Research Article

Innovative Molecular Design of Chiral 1,1′-Binaphthyl 2,2′-Disulfonic Acid (BINSA)

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1. Introduction

In modern organic synthesis, design-elegant, practical, cost-effective, and environmentally benign catalytic synthetic methods are important. In particular, more useful and straightforward chiral catalysts are needed to achieve highly enantioselective control to obtain desired optically-pure enantiomers. In this regard, chiral Brønsted acid catalysts which are derived from (*R*)- or (*S*)-BINOL (1,1′-bi-2-naphthol)[1] have found widespread application as chiral organocatalysts and chiral ligands for metal species (Figure 1). Unlike natural chiral auxiliaries, both enantiomers of these artificial Brønsted acid catalysts can be readily prepared from (*R*)- and (*S*)-BINOL, and we can use both catalysts to obtain products with the desired absolute stereochemistry. In general, the Brønsted acidity of the catalysts should be associated with their catalytic activity. Therefore, we developed chiral 1,1′-binaphthyl-2,2-disulfonic acid (BINSA)[2] as a stronger chiral Brønsted acid catalyst than carboxylic acid,[3] phosphoric acid,[4] and phosphoramide[5]. This article outlines of our recent progress in chiral BINSA chemistry, based on the asymmetric synthesis of chiral BINSAs and their use in asymmetric catalyses as organocatalysts and chiral metal-ligands.

2. Asymmetric Synthesis of (*R*)-BINSA ((*R*)-1)

Racemic BINSA was first synthesized by Barber and Smiles in 1928 from potassium 1-iodonaphthalene-2-sulfonate with copper powder in the Ullmann coupling reaction.[6] After 80 years, we reported the preparation of chiral BINSA ((*R*)-**1**) from (*R*)-BINOL (Scheme 1).[7] *O*-Thiocarbamoylation of (*R*)-BINOL, followed by thermolysis in Newman–Kwart rearrangement to the *S*-thiocarbamoyl compound by a microwave technique, reduction to the dithiol by $LiAlH_4$, oxidation with 10 atm of O_2/KOH, and protonation by ion exchange provided (*R*)-**1** on a >10 g scale without a loss of optical purity.

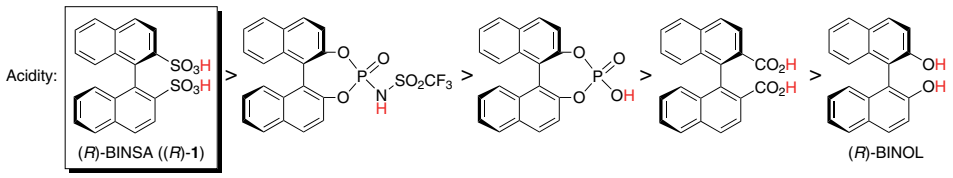
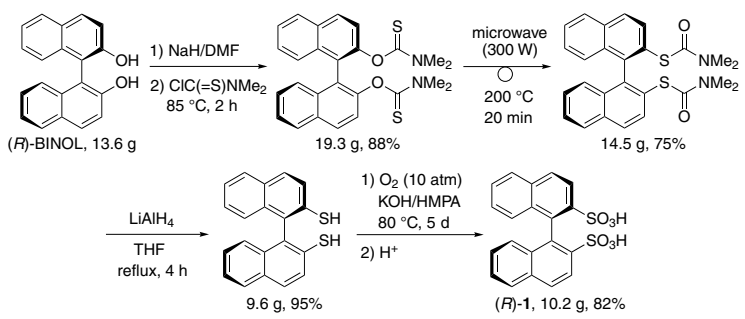
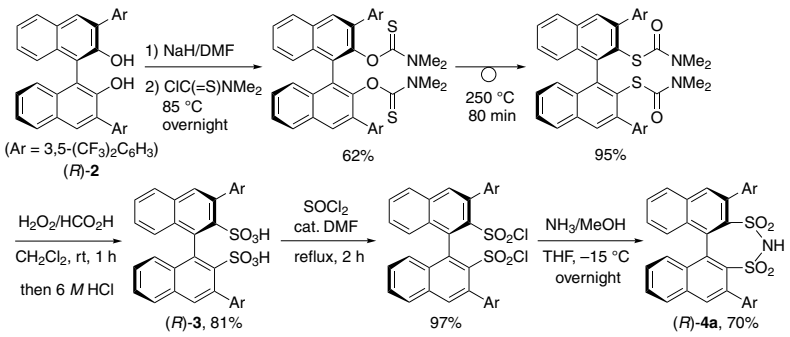


Figure 1. Chiral 1,1′-binaphthyl Brønsted acids and their acidity.

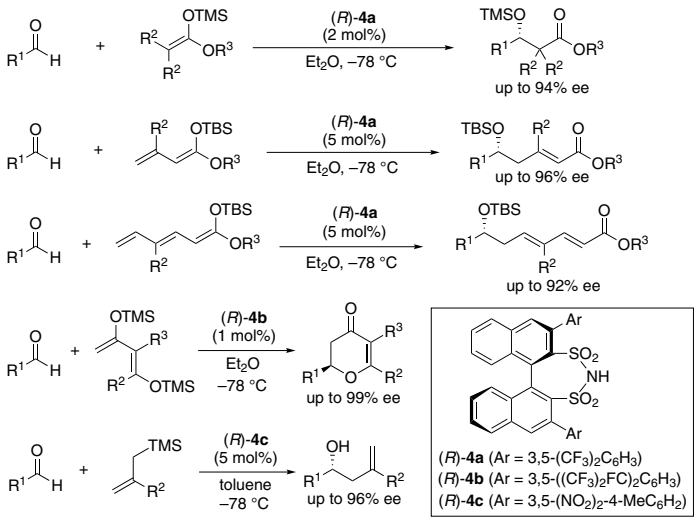


Scheme 1. Asymmetric synthesis of (*R*)-BINSA ((*R*)-**1**) from (*R*)-BINOL.

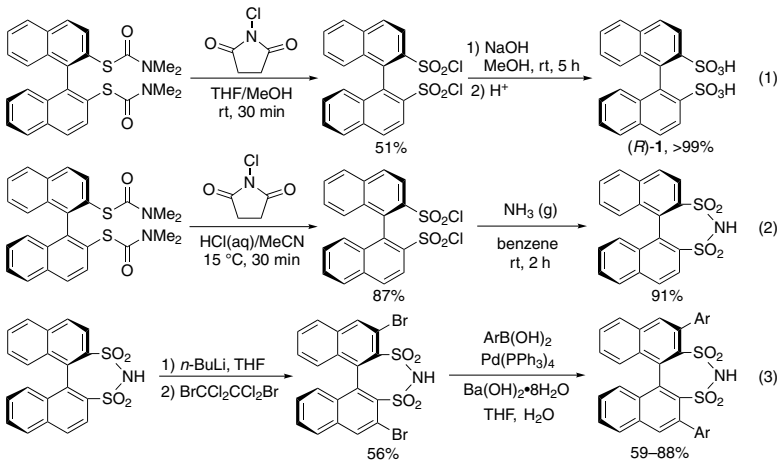
At almost the same time as our report,[7] List independently reported the catalytic asymmetric acylcyanation of aldimines and Hosomi–Sakurai reactions among aldehydes, silylethers, and allylsilanes in the presence of (*R*)-**1**.[8] However, enantioselectivity was not induced (<5% ee) in these reactions. Later, List synthesized (*R*)-3,3′-[3,5-$(CF_3)_2C_6H_3]_2$-BINSA ((*R*)-**3**) and the corresponding chiral sulfonimide ((*R*)-**4a**) from (*R*)-3,3′-[3,5-$(CF_3)_2C_6H_3]_2$-BINOL ((*R*)-**2**) (Scheme 2).[9] In the synthesis of (*R*)-**3**, Newman–Kwart rearrangement and the subsequent oxidation would be facilitated by taking advantage of strong electron-withdrawing substituents at the 3,3′-positions. Moreover, List developed a highly enantioselective Mukaiyama aldol reaction, vinylogous Mukaiyama aldol reaction, hetero-Diels–Alder reaction, and Hosomi–Sakurai reaction with the use of (*R*)-**4a** (Scheme 3).[9,10] Overall, the pioneering results reported by List and us might trigger rapid developments by other many research groups.[9–13]



Scheme 2. Asymmetric synthesis of (*R*)-3,3′-[3,5-$(CF_3)_2C_6H_3]_2$-BINSA ((*R*)-**3**) and the corresponding chiral sulfonamide (*R*)-**4a** by List.



Scheme 3. A variety of asymmetric catalyses with chiral sulfonimides (**4**) described by List.



Scheme 4. Synthesis of chiral BINSA derivatives by Sumitomo Chemical, Giernorth, and Lee.

Interestingly, Sumitomo Chemical reported a patent in 2008, the same year as our report on the synthesis of chiral BINSA[7] (Scheme 4, eq 1).[12] The Sumitomo group developed an alternative oxychlorination of *S*-thiocarbamoyl compound to sulfonic acid with the use of *N*-chlorosuccinimide (NCS), while our synthetic method[7] needed 10 atm of O_2 for the oxidation of thiol to sulfonic acid. Although NCS is more expensive than O_2, this reaction is highly attractive since the reaction proceeded within 30 min under mild conditions. In 2009, Giernoth independently reported[13] the same oxychlorination with NCS as in the Sumitomo method[12] and the subsequent synthesis of (*R*)-BINSA-derived sulfonimide as reported previously by List[9] (Scheme 4, eq 2). Moreover, in 2010, Lee developed a practical synthesis of (*R*)-3,3′-diaryl-1,1′-binaphthyl-2,2′-sulfonimides from the parent (*R*)-3,3′-dibromo compound by Suzuki–Miyaura coupling with $ArB(OH)_2$ (Scheme 4, eq 3).[14] Lee's synthetic method is valuable since the aryl moiety with both electron-donating and electron-withdrawing groups can be introduced at the 3,3′-positions of the binaphthyl structure.

3. Design of Chiral BINSA Ammonium Salts

A chiral organic salt which consists of a Brønsted acid and a Brønsted base is one of the most promising catalysts in modern asymmetric chemical synthesis. In general, acid–base combined salts[15] have several advantages over single-molecule catalysts, with regard to their easy preparation from simple low-molecular-weight compounds and the flexibility in the design of their dynamic complexes. In particular, chiral BINSA should be a promising chiral Brønsted acid catalyst, since both its strong Brønsted acidity and bulkiness can be easily controlled by complexation with achiral amines without substitutions at the 3,3′-positions in a binaphthyl skeleton (Scheme 5). Moreover, acid–base complexation can greatly promote the solubility of chiral BINSA even in non-polar solvents. Overall, chiral BINSA ammonium salts might be useful tailor-made catalysts due to the ease with which they can be optimized for specific substrates or reagents, and they should be able to induce the desired reactivity and stereoselectivity in each situation.

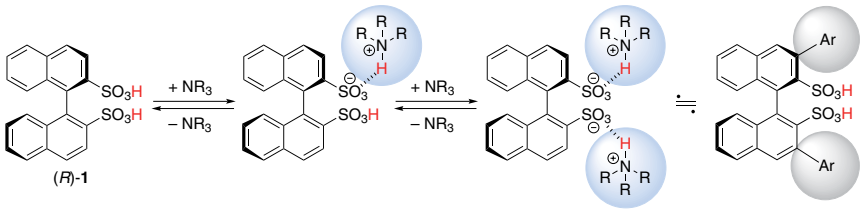
4. Enantioselective Mannich-Type Reaction Catalyzed by Chiral BINSA Pyridinium Salts

To evaluate the performance of (*R*)-**1**, we examined the enantioselective direct Mannich-type reaction between *N*-Cbz-phenylaldimine (**5a**) and acetylacetone (**6a**), which has been reported by Terada with the use of a chiral phosphoric acid catalyst (Table 1).[3b,7] We examined chiral BINSA ammonium salts as chiral Brønsted acid–base catalysts, which were prepared *in situ* (Scheme 5). Some preliminary results using (*R*)-**1** (5 mol%) and achiral amine (10 mol%) suggested that pyridines with weak Brønsted basicity would be effective, while trialkylamines with strong Brønsted basicity were much less active, and anilines caused side reactions such as the Friedel–Crafts reaction. In particular, 2,6-diphenylpyridine (**8a**) improved the enantioselectivity of **7a** to 92% ee.

Next, the molar ratio of **8a** (0–15 mol%) to (*R*)-**1** (5 mol%) was optimized (Table 2). Interestingly, the enantioselectivity of **7a** was dramatically improved with a (*R*)-**1**:**8a** ratio of more than 1:0.75 (i.e., (*R*)-**1**•**8a**$_{0.75}$). We found that a 1:1.5 to 1:2.5 ratio of (*R*)-**1**:**8a** was effective for achieving both a high yield and a high enantioselectivity (90~95% ee). The wide range for the suitable ratio of (*R*)-**1**:**8a** was probably due to the dynamic structure of the catalysts (see Scheme 5).

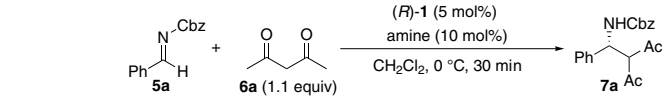
Fortunately, **7a** was obtained in 91% yield with 90% ee with the use of 1 mol% of (*R*)-**1**•**8a**$_2$ in the presence of $MgSO_4$, which would prevent the decomposition of the aldimine due to adventitious moisture (Table 3). From a variety of *N*-Cbz arylaldimines (**5**) bearing electron-donating or electron-withdrawing groups in the aryl or heteroaryl moiety and acetylacetone (**6a**), the corresponding adducts (**7**) were obtained in excellent yields with high enantioselectivities (up to 98% ee). Moreover, cyclic 1,3-diketone could also be used, and the corresponding adduct with a quaternary carbon center was obtained in 98% yield with a *syn/anti* diastereomer ratio of 83/17 and high enantioselectivity.

The absolute stereochemistry of the products **7** was determined by oxidative transformation. Unexpectedly, tertiary alcohol **10** was obtained instead of the expected Baeyer–Villiger products[3b] when Mannich adduct **7b** was oxidized by oxone/K_2CO_3, and the absolute stereochemistry of **10** was analyzed by X-ray diffraction (Scheme 6).



Scheme 5. Design of chiral BINSA ammonium salts as dynamic acid–base combined catalysts.

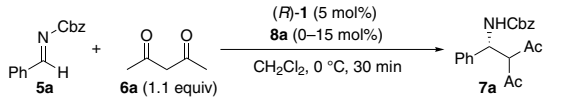
Table 1. Optimization of (*R*)-BINSA ammonium salts in an enantioselective Mannich-type reaction.



Amine, yield, enantioselectivity						
(none)	Et_3N	NH_2	N	N	*t*-Bu N *t*-Bu	Ph N Ph
81%, 17% ee	trace	trace	8%, 5% ee	19%, 0% ee	32%, 76% ee	**8a**, 74%, **92% ee**

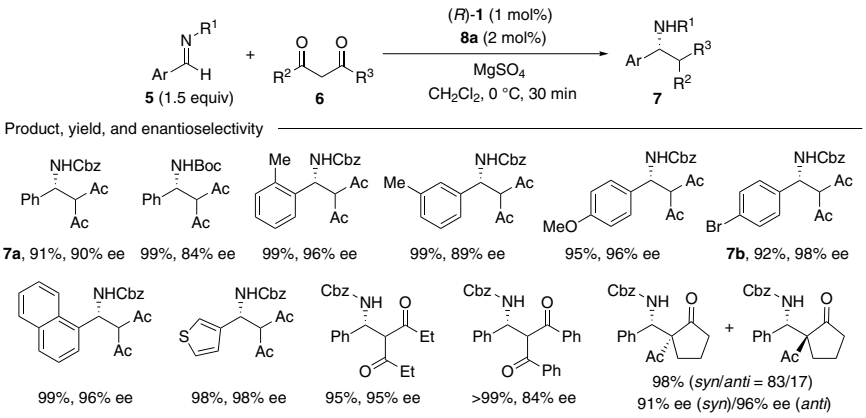
A suitable chiral ammonium salt was easily tailor-made for a ketoester equivalent such as 3-acetoacetyl-2-oxazolidinone (**11**) (Scheme 7). Actually, (*R*)-**1**•**8a**$_2$ was not effective, and **12** was obtained with low enantioselectivity. In contrast, the enantioselectivity of **12** increased to 90~93% ee when 2,6-dimesitylpyridine (**8b**) was used in place of **8a**. In this way, tailor-made salts (*R*)-**1**•**8**$_2$ made it possible to avoid having to prepare single-molecule catalysts in advance and offered a quick solution to this optimization problem. Moreover, compounds **12** were easily transformed to β-amino carbonyl compounds **13** *via* deprotection of the oxazolidinone moiety without a loss of enantioselectivity.

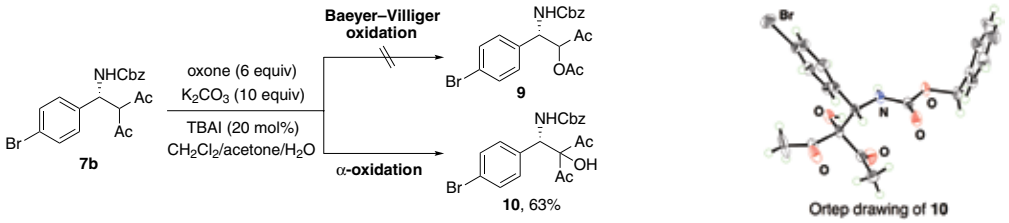
Table 2. Effect of the ratio of (*R*)-**1**:**8a**.



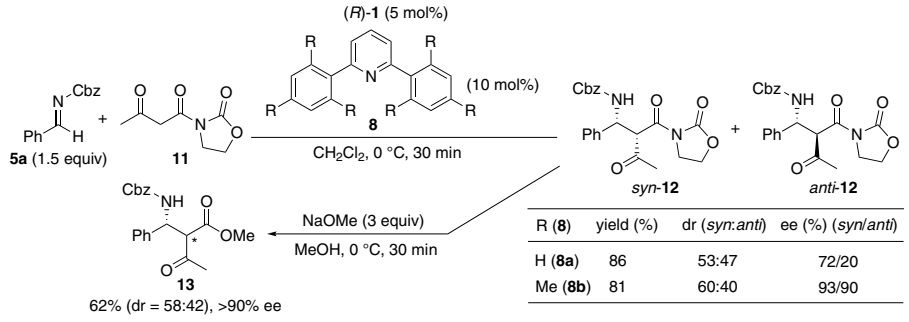
(*R*)-**1**•**8a**$_n$	yield (%)	ee (%)	(*R*)-**1**•**8a**$_n$	yield (%)	ee (%)
(*R*)-**1**	81	17	(*R*)-**1**•**8a**$_{1.5}$	84	**90**
(*R*)-**1**•**8a**$_{0.25}$	82	17	(*R*)-**1**•**8a**$_2$	74	**92**
(*R*)-**1**•**8a**$_{0.5}$	83	34	(*R*)-**1**•**8a**$_{2.5}$	76	**95**
(*R*)-**1**•**8a**$_{0.75}$	81	79	(*R*)-**1**•**8a**$_3$	68	86
(*R*)-**1**•**8a**	82	84			

Table 3. Enantioselective direct Mannich-type reaction catalyzed by chiral BINSA pyridinium salt.





Scheme 6. Oxidative transformation of **7b** and X-ray analysis of **10**.



R (**8**)	yield (%)	dr (*syn*:*anti*)	ee (%) (*syn*/*anti*)
H (**8a**)	86	53:47	72/20
Me (**8b**)	81	60:40	93/90

Scheme 7. Enantioselective direct Mannich-type reaction with a 1,3-ketoester equivalent (**11**).

5. Enantioselective Aza-Friedel–Crafts Reaction Catalyzed by Chiral BINSA Ammonium Salts

A catalytic enantioselective aza-Friedel–Crafts reaction between aldimines and pyrroles is highly useful for synthesizing the chiral building blocks of biologically and pharmaceutically active aryl(1*H*-pyrrol-2-yl)methanamines. Over the past several years, much attention has been devoted to methods for the catalytic enantioselective aza-Friedel–Crafts reaction using chiral metal catalysts. Recently, as alternative organocatalysts, chiral BINOL-derived phosphoric acids were independently developed by Antilla et al. and Nakamura et al., although the reaction time was as long as 12~41 h.[16] Therefore, we envisioned that more acidic sulfonic acid catalysts, such as chiral BINSA, might be effective for improving the reactivity.[17]

First, we optimized ammonium salts by tuning the achiral amines for (*R*)-**1** (5 mol%) in the reaction between benzyl benzylidenecarbamate (**5a**) and *N*-benzylpyrrole (**14**) in dichloromethane at –78 °C for 30 minutes (Table 4). The previous catalyst (*R*)-**1**•**8a**$_2$, which was optimized for the direct Mannich-type reaction,[7] promoted the reaction but showed only moderate enantioselectivity for **15a** (45% ee). In sharp contrast, tertiary aliphatic amines gave better enantioselectivities, and the less sterically hindered *N*,*N*-dimethylbutylamine (**16**) (5 mol%) was the most effective. In the absence of additional amines, **14** itself acted as a component of the corresponding ammonium salt, and **15a** was obtained in 33% yield with 30% ee. Therefore, the additional amine plays an important role in controlling such competitive background reaction pathways.

With the optimized reaction conditions using (*R*)-**1**•**16**, we next examined the scope of aldimines (**5**) (Table 5). The reaction of aromatic aldimines with an electron-donating or electron-withdrawing substituent with *N*-benzylpyrrole (**14**) proceeded smoothly, and the desired products were obtained with high enantioselectivities. Remarkably, the reactions were complete within 30 minutes in all cases. Fortunately, recrystallization of the products increased the enantioselectivity (89~>99% ee) without any serious loss of yield. Moreover, the absolute stereochemistry of the products was determined by X-ray analysis.

Table 4. Optimization of (*R*)-BINSA ammonium salts in the enantioselective aza-Friedel–Crafts reaction.

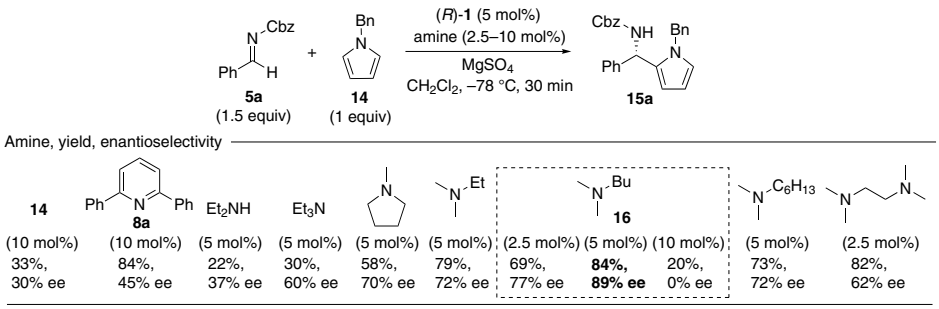
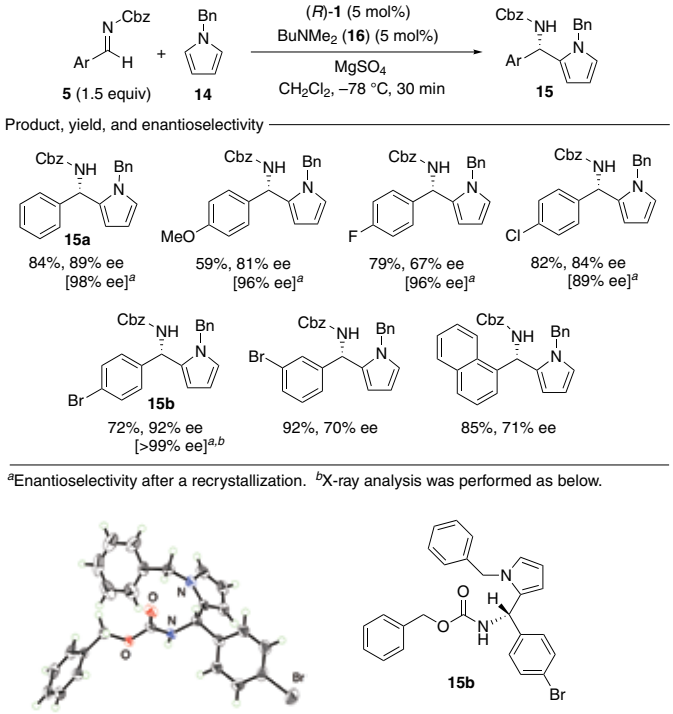


Table 5. Catalytic enantioselective aza-Friedel–Crafts reaction with (*R*)-BINSA ammonium salt.



[a]Enantioselectivity after a recrystallization. [b]X-ray analysis was performed as below.

The postulated structures of the catalyst and the substrate were considered based on theoretical calculations (M05-2X/6-31G*) for a monomeric (*R*)-**1•16** complex as a working model. As shown in Figure 2, **16** is protonated by a bridged proton between the two SO_3^- moieties and oriented outward. Moreover, **5** is protonated and thus activated by the other proton of the disulfonic acid. In this calculated complex, an attractive π–π interaction is observed between the electronically positive protonated **5** and the electronically negative naphthyl–SO_3^- moiety. Therefore, in the possible transition state, **14** would predominantly attack the *re*-face side of aldimines.

6. Enantioselective Direct Aminalization with Primary Carboxamides Catalyzed by Chiral BINSA Ammonium Salts

Aminals, which are nitrogen equivalents of acetals, are synthetically and medicinally useful compounds in natural products and pharmaceuticals. However, practical catalytic methods for the synthesis of optically active acyclic aminals are still limited, and thus the Curtius rearrangement of chiral acyl azides and Hofmann rearrangement of chiral α-amino amides have traditionally been used, although a serious loss of optical purity is sometimes observed due to epimerization. In this context, Antilla, List, and Rueping independently reported a catalytic enantioselective aminal synthesis by the direct amidation of aldimines in the presence of a chiral phosphoric acid as a Brønsted acid catalyst.[18] According to Antilla's reports,[18a,b] acidic sulfonamides and phthalimides could be used successfully, but the use of primary carboxamides, which are less acidic and strong nucleophiles, showed unsatisfactory enantioselectivities (21~34% ee). We assumed that the strong basicity of the phosphoryl moiety in the phosphoric acid can promote deprotonation of the acidic nucleophiles, such as sulfonamides and phthalimides, and thus a cyclic transition state would be favored via anionic activation with increased nucleophilicity (Figure 3, left). In sharp contrast, since carboxamides are basically more nucleophilic and less acidic, they cannot be easily activated through deprotonation with the phosphoric acid catalyst, and carboxamides may directly react with aldimines through an extended transition state (Figure 3, right).

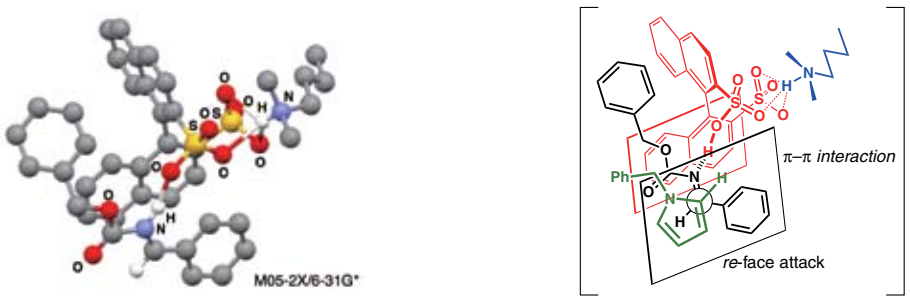


Figure 2. M05-2X/6-31G* optimized geometry of (*R*)-**1•16** and a proposed transition state.

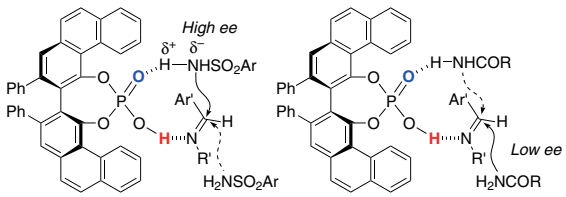
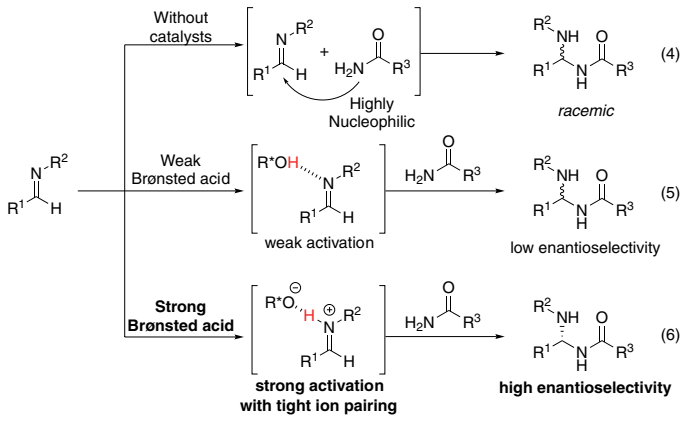


Figure 3. Assumed activation mechanism by the phosphoric acid catalyst.



Scheme 8. Enantioselective direct aminal synthesis with chiral Brønsted acid catalysts.

In general, highly nucleophilic reagents can react with the substrate in the presence of a weak Brønsted acid catalyst, or even without catalysts (Scheme 8, eqs 4,5). Therefore, in particular, enantiofacial discrimination of the substrates cannot be controlled by a weak Brønsted acid in these cases. To overcome this problem, a stronger Brønsted acid catalyst might be able to activate aldimines with tight ion pairing (Scheme 8, eq 6). In this regard, chiral BINSA should be attractive, since both its Brønsted acidity and bulkiness can be easily controlled by complexation with achiral amines.[19)]

First, we optimized achiral amine (5 mol%) for (*R*)-**1** (5 mol%) (Table 6). Poor enantioselectivities (<5% ee) were observed for the product (**18a**) in the absence of achiral amine or in the presence of primary and secondary amines. In sharp contrast, we eventually found that more sterically hindered 2,6-dimesitylpyridine (**8b**) and 2,6-(2,4,6-*i*-$Pr_3C_6H_2)_2$pyridine (**8c**) were effective (78% ee and 82% ee, respectively). In this reaction, a molar ratio of (*R*)-**1** and **8c** of more or less than 1:1 was not effective.

Next, we examined the scope of the aryl aldimine by using the optimum (*R*)-**1**•**8c** catalyst (Table 7). When aryl aldimines with an electron-donating or electron-withdrawing group were used, the desired products were obtained with high enantioselectivity (up to 89% ee). Moreover, acrylamide was also tolerable, and high enantioselectivity was observed (89% ee). Acyclic aminals, unlike cyclic aminals, are often unstable, epimerize, and are not isolable. However, the acyclic *N*-protected aminals (**18**) obtained here were highly stable, and could be purified by silica gel column chromatography without decomposition and/or epimerization. Moreover, since many of the products were highly crystalline, the enantioselectivity values of **18** increased to 93~98% ee without any serious loss of yield.

As a more nucleophilic non-conjugate carboxamide, pivalamide (**17b**) gave the corresponding aminal **18b** with low enantioselectivity (30% ee) when (*R*)-**1**•**8c** was used (Table 7). However, tailor-made optimization of achiral amines for (*R*)-**1** proved that more basic trioctylamine (**19**) was effective, and the enantioselectivity was greatly improved to 80% ee (Scheme 9).

In place of carboxamide (**17**), allyl carbamate **20** was

Table 6. Optimization of (*R*)- BINSA ammonium salts in enantioselective direct aminal synthesis.

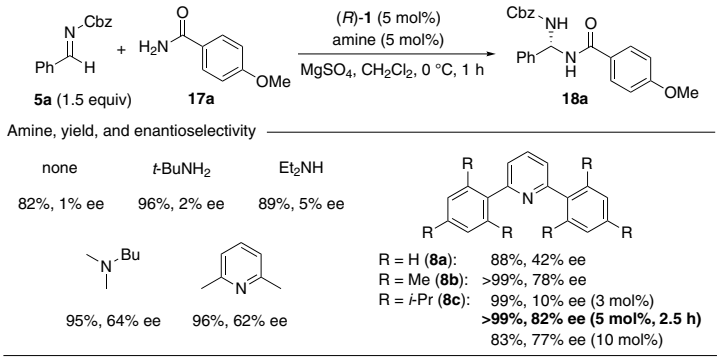
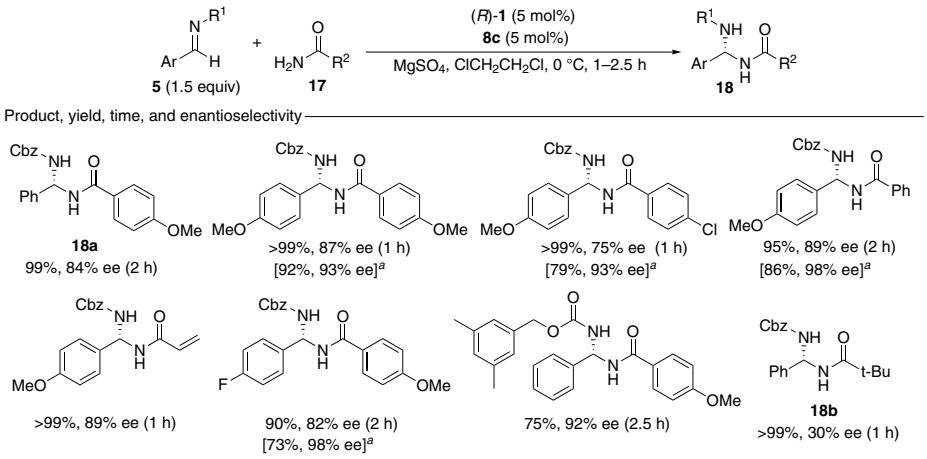
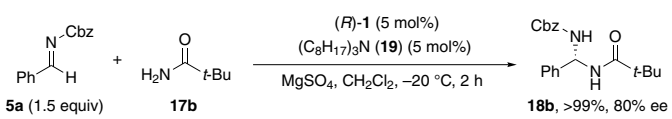


Table 7. Catalytic enantioselective direct aminal synthesis with the use of (*R*)-BINSA ammonium salt.



[a]Yield and enantioselectivity after a recrystallization.



Scheme 9. Catalytic enantioselective aminal synthesis from pivalamide (**17b**).

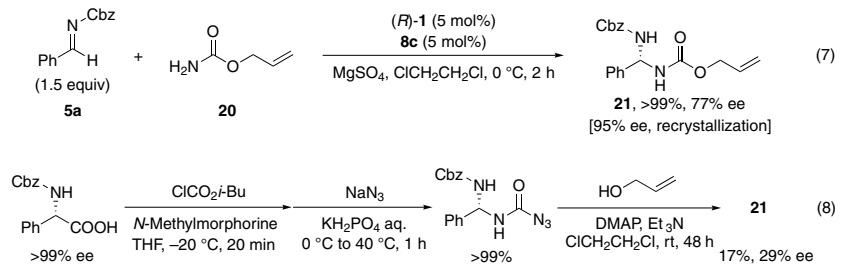
used in the reaction of **5a**. Fortunately, the reaction proceeded smoothly, and the corresponding product **21** was obtained in >99% yield with 77% ee (Scheme 10, eq 7). Moreover, a single recrystallization increased the enantiopurity up to 95% ee. In sharp contrast, the conventional synthesis of **21** from *N*-Cbz-L-phenylglycine *via* Curtius rearrangement to azide carbonyl compound failed (Scheme 10, eq 8). Accordingly, enantioselective direct aminal synthesis with such a chiral Brønsted acid catalyst under mild reaction conditions is highly useful.

7. Chiral BINSA-lanthanum(III) complexes for the catalytic enantioselective Strecker-type reaction

As well as an organocatalyst, chiral BINSA should be a highly promising chiral ligand for metal-mediated enantioselective catalysis, since the bidentate electron-withdrawing sulfonate groups should effectively chelate and thus activate the metal center, unlike monodentate TsO^- and TfO^-. Moreover, high enantioselectivity may be induced even with the use of chiral BINSA without 3,3′-modification of the binaphthyl skeleton, if we use highly coordinatable lanthanide species.[20] In particular, we developed the catalytic enantioselective Strecker-type reaction of aldimines through the use of highly Lewis acidic lanthanum(III) catalysts with chiral BINSA ((*R*)-**1**).[21]

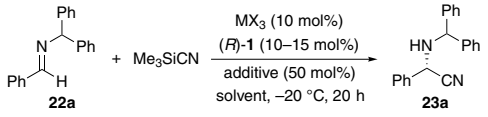
First, we examined the metal tuning for (*R*)-**1** (10–15 mol%) in the reaction of aldimine **22a** with trimethylsilyl cyanide (TMSCN) (1.5 equiv) at –20 °C for 20 h (Table 8). As expected, trivalent precursors promoted the reaction moderately. In particular, La(O*i*-Pr)$_3$ gave the product (**23a**) with 54% ee (entry 2). When more polar EtCN was used in place of toluene, the solubility of the heterogeneous La(III) catalysts was slightly improved. La(OPh)$_3$ gave better results than La(O*i*-Pr)$_3$, and the enantioselectivity was improved to 65% ee when we used 10 mol% each of (*R*)-**1** and La(OPh)$_3$. Further optimization was examined with the addition of protic compounds, and we found that 50 mol% of AcOH or *i*-PrCO$_2$H significantly improved the catalytic activity; **23a** was obtained with 84% ee (entries 11,12). The amount of these acids was also important, and less or more than 50 mol% of the acid decreased the catalytic activity.

A direct comparison with HCN was also examined since the mixture of TMSCN and proton source can easily generate HCN (Scheme 11). In fact, the reaction proceeded smoothly with 3 equiv of HCN, and **23a** was obtained in 86% yield with 56% ee. Although the enantioselectivity was not as high as under the conditions using TMSCN (Table 8, entries 11,12), these results strongly suggest that HCN is a key reagent in this reaction.

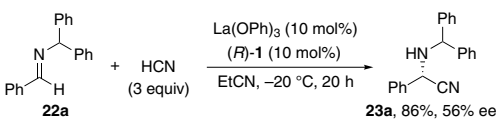


Scheme 10. Catalytic enantioselective direct aminal synthesis from allyl carbamate (**20**).

Table 8. Optimization of (*R*)-BINSA-lanthanide catalysts in the enantioselective Strecker-type reaction.



entry	MX_3	(*R*)-**1**	additive	solvent	yield (%)	ee (%)
1	Sc(O*i*-Pr)$_3$	15	–	toluene	56	18
2	La(O*i*-Pr)$_3$	15	–	toluene	34	54
3	Pr(O*i*-Pr)$_3$	15	–	toluene	24	46
4	Nd(O*i*-Pr)$_3$	15	–	toluene	29	49
5	Yb(O*i*-Pr)$_3$	15	–	toluene	29	10
6	La(O*i*-Pr)$_3$	15	–	EtCN	27	55
7	La(OPh)$_3$	15	–	EtCN	38	57
8	La(OPh)$_3$	10	–	EtCN	22	65
9	La(OPh)$_3$	10	H_2O	EtCN	46	65
10	La(OPh)$_3$	10	PhOH	EtCN	42	53
11	La(OPh)$_3$	10	**AcOH**	EtCN	**98**	**84**
12	La(OPh)$_3$	10	***i*-PrCO$_2$H**	EtCN	**86**	**84**
13	La(OPh)$_3$	10	CF_3CO_2H	EtCN	34	38



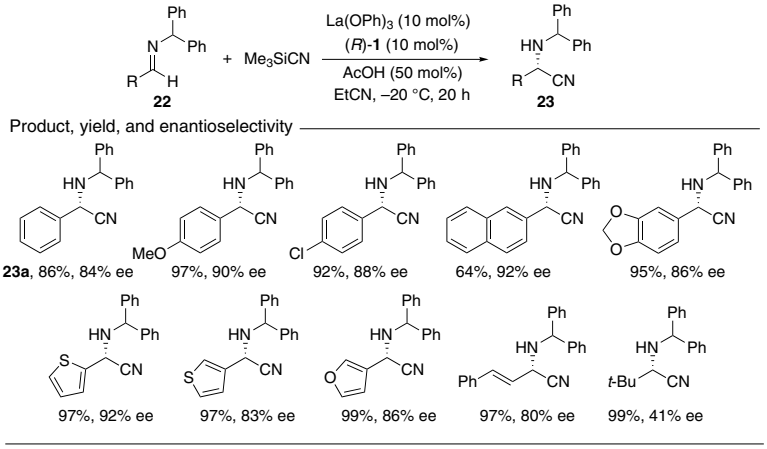
Scheme 11. Reaction with HCN.

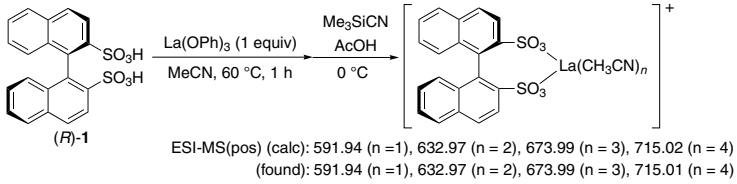
Next, we examined the scope of the aldimines (**22**) in the presence of (*R*)-**1** (10 mol%), La(OPh)$_3$ (10 mol%), AcOH (50 mol%), and TMSCN (1.5 equiv) in EtCN at –20 °C (Table 9). The reactions of aromatic and heteroaromatic aldimines bearing an electron-withdrawing or electron-donating group proceeded in high yields with moderate to high enantioselectivities. In particular, thienyl and furyl groups can be tolerated, and the corresponding products were obtained in high yields with up to 92% ee. α,β-Unsaturated aldimines gave the corresponding 1,2-adducts with moderate to good enantioselectivities, although aliphatic aldimine showed moderate enantioselectivity.

ESI-MS analysis of the catalyst, which was prepared *in situ* from La(OPh)$_3$ (1 equiv) and **1** (1 equiv) in AcOH (5 equiv) and MeCN, suggested that monomeric La(III) complexes were predominantly generated (Scheme 12). The observed species may be derived from a parent complex [Ar*(SO$_3$)$_2$La(OAc)(MeCN)$_n$]$^+$, since the p*K*a value of HCN is smaller than that of AcOH.

A postulated catalytic cycle is shown in Figure 4 as a working model. Acetic acid would provide a counteranion for monomeric La(III) and generate HCN *via* proton-exchange reactions. HCN would then be added to **22** in the transition states, in which *re*-face attack should be favored without conspicuous steric repulsion between the substrate and the ligand.

Table 9. (*R*)-BINSA–La(OPh)$_3$-catalyzed enantioselective Strecker-type reaction.





Scheme 12. ESI-MS analysis of chiral BINSA-La(III) complexes.

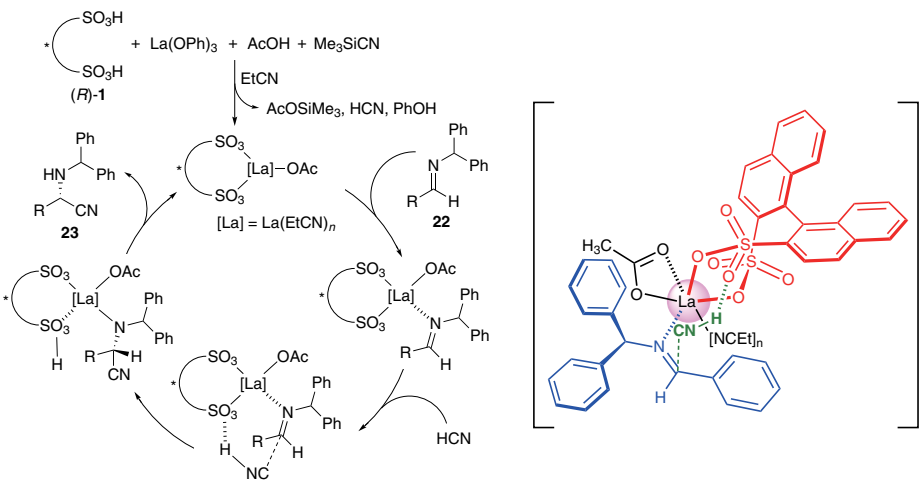


Figure 4. Postulated catalytic cycle and transition state.

8. Synthesis of Optically Pure 3,3′-Diaryl Binaphthyl Disulfonic Acids via Stepwise *N–S* Bond Cleavage

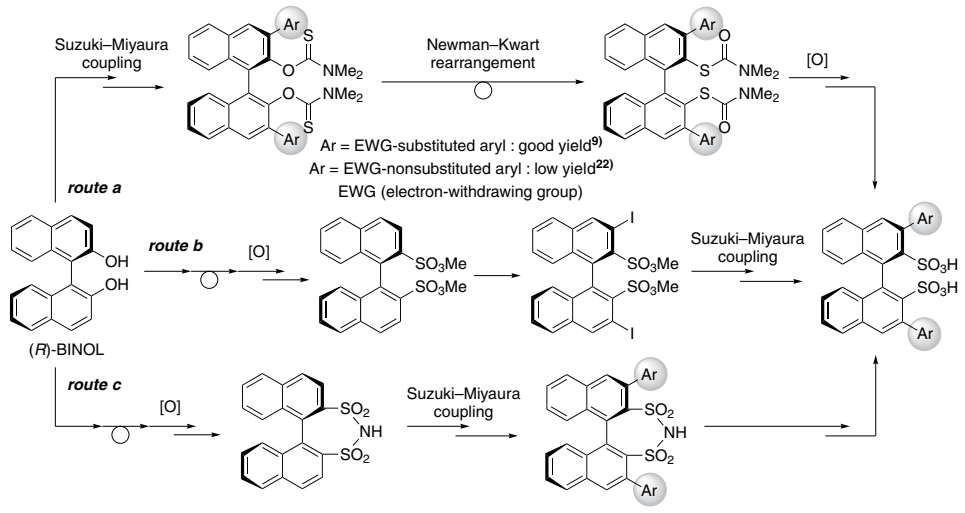
The introduction of 3,3′-disubstituents has not been well established for chiral 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA), due to synthetic difficulties, unlike for chiral binaphthyl phosphoric acid, dicarboxylic acid, etc. In particular, the key to synthesizing chiral 3,3′-Ar_2-BINSAs from chiral BINOL should be Suzuki–Miyaura coupling, Newman–Kwart rearrangement, and oxidation (Scheme 13). Only one successful example has been reported by List, who synthesized (*R*)-3,3′-[3,5-$(CF_3)_2C_6H_3]_2$-BINSA, by taking advantage of electron-withdrawing substituents at the 3,3′-positions (Scheme 2, Scheme 13, **route a**).[9] In this regard, we have reported a similar synthesis of (*R*)-3,3′-Ph_2-BINSA, but the yield was low in both rearrangement (25%) and oxidation (30%) (Scheme 14).[22]

Moreover, we also reported a second synthetic route, which used Suzuki–Miyaura coupling in the last step (Scheme 13, **route b**).[22] The key step was directed *ortho*-lithiation of chiral BINSA methyl ester ((*R*)-**24**) with *n*-BuLi and subsequent reaction with an electrophile. We examined some electrophiles such as Br_2, I_2, Me_3SiOTf, and *i*-PrOB(Pin), and the corresponding 3,3′-dihalo-, 3,3′-bis(trimethylsilyl)-, and 3,3′-diboryl-BINSA derivatives were obtained in yields of 48~78% (Scheme 15, eq 9). Unfortunately, however, the introduction of aryl moieties to the 3,3′-positions by Suzuki–Miyaura coupling was difficult, and the yield was low (ca. 10%) (Scheme 15, eqs 10,11).

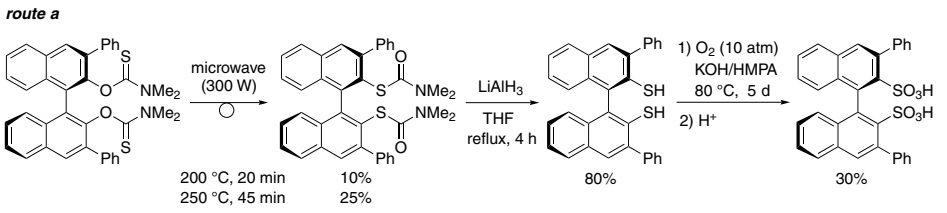
As a third synthetic route to chiral 3,3′-Ar_2-BINSAs, the deprotection of 3,3′-diaryl-1,1′-binaphthyl-2,2′-sulfonimides may be possible (Scheme 13, **route c**). Remarkably, Lee reported a practical synthesis of (*R*)-3,3′-diaryl-1,1′-binaphthyl-2,2′-sulfonimides from the parent (*R*)-3,3′-dibromo compound by Suzuki–Miyaura coupling with $ArB(OH)_2$ (Scheme 4, eq 3).[14] Therefore, we envisioned that it may be possible to efficiently obtain chiral 3,3′-Ar_2-BINSAs if we cleave the two stable *N–S* bonds in the sulfonimides.[23]

In general, arylsulfonic acids have been used to protect amino functions due to the high stability of the corresponding arylsulfonamides. Inevitably, for cleavage of the protecting sulfone group from the amino group, drastic reaction conditions are usually needed. Most importantly, cleavage methods have been developed for amines, but not for sulfonic acids, and thus we can obtain deprotected amines selectively, while sulfonic acids usually decompose and are discarded. As a good example, Fukuyama and Kan's nitrobenzenesulfonamide (Ns amide) provides the desired amines even under mildly basic conditions with thiolates (Scheme 16).[24] However, an arylsulfone moiety would decompose with the release of SO_2 *via* the Meisenheimer complex.

We initially examined the *N–S* cleavage of (*R*)-3,3′-Ph_2-1,1′-binaphthyl-2,2′-sulfonimide ((*R*)-**27a**)[14] as a probe compound (Scheme 17). However, (*R*)-**27a**[14] was perfectly intact under strong acidic (8 *M* HCl aq.) or strong basic (2 *M* NaOH/MeOH) conditions, since NH_3 is a poor leaving group. In particular, the deprotonation of sulfonimide under basic conditions might strengthen the *N–S* bond due to the conjugated structure. Therefore, compound (*R*)-**27a** was transformed to a *N*-Me compound ((*R*)-**28a**) by $Me_3O•BF_4$, and we could cleave the first *N–S* bond of sulfonimide (*R*)-**28a** with the use of 2 *M* NaOH in MeOH at reflux temperature, to give (*R*)-**29a** in quantitative yield. Compound (*R*)-**29a** still has an active proton, and we protected the SO_3Na moiety with $Et_3O•BF_4$ ((*R*)-**30a**,



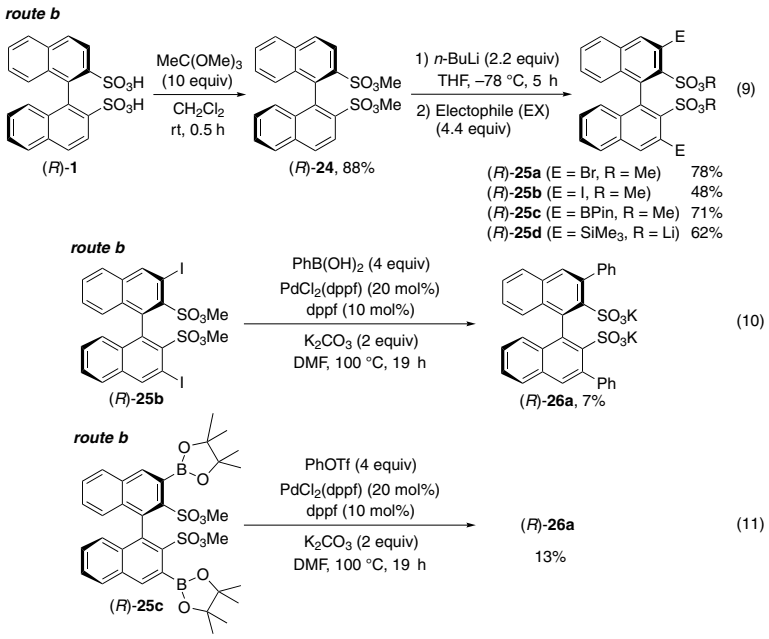
Scheme 13. Synthesis of (*R*)-3,3′-Ar_2-BINSAs.



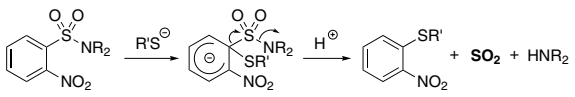
Scheme 14. Synthesis of (*R*)-3,3′-Ph_2-BINSA *via* **route a**.

98% yield) and the SO_2NHMe moiety with $Me_3O•BF_4$ ((*R*)-**31a**, 85% yield). Unfortunately, however, treatment of (*R*)-**31a** with either an acid or base was again ineffective for cleaving the *N*–*S* bond in sulfonamide. Moreover, we also examined the reaction of (*R*)-**31a** with $KPPh_2$, with which Tomooka reported a nucleophilic substitution reaction at the nitrogen of arylsulfonamides,[25] but the sulfonamide moiety of (*R*)-**31a** was completely intact.

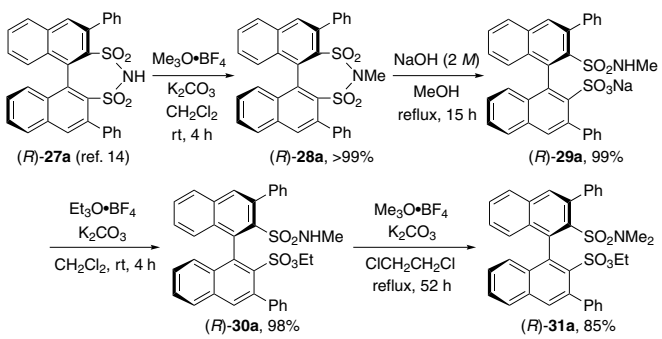
Finally, we examined reductive cleavage of the *N*–*S* bond of sulfonamides with aluminum hydride reagents, which has scarcely been developed since the products would be a mixture of unstable sulfinic acids, sulfenic acids, thiols, and disulfides. We expected that the desired sulfonic acids could be convergently obtained if we treated the mixture without purification with suitable strong oxidants.[7] Fortunately, for the model substrate **32**, we could isolate 2-naphthalenesulfinic acid (**33**) in 95% yield with the use of sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al®) (5 equiv) in THF at room temperature, while 2-naphthyl disulfide (**34**) was obtained in 70% yield at 40 °C (Scheme 18, eq 12). Moreover, we found that the oxidation of **33** can readily proceed (up to 97% yield) with or without KOH under O_2 (balloon) conditions (Scheme 18, eq 13), while the oxidation of **34** was sluggish (64% yield) even if KOH was used under O_2 (balloon) (Scheme 18, eq 14). This result means that the selective reduction of sulfonamide to sulfinic acid is important for stepwise reduction and oxidation to give sulfonic acid from sulfonamide.



Scheme 15. Synthesis of (*R*)-3,3′-Ph_2-BINSA *via* **route b**.



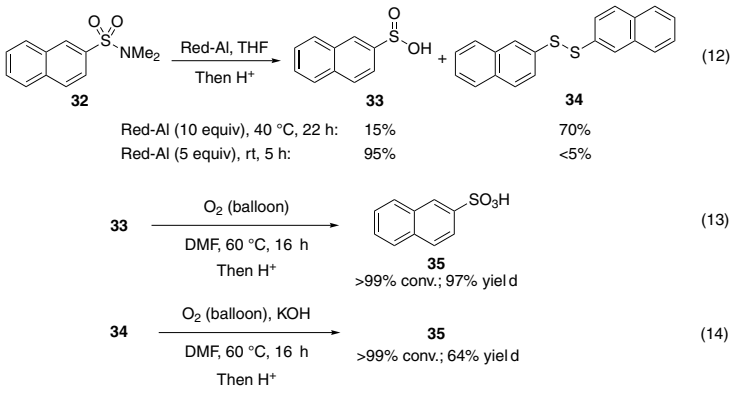
Scheme 16. Deprotection of nitrobenzenesulfonamide (Ns amide) with the release of SO_2.



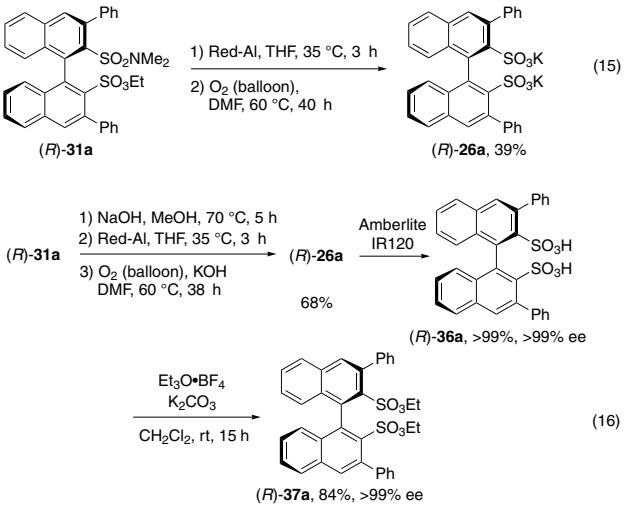
Scheme 17. Cleavage of the *N*–*S* bond of sulfonimide (*R*)-**27a**.

With this optimized method in hand, we transformed sulfonamide (*R*)-**31a** to disulfonate (*R*)-**26a**, where both the SO_2NMe_2 and SO_3Et moieties might be reduced and oxidized (Scheme 19, eq 15). As a result, (*R*)-**26a** was obtained in 39% yield in two steps. Since this moderate yield was due to over-reduction of the more reactive SO_3Et moiety, (*R*)-**31a** was hydrolyzed in advance to sulfonate, and we then tried the reduction/oxidation procedure. As a result, the yield of (*R*)-**26a** was improved to 68% (Scheme 19, eq 16). Subsequent protonation by ion exchange ultimately provided the desired (*R*)-3,3′-Ph_2-BINSA ((*R*)-**36a**) without a loss of optical purity (>99% ee), as determined by HPLC analysis of diethyl ester (*R*)-**37a** and (*S*)-**37a** from (*R*)-**36a** and (*S*)-**36a**, respectively.

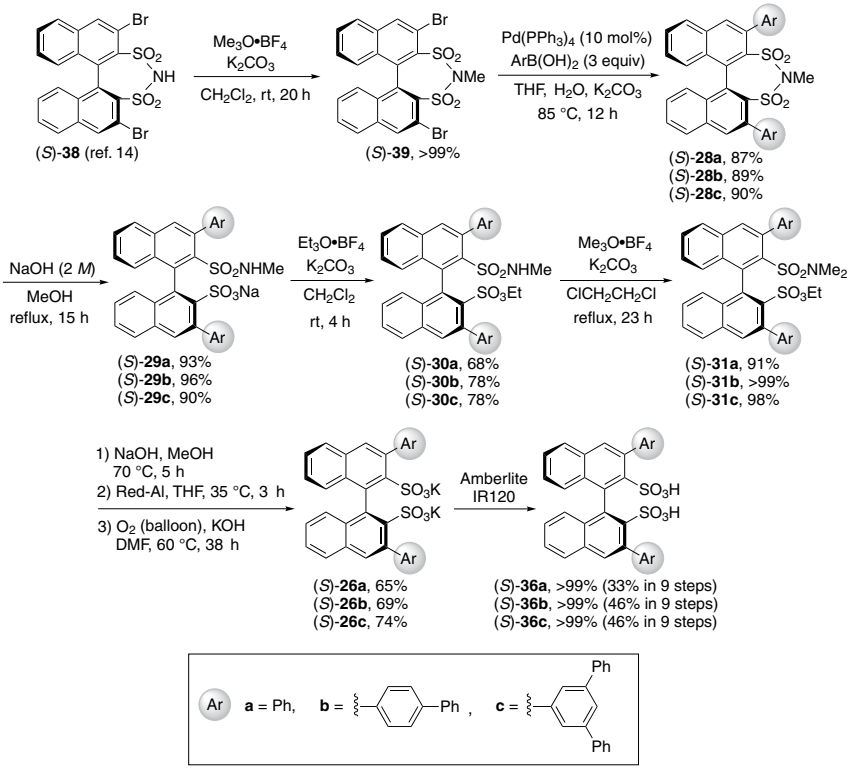
This method was effective for the synthesis of bulky (*R*)- and (*S*)-3,3′-Ar_2-BINSAs (**36**). We could use *N*-Me sulfonimide (*S*)-**39** as a common intermediate after the *N*-methylation of (*S*)-**38**[14] in the initial step (Scheme 20). Overall, we demonstrated that (*S*)-compounds with phenyl, 4-biphenyl, and 3,5-terphenyl substituents could be synthesized smoothly without serious problems, as shown in Scheme 20. The total yield of (*S*)-**36a–c** in nine steps from (*S*)-**38** was 33%, 46%, and 46%, respectively. Later, we could develop an improved method by the double *N*,*O*-methylation of (*S*)-**29b** with the use of $Me_3O{\bullet}BF_4$ and hydrolysis (Scheme 21). Since the corresponding product would be transformed to (*S*)-**26b** *via* reduction and oxidation, we can synthesize chiral 3,3′-Ar_2-BINSAs from the known compound **38** in eight steps.



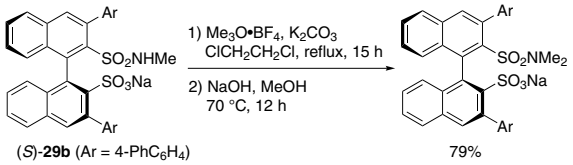
Scheme 18. Transformation of sulfonamide to sulfonic acid *via* stepwise reduction and oxidation.



Scheme 19. Synthesis of (*R*)-3,3′-Ph_2-BINSA ((*R*)-**36a**) *via* reduction and oxidation.



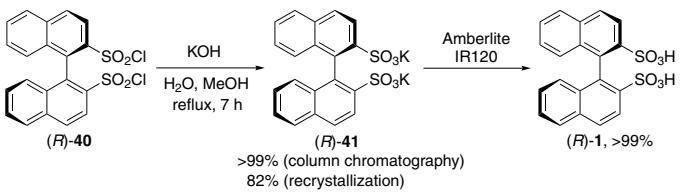
Scheme 20. Synthesis of (*S*)-3,3′-Ar$_2$-BINSAs ((*S*)-**36a–c**) (**a**: Ar = Ph, **b**: Ar = 4-biphenyl, **c**: Ar = 3,5-terphenyl).



Scheme 21. Improved method by the double *N*,*O*-methylation of (*S*)-**29b** and hydrolysis.

9. Summary

In summary, this article outlined our recent progress in chiral BINSA chemistry. Chiral BINSA acts as not only as an organocatalyst, but also as a chiral ligand for metal species. In particular, we developed chiral BINSA ammonium salts as acid–base combined catalysts which can be tailor-made for each substrate and/or reagent in catalytic enantioselective direct Mannich-type reaction, aza-Friedel–Crafts reaction, and direct aminalization. Interestingly, both the strong Brønsted acidity and bulkiness of chiral BINSA ammonium salts can be easily controlled by simple achiral amines without substitutions at the 3,3′-positions in a binaphthyl skeleton. As an approach for chiral ligands, a Strecker-type reaction was also developed with the use of chiral BINSA-lanthanum(III) complexes. Moreover, we developed a practical synthesis of optically pure 3,3′-Ar$_2$-BINSAs from the parent sulfonimides. In the stepwise *N*–*S* bond cleavage of the sulfonimides and the resultant sulfonamides, the key steps were hydrolysis, selective reduction by Red-Al®, and convergent oxidation by O_2. Overall, (*R*)- or (*S*)-3,3′-Ar$_2$-BINSAs may be highly attractive as chiral organocatalysts and chiral bidentate ligands in the near future. Currently, (*R*)-1,1′-binaphthalene-2,2′-disulfonyl dichloride ((*R*)-**40**) is commercially available from TCI (Scheme 22). Therefore, we expect that there will be further developments in chiral BINSA chemistry by many research groups worldwide.



Scheme 22. Preparation of (*R*)-BINSA ((*R*)-**1**) from the acid chloride ((*R*)-**40**) and potassium salt ((*R*)-**41**).

Procedures in Scheme 22:[7] To a solution of KOH (3.58 g, 64 mmol) in water (15 mL) and methanol (30 mL) was added (*R*)-1,1′-binaphthalene-2,2′-disulfonyl dichloride ((*R*)-**40**) (2.89 g, 6.4 mmol) at room temperature. The solution was heated at reflux temperature for 7 h. Volatiles were then removed by a rotary evaporator, and the resultant residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH = 2/1 to 1/4) to give the product (3.09 g, >99% yield). Recrystallization from methanol gave the pure potassium (*R*)-1,1′-binaphthalene-2,2′-disulfonate ((*R*)-**41**) (2.57 g, 82% yield).

A cation exchange column (400 cm^3, Amberlite® IR120H ion-exchange resin) was washed with water (500 mL) until the brown eluate was colorless. The resin was washed with 3 *M* NaOH aqueous solution (500 mL) and water (500 mL). The resin was then washed with 3 *M* HCl aqueous solution (500 mL) and then water (500 mL). A solution of (*R*)-**41** (0.735 g, 1.5 mmol) in water (10 mL) was passed through the prepared cation exchange column. Water (500 mL) was poured into the column until the acidic eluate was neutral. The eluate was concentrated by a rotary evaporator, and the remaining water was removed by azetropic reflux in toluene (30 mL) for 12 h. Toluene was then removed *in vacuo* (1~3 Torr) for 24 h at room temperature to give of (*R*)-1,1′-binaphthalene-2,2′-disulfonic acid ((*R*)-**1**) as a white-brown powder (0.621 g, >99% yield). ^{1}H NMR (300 MHz, CD_3CN) δ 6.94 (d, *J* = 8.4 Hz, 2H), 7.30 (m, 2H), 7.59 (m, 2H), 8.04 (d, *J* = 8.1 Hz, 2H), 8.16 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 10.47 (br, 2H). ^{13}C NMR (75 MHz, CD_3CN) δ 124.9 (2C), 128.4 (2C), 128.5 (2C), 129.0 (2C), 129.2 (2C), 130.4 (2C), 134.1 (2C), 135.4 (2C), 135.5 (2C), 137.7 (2C). IR(KBr) 3300, 1635, 1503, 1308, 1172, 1069, 1040 cm^{-1}. $[\alpha]_D^{23}$ = +61.4 (*c* 2.2, MeOH). HRMS(FAB–) calcd for $C_{20}H_{13}O_6S_2$ $[M–H]^-$ 413.0154, found 413.0154. HRMS(FAB+) calcd for $C_{20}H_{14}O_6S_2$ $[M]^+$ 414.0232, found 414.0230.

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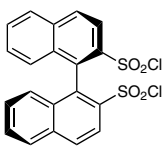
TCI Related Compound



B4187 (*R*)-1,1'-Binaphthyl-2,2'-disulfonyl Dichloride
200mg, 1g