Design of chiral bifunctional secondary amine catalysts for asymmetric enamine catalysis

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A series of binaphthyl-based secondary amine catalysts containing various functional groups have been designed as new chiral bifunctional amine catalysts. These chiral organocatalysts have been successfully applied to several asymmetric reactions *via* enamine intermediates and exhibit unique reactivity and selectivity in comparison with proline and its derivatives.

1. Introduction

The development of organocatalytic reactions is one of the most exciting topics in practical organic synthesis because of their operational simplicity, mild reaction conditions and environmental advantages.[1] In this area, chiral secondary amine catalysts have been utilized frequently in various asymmetric reactions *via* enamine intermediates.[2] Most such efficient chiral secondary amine catalysts have been derived from proline, and a pyrrolidine core structure with at least one α-substituent seemed indispensable for rational catalyst design. In this context, we have been interested in designing a structurally novel secondary amine catalyst to extend the possibility of enamine catalysis, and several binaphthyl-based secondary amine catalysts having various functional groups at the 3-position have been developed to date (Fig. 1). Our bifunctional binaphthyl-based secondary amine catalysts are characterized by the following features: (1) a 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 this distance between the functional groups; (3) the absence of an α-substituent, which decreases the steric repulsion in the enamine intermediate; (4) ease of introduction of various 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 this *feature article*, we wish to review our recent

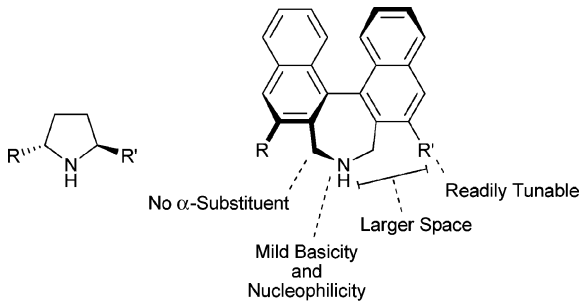

Fig. 1 Binaphthyl-based bifunctional secondary amine catalysts.

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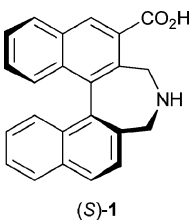
achievements on the development of organocatalytic asymmetric reactions with binaphthyl-based bifunctional secondary amine catalysts and related catalysts.

2. Design of chiral bifunctional secondary amine catalysts

2.1 Direct asymmetric aldol reaction of ketones with aldehydes

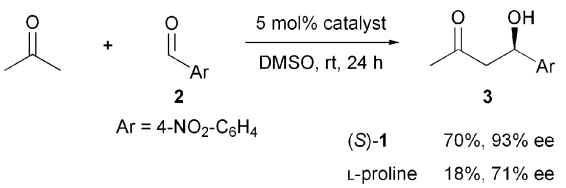
In the area of organocatalysis, proline has been utilized in various asymmetric reactions including direct asymmetric aldol reactions.[2,3] Some such proline-catalyzed aldol reactions, however, have serious limitations on the reactivity and selectivity. Although these problems were overcome through the 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*)-**1** (Fig. 2) having a binaphthyl backbone as a frequently utilized chiral unit in asymmetric catalysts.[4]

We first examined the direct asymmetric aldol reaction of acetone with the newly synthesized binaphthyl-based amino acid catalyst (*S*)-**1**. In the presence of 5 mol% of (*S*)-**1**, the reaction of 4-nitrobenzaldehyde **2** with acetone in DMSO at room temperature proceeded gradually to afford the aldol adduct **3** in 70% yield with 93% ee (Scheme 1). In contrast, the reaction with L-proline under the same reaction conditions gave **3** in low yield with moderate enantioselectivity, together with 1,3-oxazolidine **4** (Fig. 3, 48% yield based on proline) derived from proline and two equivalents of **2**. Kinetic studies revealed that the reaction with the proline catalyst proceeded more rapidly than that with (*S*)-**1** 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 2, 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.[5] On the other hand, binaphthyl-based amino acid (*S*)-**1** is chemically stable, and hence the reaction promoted by (*S*)-**1** leads to a better yield despite the slower reaction rate owing to the moderate nucleophilicity of the benzylic amine moiety in (*S*)-**1**.



(*S*)-**1**

Fig. 2 Binaphthyl-based amino acid (*S*)-**1**.



2 **3**

Scheme 1 Direct asymmetric aldol reaction of acetone with **2**.

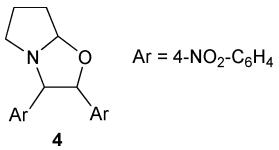


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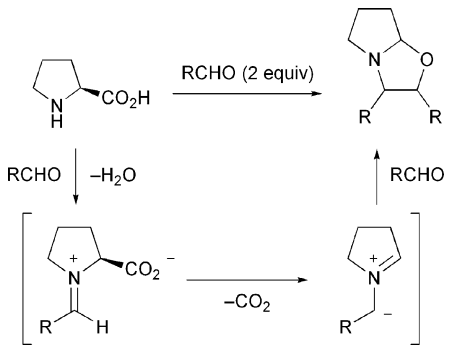
Fig. 3 1,3-Oxazolidine **4**.

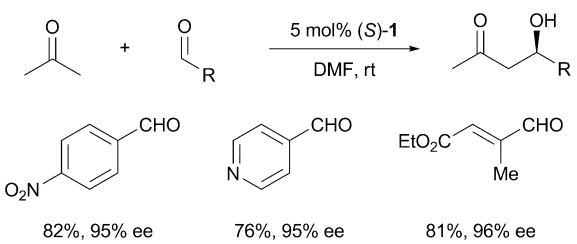


Scheme 2 Decomposition of proline and formation of 1,3-oxazolidine.

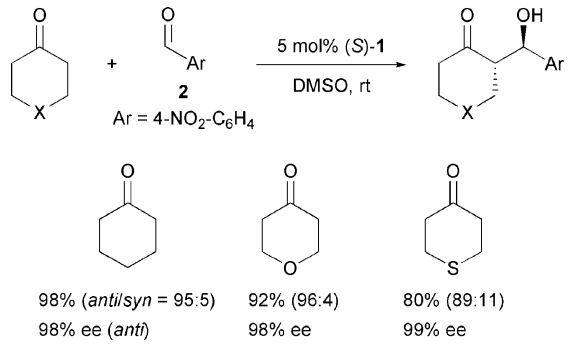
Under optimized conditions, electron-deficient aromatic, heteroaromatic and olefinic aldehydes were found to be suitable substrates, with the direct aldol reactions generally giving the corresponding aldol adducts in moderate to good yields with excellent enantioselectivities in most cases (>95% ee) (Scheme 3). Unfortunately, however, the reaction of a simple aldehyde, benzaldehyde, gave the aldol adduct in low yield (22%), albeit with excellent enantioselectivity (96% ee).

Binaphthyl-based amino acid catalyst (*S*)-**1** 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 4).

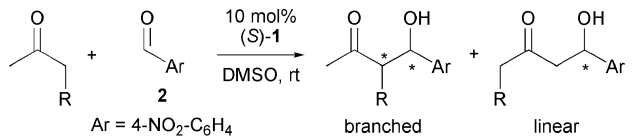
We also investigated the use of a series of acyclic unsymmetrical ketones (Scheme 5). Surprisingly, the reaction of 2-butanone with **2** took place mainly at the methylene position to afford the branched *anti*-aldol adduct as a major regioisomer and diastereomer, with virtually complete enantioselectivity,



Scheme 3 Direct asymmetric aldol reaction of acetone with aldehydes catalyzed by (*S*)-**1**.



Scheme 4 Direct asymmetric aldol reaction of cyclic ketones with **2** catalyzed by (*S*)-**1**.



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 5 Direct asymmetric aldol reaction of acyclic ketones with **2** catalyzed by (*S*)-**1**.

while the use of proline as catalyst for this reaction exclusively gave the linear aldol adduct.[6] 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.

In the reaction catalyzed by (*S*)-**1**, both s-*trans*- and s-*cis*-enamines are possible as shown in Fig. 4. The absolute stereochemistry of the *anti*-aldol adduct **5**, which was obtained as a major isomer in the reaction of cyclohexanone with **2** catalyzed by (*S*)-**1**, was determined to be (2*S*,1′*R*) (Scheme 6). 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 **6**. Hence, the reaction of an aldehyde with other ketones in the presence of (*S*)-**1** presumably proceeds by way of an s-*trans*-enamine structure, similar to the transition state involving the s-*trans*-enamine in the proline-catalyzed reaction.[6]

Although the robust binaphthyl-based amino acid (*S*)-**1** gave a higher yield than the proline catalyst in the direct asymmetric aldol reaction with electron-deficient aldehydes,

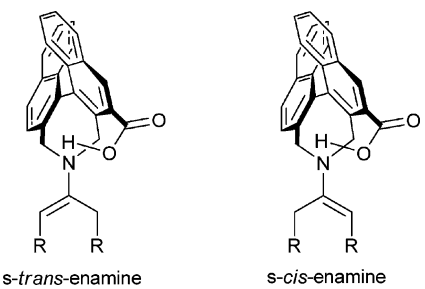
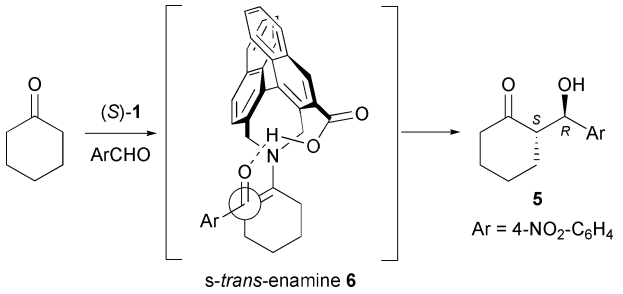


Fig. 4 Possible enamine intermediates generated from (*S*)-**1**.



Scheme 6 Plausible transition state model for the direct asymmetric aldol reaction catalyzed by (*S*)-**1**.

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*)-**1**. Accordingly, we designed a biphenyl-based amino acid of type (*S*)-**7** (Fig. 5), which is highly substituted with electron-donating methoxy groups, with the expectation of an increased nucleophilicity of the amine moiety.[7]

As expected, the aldol reaction of acetone with **2** catalyzed by (*S*)-**7** was significantly accelerated in comparison with (*S*)-**1**, and only 0.5 mol% of (*S*)-**7** 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*)-**7** was sufficient to achieve a high yield (91%) and an excellent enantioselectivity (96% ee) in the reaction of acetone with **2** (Scheme 7). 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*)-**7**. Olefinic, heteroaromatic, and aromatic aldehydes with electron-withdrawing groups were found to be suitable substrates (> 68%, > 94% ee). With 2 mol% of (*S*)-**7**, even simple aromatic aldehydes such as benzaldehyde and β-naphthylaldehyde gave

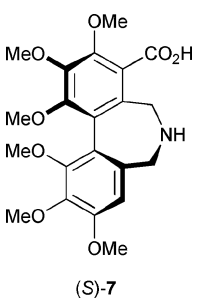
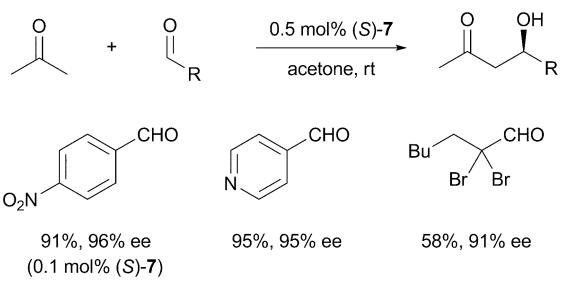


Fig. 5 Biphenyl-based amino acid (*S*)-**7**.



Scheme 7 Direct asymmetric aldol reaction of acetone with aldehydes catalyzed by (*S*)-**7**.

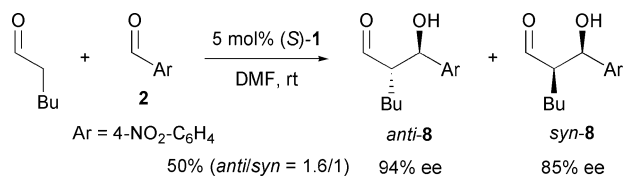
the corresponding aldol adducts in moderate yields (50%, 95% ee and 50%, 94% ee). Furthermore, the reaction of α,α-dibromoheptanal as an aliphatic aldehyde substitute was also found to proceed with high enantioselectivity (91% ee).

2.2 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,[8] and *anti*-aldol adducts have been obtained in a highly enantioselective fashion using proline and related catalysts. We then examined the cross-aldol reaction between hexanal and 4-nitrobenzaldehyde **2** using the binaphthyl-based amino acid (*S*)-**1** as catalyst (Scheme 8). The reaction proceeded to give the *anti*-aldol adduct **8** as a major diastereomer with excellent enantioselectivity, and the transition state seemed to involve the s-*trans*-enamine intermediate, which is similar to that of the proline-catalyzed reaction (Fig. 6). Interestingly, however, a substantial amount of the *syn*-aldol adduct **8** was also obtained, suggesting the existence of the s-*cis*-enamine intermediate, in which a steric repulsion between the enamine and the carboxylic acid group is much smaller than that on using proline.

These observations prompted us to develop a hitherto difficult *syn*-selective direct cross-aldol reaction and design a new axially chiral amino sulfonamide (*S*)-**9** (Fig. 7) with an acidic proton more remote from the secondary amino group than that of the carboxylic acid group in (*S*)-**1**.[9]

Since it would be difficult for s-*trans*-enamine **A**, which is generated from a donor aldehyde and (*S*)-**9**, to react with an acceptor aldehyde that is activated by the distal acidic proton of the triflamide of (*S*)-**9**, the cross-aldol reaction catalyzed by (*S*)-**9** would be expected to proceed through s-*cis*-enamine **B**, thus giving the desired unusual *syn*-product as shown in Scheme 9.



Scheme 8 Direct asymmetric cross-aldol reaction between aldehydes.

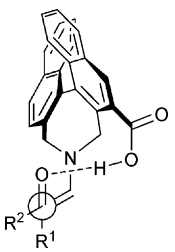


Fig. 6 Plausible transition state model for the cross-aldol reaction catalyzed by (*S*)-**1**.

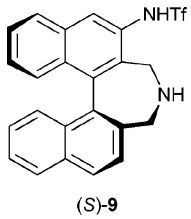
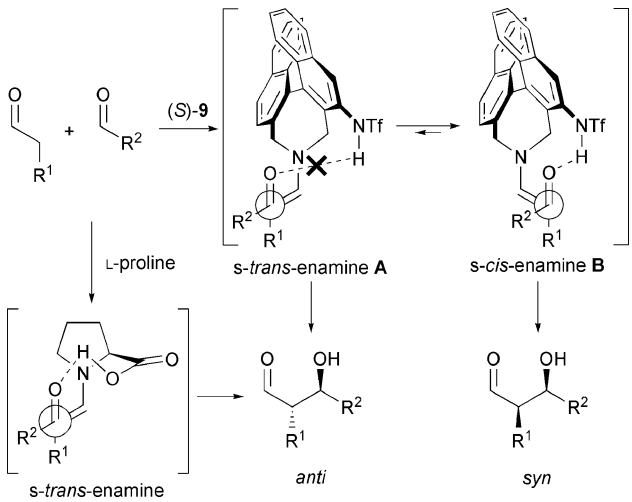
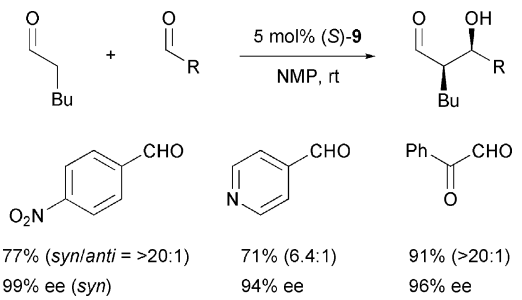


Fig. 7 Binaphthyl-based amino sulfonamide (*S*)-**9**.



Scheme 9 Possible transition states for the direct asymmetric cross-aldol reaction catalyzed by (*S*)-**9**.

We first examined the reaction between hexanal and **2** in the presence of 5 mol% (*S*)-**9** 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*)-**9**, depending on the solvent used.[10] The reaction catalyzed by (*S*)-**9** was also applicable to 4-pyridylcarbaldehyde and phenylglyoxal as its monohydrate (Scheme 10). In all cases, the (*S*)-**9**-catalyzed method was complementary to the proline-catalyzed reactions



Scheme 10 Direct asymmetric cross-aldol reaction between aldehydes catalyzed by (*S*)-**9**.

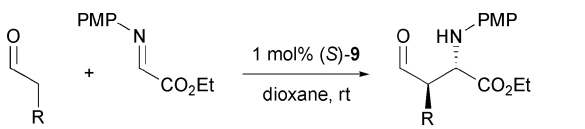
in terms of the *syn*/*anti* selectivity. It should also be noted that more than 95% of (*S*)-**9** was recovered unchanged after column chromatography.

2.3 Direct asymmetric *anti*-selective Mannich reaction of aldehydes

The axially-chiral amino sulfonamide (*S*)-**9** was also successfully applied to the direct asymmetric Mannich reaction of aldehydes with α-imino esters.[11] Catalyst (*S*)-**9** has the advantage of giving mainly *anti*-products, while proline shows the opposite *syn*-selectivity.[12] In the case of primary-alkyl aldehydes, 1 mol% of (*S*)-**9** 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 11). The catalyst loading can be reduced to less than 1 mol% of (*S*)-**9** 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.

Based on the observed stereochemistry in the cross-aldol and Mannich reactions catalyzed by (*S*)-**9**, transition state models can be proposed as shown in Fig. 8. In each case, the *Re* face of the aldehydes or the *Si* face of the imines approaches the enamine intermediate as directed by the distant acidic proton of the triflamide group and, consequently, the C–C bond forming reaction takes place on the *Si* face of the s-*cis*-enamine in a highly diastereo- and enantioselective fashion, giving *syn*-aldol adducts or *anti*-Mannich adducts, respectively.

The moderate yields in the Mannich reactions of sterically hindered aldehydes can be explained by the moderate nucleophilicity of the binaphthyl-based amino sulfonamide (*S*)-**9**. Thus, we have designed and synthesized new chiral amino sulfonamide catalysts (*R*,*R*)-**10**,[13] (*S*)-**11**[14] and (*S*)-**12**[15] (Fig. 9)



R = Me	0.2 mol% (*S*)-**9**	R = Bu	R = Bn
93% (*anti*/*syn* = 13:1)	82% (11:1)	93% (>20:1)	92% (11:1)
>99% ee (*anti*)	97% ee	99% ee	>99% ee

Scheme 11 Direct asymmetric Mannich reaction of aldehydes catalyzed by (*S*)-**9**.

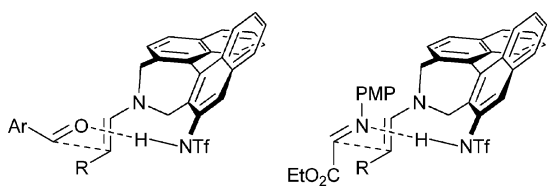
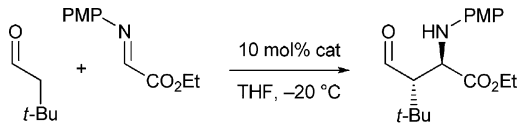


Fig. 8 Plausible transition state models for the direct asymmetric cross-aldol and Mannich reactions catalyzed by (*S*)-**9**.

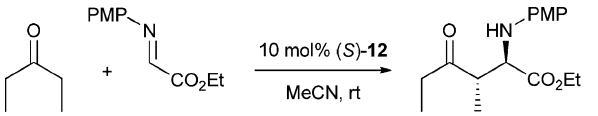
(*R*,*R*)-**10** (*S*)-**11** (R = Tf)
(*S*)-**12** (R = Nf)

Fig. 9 Pyrrolidine-based amino sulfonamides (*R*,*R*)-**10**, (*S*)-**11** and (*S*)-**12** (Nf = $C_4F_9SO_2$).



(*R*,*R*)-**10**	(*S*)-**11**	(*S*)-**12**
88% (*anti*/*syn* = 18:1)	92% (20:1)	99% (>20:1)
90% ee (*anti*)	99% ee	98% ee

Scheme 12 Direct asymmetric Mannich reaction of 3,3-dimethylbutanal catalyzed by (*R*,*R*)-**10**, (*S*)-**11** and (*S*)-**12**.



82% (*anti*/*syn* = 5.8:1)
98% ee (*anti*)

Scheme 13 Direct asymmetric Mannich reaction of 3-pentanone catalyzed by (*S*)-**12**.

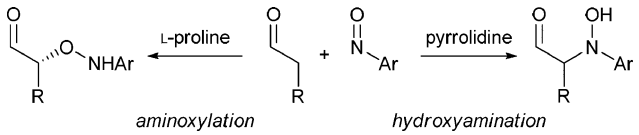
possessing a highly nucleophilic pyrrolidine core and one or two acidic sulfonamide groups.

New pyrrolidine-based amino sulfonamides (*R*,*R*)-**10**, (*S*)-**11** and (*S*)-**12** effectively catalyzed the Mannich reactions of sterically demanding 3,3-dimethylbutanal and less reactive acyclic ketone 3-pentanone to give the *anti*-adducts predominantly in good to excellent yields and enantioselectivities (Schemes 12 and 13).

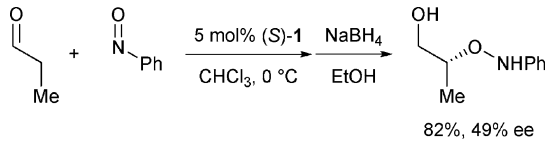
2.4 Direct asymmetric aminoxylation reaction of aldehydes with nitrosobenzene

Nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry,[16] and various organocatalytic asymmetric reactions have recently been developed by exploiting their unique properties. The reactions between nitrosobenzene and enamines as activated carbonyl compounds were 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,[17] use of pyrrolidine as catalyst affords a hydroxyamination product exclusively (Scheme 14).

We then investigated the aminoxylation of aldehydes by using our binaphthyl-based amino acid (*S*)-**1** to understand the selectivity difference between proline and (*S*)-**1**.[18] As expected, the reaction of propanal with nitrosobenzene in the



Scheme 14 Direct aminoxylation and hydroxyamination reactions in enamine catalysis.

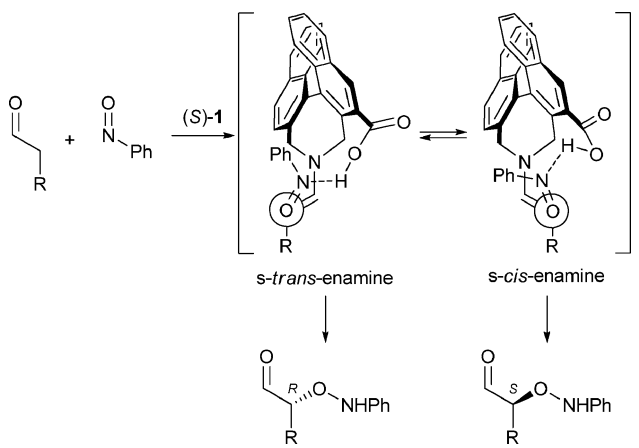


Scheme 15 Direct asymmetric aminoxylation reaction catalyzed by (*S*)-**1**.

presence of 5 mol% of (*S*)-**1** gave the aminoxylation product with moderate enantioselectivity (49% ee) (Scheme 15).

Since activation of nitrosobenzene by strong acids such as carboxylic acids and tetrazoles is necessary to obtain the aminoxylation product,[16f] only the combination of the s-*cis*-enamine and nitrosobenzene activated on the β-face of the enamine could provide the (*S*)-isomer as shown in Scheme 16. The moderate enantioselectivity in the reaction catalyzed by (*S*)-**1** 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*)-**1** (Scheme 8).

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*)-**1**. Contrary to our expectation, however, the reaction using new catalysts having an aromatic substituent gave the (*R*)-isomer as a major enantiomer, with higher enantioselectivity than that of (*S*)-**1**. For instance, the reaction using (*S*)-**13** (Fig. 10) provided the (*R*)-isomer with good enantioselectivity (91% ee) (Scheme 17), and consequently, the preferential formation of the s-*trans*-enamine intermediate was suggested.[18] The reason the reaction catalyzed by (*S*)-**13** proceeds through the s-*trans*-enamine intermediate is not clear at this stage.



Scheme 16 Possible transition states for the direct asymmetric aminoxylation reaction catalyzed by (*S*)-**1**.

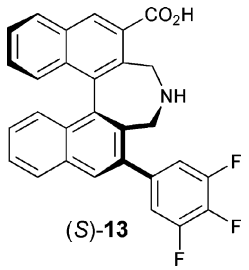
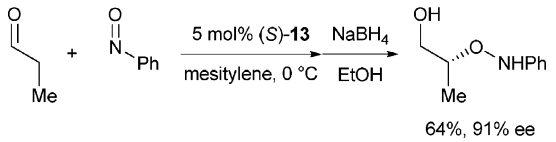
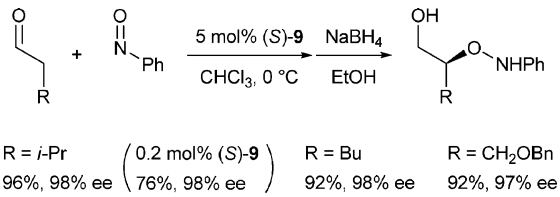


Fig. 10 Binaphthyl-based amino acid (*S*)-**13**.



Scheme 17 Direct asymmetric aminoxylation reaction catalyzed by (*S*)-**13**.



Scheme 18 Direct asymmetric aminoxylation reaction of aldehydes catalyzed by (*S*)-**9**.

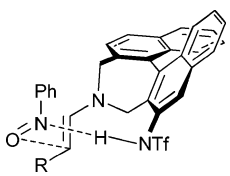
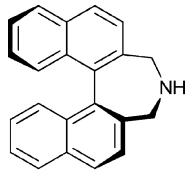


Fig. 11 Plausible transition state model for the direct asymmetric aminoxylation reaction catalyzed by (*S*)-**9**.

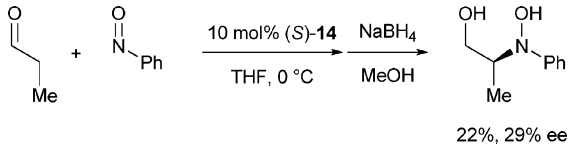
Since the direct asymmetric aldol reaction and Mannich reaction using the binaphthyl-based amino sulfonamide (*S*)-**9** gave a single stereoisomer predominantly through the s-*cis*-enamine intermediate, the direct asymmetric aminoxylation reaction with (*S*)-**9** was then examined.[19] In the presence of 5 mol% of (*S*)-**9**, the reaction of aldehydes with nitrosobenzene proceeded smoothly to give aminoxylation products in good yields (>86%) with excellent enantioselectivities (>97% ee) (Scheme 18). 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*)-**9** was found to have enough acidity for the aminoxylation reaction, similar to those of carboxylic acid and tetrazole groups.

In all cases examined in this study, the absolute configuration of the aminoxylated products was determined to be 7*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 the triflamide



(*S*)-**14**

Fig. 12 Binaphthyl-based secondary amine (*S*)-**14**.



Scheme 19 Direct asymmetric hydroxyamination reaction catalyzed by (*S*)-**14**.

group (Fig. 11). 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*)-**9** (Fig. 8).

2.5 Direct asymmetric hydroxyamination reaction of aldehydes with nitroso compounds

In the absence of relatively strong acids such as carboxylic acids, tetrazoles and sulfonamides, the organocatalytic reaction of aldehydes with nitrosobenzene gives hydroxyamination products exclusively. For instance, a binaphthyl-based secondary amine (*S*)-**14** (Fig. 12) having no acidic group catalyzed the reaction of propanal with nitrosobenzene to give the hydroxyamination product exclusively (Scheme 19).[20]

The hydroxyamination reaction with nitrosobenzene is known to be accelerated by the addition of alcohols, probably due to the activation of nitrosobenzene through the weak hydrogen bonding between the hydroxyl group of the alcohol and the nitroso group. However, since the hydroxyamination

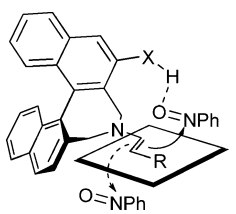
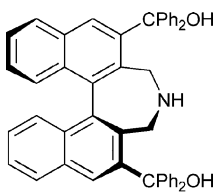


Fig. 13 Direct asymmetric hydroxyamination reaction catalyzed by a secondary amine with a functional group (X–H).



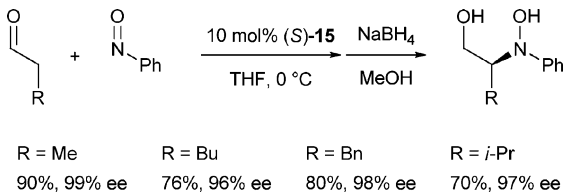
(*S*)-**15**

Fig. 14 Binaphthyl-based amino alcohol (*S*)-**15**.

of aldehydes proceeds with or without such activation, a binaphthyl-based amine catalyst having a mono activating group was not expected to be the optimal catalyst for the highly enantioselective hydroxyamination reaction, unlike the previous aminoxylation reaction (Fig. 13). Thus we have designed a novel C_2-symmetric binaphthyl-based amino alcohol catalyst (*S*)-**15** (Fig. 14) having hydroxyl groups at the appropriate positions to improve both reactivity and enantioselectivity.[20]

In the presence of 10 mol% of (*S*)-**15**, which has sterically congested *tert*-alcohol moieties at 3,3′-positions, the reaction of various aldehydes with nitrosobenzene in THF proceeded smoothly to give the desired hydroxyamination products in good yields (>70%) with excellent enantioselectivities (>96% ee) without forming aminoxylation products (Scheme 20).

A plausible transition state model has been proposed to account for the high selectivity of the catalyst (*S*)-**15** (Fig. 15).



Scheme 20 Direct asymmetric hydroxyamination reaction catalyzed by (*S*)-**15**.

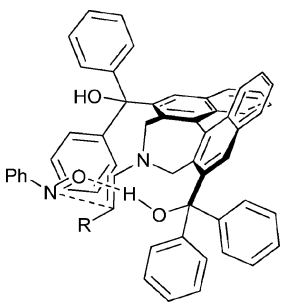
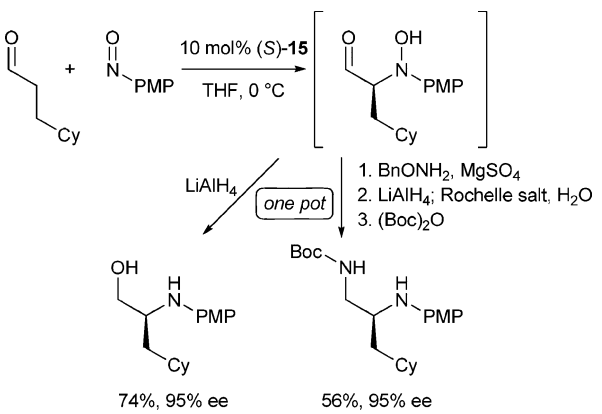


Fig. 15 Plausible transition state model for the direct asymmetric hydroxyamination reaction catalyzed by (*S*)-**15**.



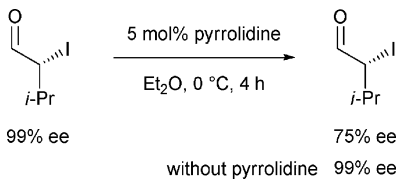
Scheme 21 One-pot asymmetric synthesis of β-amino alcohol and 1,2-diamine.

Each of the hydroxydiphenylmethyl groups on the catalyst (*S*)-**15** might play a different role in the present reaction. After formation of the enamine intermediate from aldehydes and (*S*)-**15**, 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.

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 having cleavable protecting groups were also developed (Scheme 21).

2.6 Direct asymmetric iodination reaction of aldehydes

The development of a highly enantioselective α-halogenation of aldehydes is an important transformation because of the high synthetic utility of the optically active α-haloaldehydes. Among 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,[21–23] examples of asymmetric synthesis of α-iodoaldehydes as members of the synthetically valuable α-haloaldehydes are especially scarce, probably due to the ease of undesired racemization of α-iodoaldehydes (Scheme 22).[23] In an effort to address this issue, we designed a new bifunctional organocatalyst (*S*)-**16** (Fig. 16),



Scheme 22 Racemization of an α-iodoaldehyde catalyzed by pyrrolidine.

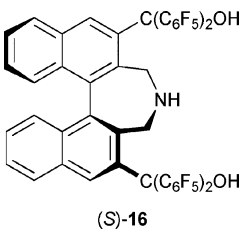
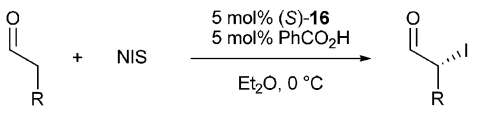


Fig. 16 Binaphthyl-based amino alcohol (*S*)-**16**.



Scheme 23 Direct asymmetric iodination reaction catalyzed by (*S*)-**16**.

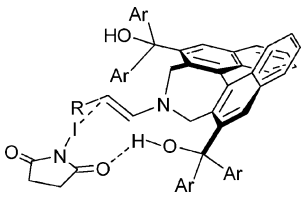
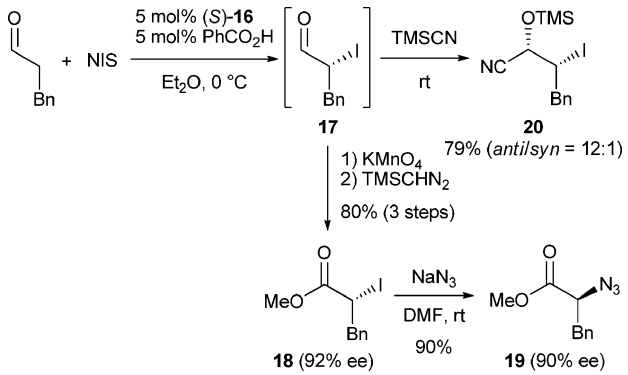


Fig. 17 Plausible transition state model for the direct asymmetric iodination reaction catalyzed by (*S*)-**16**.



Scheme 24 Applications of an α-iodoaldehyde.

which consists of a less basic binaphthyl-based amine moiety and hydroxyl groups as activators of an iodination agent.[24]

The iodination reaction of aldehydes with *N*-iodosuccinimide (NIS) in the presence of the catalyst (*S*)-**16** (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 23).

On the basis of the observed stereochemistry, a plausible transition state is proposed, as shown in Fig. 17. The NIS, activated and directed by a hydroxyl group on (*S*)-**16**, approaches the *Re* face of the enamine. Hence, the reaction of an aldehyde with NIS catalyzed by (*S*)-**16** provides the *R* isomer predominantly, in contrast to the direct asymmetric hydroxyamination reaction of aldehydes using a similar catalyst (*S*)-**15**, which gives the opposite *S* isomer (Scheme 20 and Fig. 15).

To demonstrate the synthetic utility of this transformation, optically enriched α-iodoaldehyde **17** was converted to the corresponding α-amino acid derivative (Scheme 24). Thus, treatment of the α-iodoaldehyde **17** with $KMnO_4$, followed by addition of $TMSCHN_2$, resulted in clean formation of the corresponding methyl ester **18**. By treatment with NaN_3, the resulting methyl ester **18** was transformed to the α-azido ester **19**, which can be readily reduced to the corresponding α-amino ester. While the azidation of an α-chloroester needs heating (60 °C), the reaction of the corresponding α-iodoester **18** proceeded smoothly even at room temperature. Furthermore, since silylcyanation of aldehydes with TMSCN is known to be catalyzed by I_2,[25] we examined the one pot silylcyanation of the α-iodoaldehyde with TMSCN in the presence of I_2 generated from a slight excess of NIS. The α-iodoaldehyde **17** was converted to the corresponding silylcyanation product **20** 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).

Conclusions

This *feature article* has given an overview of our recent developments in organocatalytic asymmetric reactions with chiral secondary amine catalysts. Several binaphthyl-based bifunctional secondary amine catalysts were designed and synthesized by the introduction of appropriate functional groups at the 3-position of the binaphthyl backbone. Taking advantage of their characteristic features, we could realize the unique reactivity and selectivity in asymmetric aldol, Mannich, aminoxylation, hydroxyamination, and iodination reactions, respectively. Our binaphthyl-based bifunctional secondary amine catalysts offer the possibility of a new catalyst design for future research in this area.

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