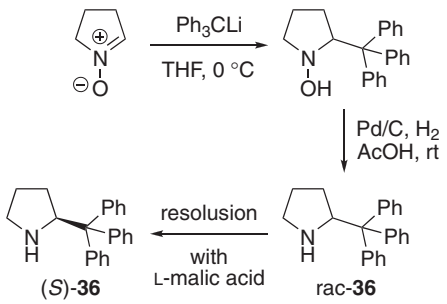


Scheme 39. One-pot oxidation–aminoxylation of 3-phenylpropanol.

3.8 Direct Asymmetric Benzoyloxylation of Aldehydes. We have also been interested in the development of an asymmetric acyloxylation of aldehydes which introduces a useful oxygen functionality.[56] When 3-phenylpropanal was treated with benzoyl peroxide (BPO) in the presence of binaphthyl-based amino alcohol (*S*)-**25** (10 mol %) and hydroquinone (10 mol %) as a radical scavenger in THF at 0 °C, the desired α-benzoyloxylated aldehyde was obtained in low yield with good enantioselectivity (29%, 88% ee) (Scheme 40).[57] Under similar conditions, the reaction catalyzed by a commercially available chiral pyrrolidine (*S*)-2-[diphenyl{(trimethylsilyl)oxy}methyl]pyrrolidine[58] gave the product in moderate yield with high enantioselectivity (45%, 93% ee). Since substantial amounts of 3-phenylpropanal remained unreacted in both cases, we assumed that the catalyst might be deactivated through benzoyloxylation of the catalyst nitrogen atom by BPO. With the expectation of suppressing such undesired catalyst deactivation by changing the steric and electronic environment of the catalyst, a novel chiral pyrrolidine (*S*)-**36** having a C_3-symmetric triphenylmethyl group was prepared (Scheme 41).[59]



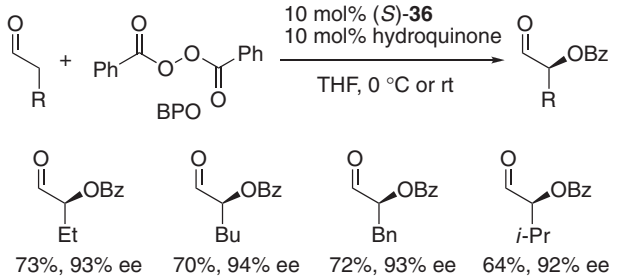
Scheme 40. Asymmetric benzoyloxylation of 3-phenylpropanal catalyzed by (*S*)-**25**.



Scheme 41. Synthesis of (*S*)-2-(triphenylmethyl)pyrrolidine (*S*)-**36**.

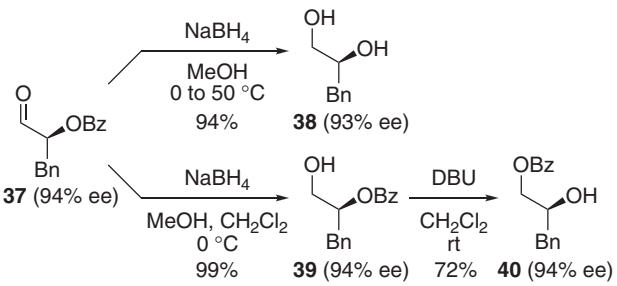
The reaction catalyzed by (*S*)-**36** proceeded smoothly to give the product in improved yield without loss of enantioselectivity (Scheme 42). In general, the direct asymmetric α-benzoyloxylation reaction of several other aldehydes with BPO in the presence of 10 mol % (*S*)-**36** and hydroquinone gave the

corresponding α-benzoyloxyaldehydes with good enantioselectivity (>92% ee). It is noteworthy that the optically enriched α-benzoyloxyaldehyde could be isolated by silica gel column chromatography without loss of enantioselectivity.



Scheme 42. Asymmetric benzoyloxylation of aldehydes catalyzed by (*S*)-**36**.

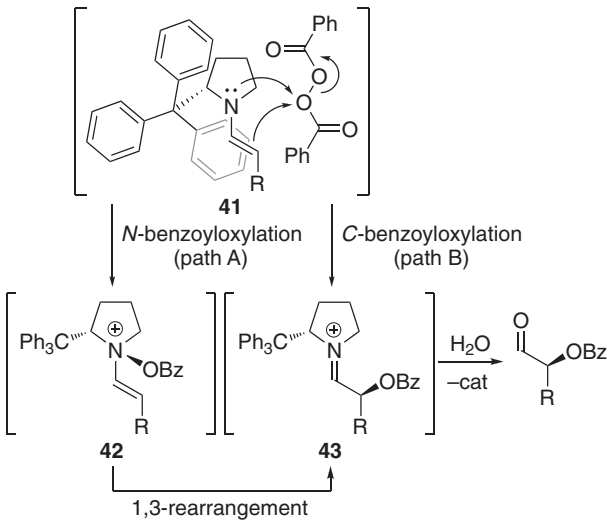
The obtained α-benzoyloxyaldehyde was a useful intermediate in organic synthesis and readily converted to the corresponding diol and mono-protected diols (Scheme 43). When a mixture of **37** in MeOH was treated with $NaBH_4$ at 0 °C and then heated to 50 °C, diol **38** was obtained in excellent yield with almost complete retention of stereochemistry. On the other hand, reduction of **37** with $NaBH_4$ at 0 °C rapidly formed a mono-protected diol **39** in quantitative yield without loss of optical purity. The benzoyl group of **39** migrated to the primary hydroxy group in the presence of DBU to give the other mono-protected diol **40**.



Scheme 43. Synthetic applications of α-benzoyloxyaldehyde.

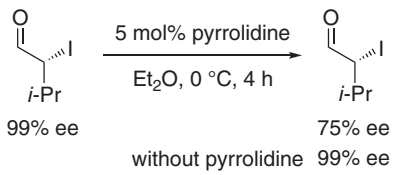
We considered the following two plausible ionic mechanisms for the present benzoyloxylation, although other plausible mechanisms via radical intermediates cannot be ruled out: (1) The enamine intermediate **41** reacts at nitrogen, giving an *N*-benzoyloxy adduct **42** that undergoes a 1,3-rearrangement to the α-benzoyloxy iminium intermediate **43** (Scheme 44, path A). (2) The enamine intermediate **41** reacts at carbon to give the α-benzoyloxy iminium intermediate **43** directly (Scheme 44, path B). In both cases, BPO would approach *s-trans*-enamine **41**, whose one face is shielded by the trityl group of catalyst (*S*)-**36**. Hence, the reaction of an aldehyde with BPO catalyzed by (*S*)-**36** provides the (*S*)-isomer predominantly.

3.9 Direct Asymmetric Halogenation of Aldehydes. The development of a highly enantioselective α-halogenation of aldehydes is an important transformation because of the high synthetic utility of optically active α-haloaldehydes. Among



Scheme 44. Possible reaction pathways of the asymmetric benzoyloxylation with BPO.

α-haloaldehydes, α-iodoaldehydes are synthetically most useful, since they have characteristic features including the high leaving group ability and the steric bulk of the iodo group. However, although some organocatalytic asymmetric α-halogenation reactions of aldehydes have been reported,[60–62] examples of asymmetric synthesis of α-iodoaldehydes as a member of synthetically valuable α-haloaldehydes are especially scarce, probably due to the ease of undesired racemization (Scheme 45).[62] In an effort to address this issue, we designed a new bifunctional organocatalyst (*S*)-**44** which consists of a less basic binaphthyl-based amine moiety and hydroxy groups as an activator of an iodination agent (Figure 26).[63]



Scheme 45. Racemization of the optically enriched α-iodoaldehyde by pyrrolidine.

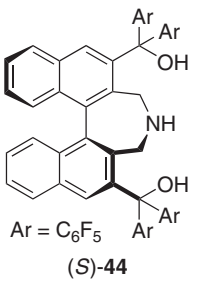
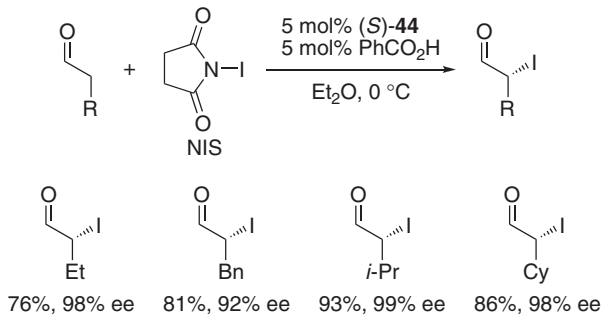


Figure 26. Binaphthyl-based amino alcohol catalyst (*S*)-**44**.

The iodination of aldehydes with NIS in the presence of the catalyst (*S*)-**44** (5 mol %) and benzoic acid (5 mol %) proceeded to furnish the corresponding α-iodoaldehydes in good to excellent yields (>74%) and enantioselectivities (>90% ee) (Scheme 46).



Scheme 46. Asymmetric iodination of aldehydes catalyzed by (*S*)-**44**.

On the basis of the observed stereochemistry, a plausible transition state is proposed as shown in Figure 27. The NIS activated and directed by the hydroxy group on (*S*)-**44** approaches the *Re* face of the enamine. Hence, the reaction of an aldehyde with NIS catalyzed by (*S*)-**44** provides the (*R*)-isomer predominantly in contrast to the direct asymmetric hydroxyamination reaction of aldehydes using a similar catalyst (*S*)-**25**, which gives the opposite (*S*)-isomer (Scheme 30 and Figure 21).

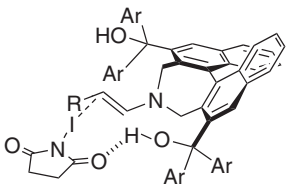
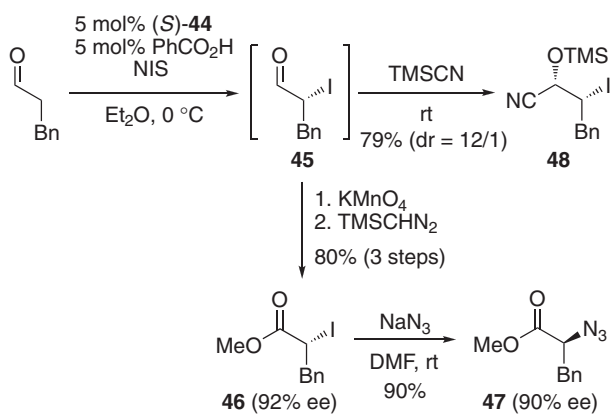


Figure 27. Plausible transition state model for the asymmetric iodination catalyzed by (*S*)-**44**.

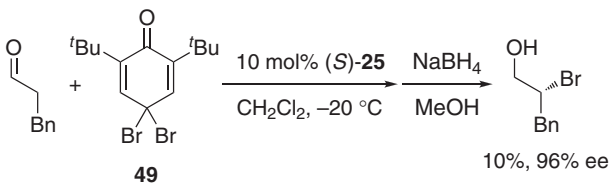
To demonstrate the synthetic utility of this transformation, the optically enriched α-iodoaldehyde was converted to the corresponding α-amino acid derivative (Scheme 47). Thus, treatment of the α-iodoaldehyde **45** with $KMnO_4$, followed by addition of $TMSCHN_2$, resulted in clean formation of the corresponding methyl ester **46**. By treatment with NaN_3, the resulting methyl ester **46** was transformed to the α-azido ester **47**, which can be readily reduced to the corresponding α-amino ester. While the azidation of α-chloroester needs heating



Scheme 47. Synthetic applications of α-iodoaldehyde.

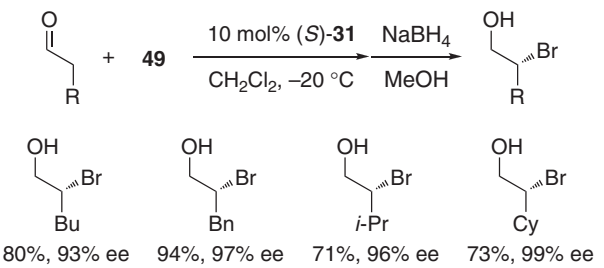
(60 °C), the reaction of the corresponding α-iodoester **46** proceeded smoothly even at room temperature. Furthermore, since silylcyanation of aldehydes with TMSCN is known to be catalyzed by I_2,[64] we examined the one-pot silylcyanation of the α-iodoaldehyde with TMSCN in the presence of I_2 generated from slightly excess NIS. The α-iodoaldehyde **45** was converted to the corresponding silylcyanation product **48** with high diastereoselectivity, probably due to the steric bulk of the iodo group. Under similar conditions the corresponding α-chloroaldehyde was silylcyanated with low diastereoselectivity (9% de).

Although optically active α-bromoaldehydes would also be useful chiral building blocks because of their size and leaving ability of bromine atoms, only a few examples of asymmetric synthesis of α-bromoaldehydes and their in situ transformations using such characteristic features have been reported to date.[62,65] In this context, we have been interested in the development of a general method for synthesis of optically active α-bromoaldehydes and utilization of their carbonyl moiety by in situ transformation. When 3-phenylpropanal was treated with a brominating agent **49** in the presence of 10 mol % of the axially chiral amino alcohol (*S*)-**25** and then with $NaBH_4$, the corresponding β-bromoalcohol was obtained in low yield with excellent enantioselectivity (Scheme 48).



Scheme 48. Asymmetric bromination of 3-phenylpropanal catalyzed by (*S*)-**25**.

An NMR study suggested that the hydroxy group of (*S*)-**25** accerelated the catalyst deactivation by the brominating agent **49**. Thus, the hydroxy-protected secondary amine catalyst (*S*)-**31** was employed with the aim of circumventing the catalyst deactivation. As a result of the protection of hydroxy group and the introduction of steric bulkiness into the catalyst, the bromination of aldehydes catalyzed by (*S*)-**31** proceeded smoothly in good to excellent yield (>71%) and enantioselectivity (>92% ee) (Scheme 49).[66]



Scheme 49. Asymmetric bromination of aldehydes catalyzed by (*S*)-**31**.

Based on the stereochemistry of the products, a transition state model can be proposed as shown in Figure 28. One face of the enamine intermediate is effectively shielded by the bulky

substituent of (*S*)-**31**, and consequently, the reaction of an aldehyde with **49** catalyzed by (*S*)-**31** provides the (*R*)-isomer predominantly.

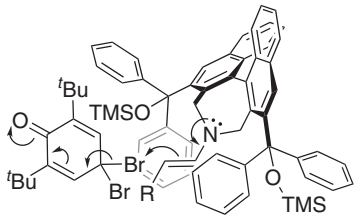
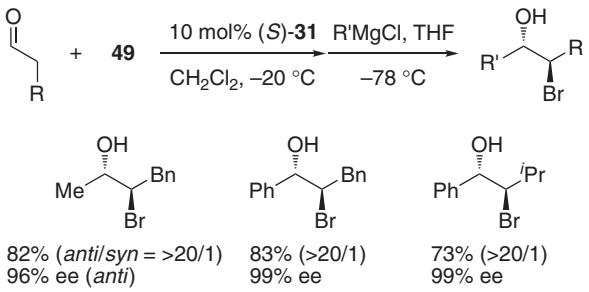


Figure 28. Plausible transition state model for the asymmetric bromination catalyzed by (*S*)-**31**.

The optically enriched α-bromoaldehydes should be reduced in situ with $NaBH_4$ to the corresponding alcohol due to the inherent instability of α-haloaldehydes. If a certain carbon anion species could be used instead of the hydride anion under the influence of the large bromine atom, an additional stereocenter could be constructed stereoselectively through the carbon–carbon bond formation. Hence, we then examined the one-pot synthesis of bromohydrins using Grignard reagents as one of the most versatile organometallic reagents. The reaction of the in situ generated optically enriched α-bromoaldehydes with methyl Grignard reagents in THF at -78 °C proceeded to give the corresponding *anti*-bromohydrins in excellent diastereoselectivity (Scheme 50). The observed diastereoselectivity is well explained by non-chelation control, which might be attributable to the large bromine atom.



Scheme 50. Enantio- and diastereoselective one-pot synthesis of bromohydrins.

Conclusion

This review has overviewed our recent developments of asymmetric reactions with chiral amine organocatalysts. In our studies, several chiral amines, which are not derived from natural products such as amino acids, were designed and synthesized. Taking advantage of their characteristic features, we could realize the unique reactivity and selectivity in asymmetric Diels–Alder, oxa-Michael addition, aldol, Mannich, hydroxyamination, aminoxylation, benzoyloxylation, and halogenation reactions, respectively. We believe that our designer amine organocatalysts offer the possibility of a new catalyst design for future research in this area.

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