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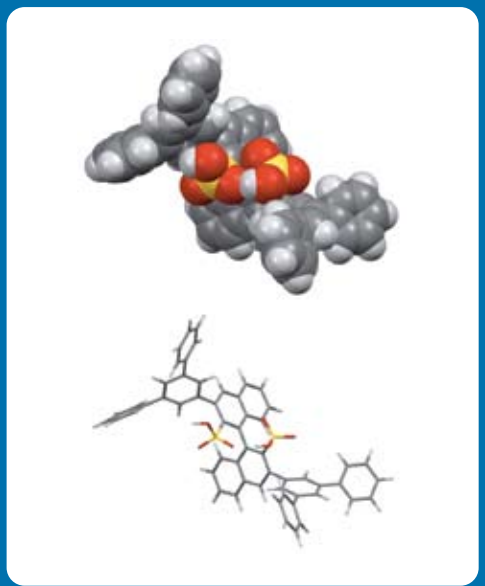

CONTENTS

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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.

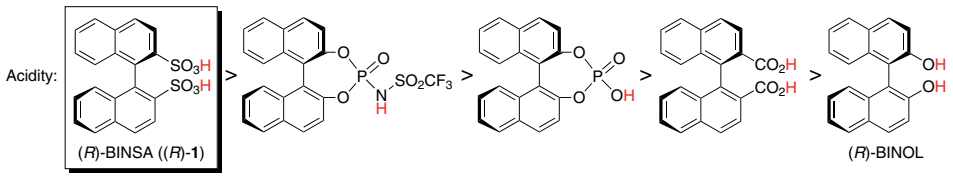
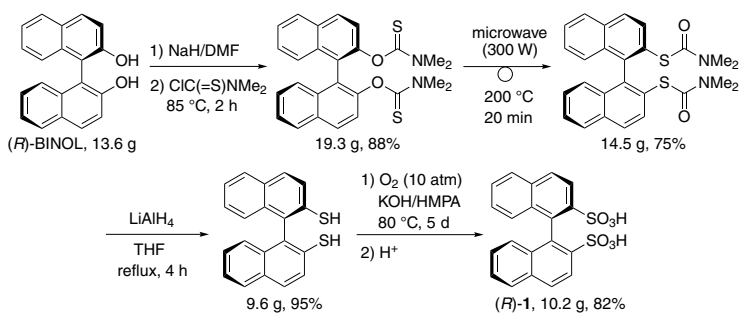
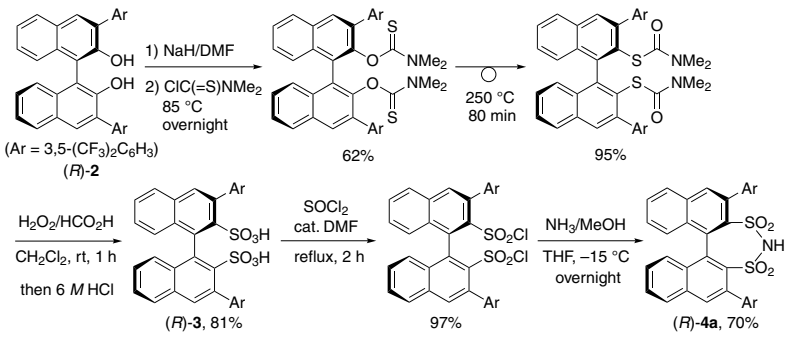


Figure 1. Chiral 1,1′-binaphthyl Brønsted acids and their acidity.

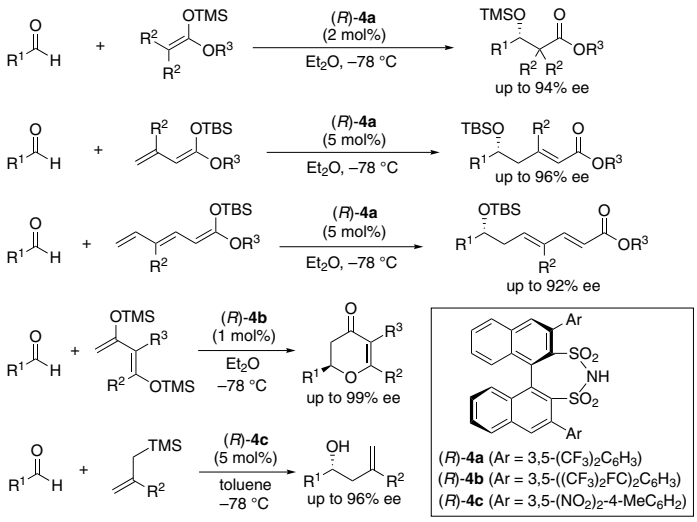


Scheme 1. Asymmetric synthesis of (*R*)-BINSA ((*R*)-**1**) from (*R*)-BINOL.

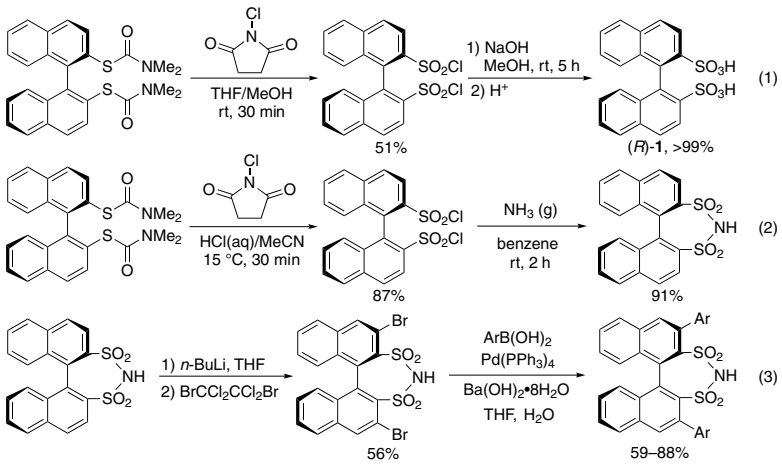
At almost the same time as our report,[7] List independently reported the catalytic asymmetric acylcyanation of aldimines and Hosomi–Sakurai reactions among aldehydes, silylethers, and allylsilanes in the presence of (*R*)-**1**.[8] However, enantioselectivity was not induced (<5% ee) in these reactions. 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.

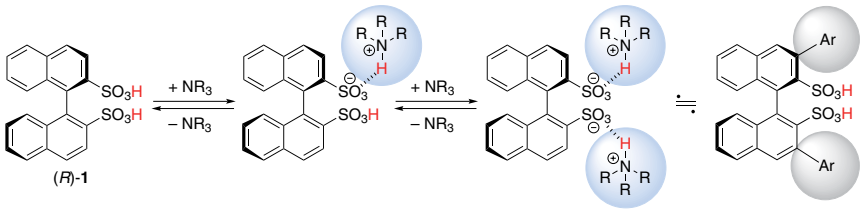
4. Enantioselective Mannich-Type Reaction Catalyzed by Chiral BINSA Pyridinium Salts

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).

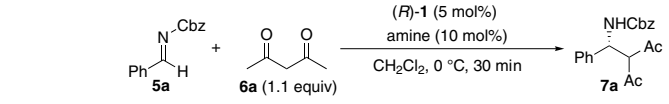
Fortunately, **7a** was obtained in 91% yield with 90% ee with the use of 1 mol% of (*R*)-**1**•**8a**$_2$ in the presence of $MgSO_4$, which would prevent the decomposition of the aldimine due to adventitious moisture (Table 3). From a variety of *N*-Cbz arylaldimines (**5**) bearing electron-donating 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.

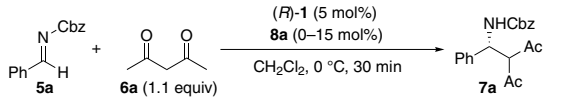
Table 1. Optimization of (*R*)-BINSA ammonium salts in an enantioselective Mannich-type reaction.



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**

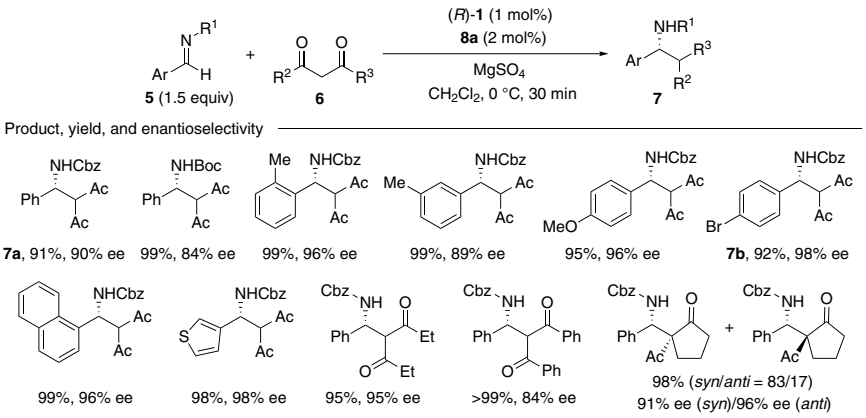
A suitable chiral ammonium salt was easily tailor-made for a ketoester equivalent such as 3-acetoacetyl-2-oxazolidinone (**11**) (Scheme 7). Actually, (*R*)-**1**•**8a**$_2$ was not effective, and **12** was obtained with low enantioselectivity. In contrast, the enantioselectivity of **12** increased 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.

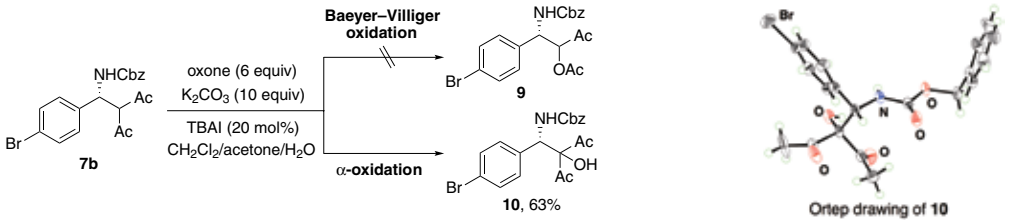
Table 2. Effect of the ratio of (*R*)-**1**:**8a**.



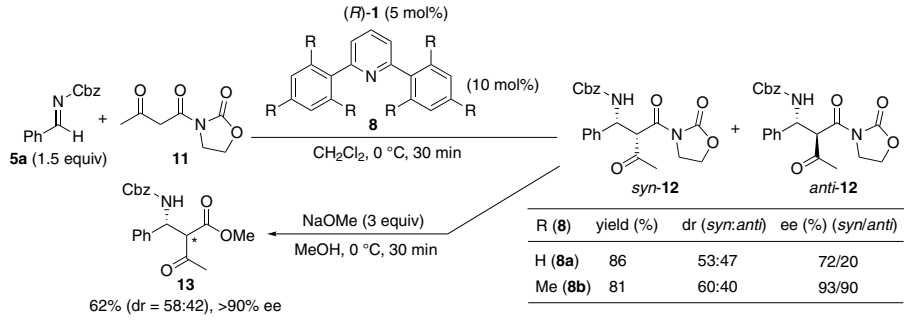
(*R*)-**1**•**8a**$_n$	yield (%)	ee (%)	(*R*)-**1**•**8a**$_n$	yield (%)	ee (%)
(*R*)-**1**	81	17	(*R*)-**1**•**8a**$_{1.5}$	84	**90**
(*R*)-**1**•**8a**$_{0.25}$	82	17	(*R*)-**1**•**8a**$_2$	74	**92**
(*R*)-**1**•**8a**$_{0.5}$	83	34	(*R*)-**1**•**8a**$_{2.5}$	76	**95**
(*R*)-**1**•**8a**$_{0.75}$	81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

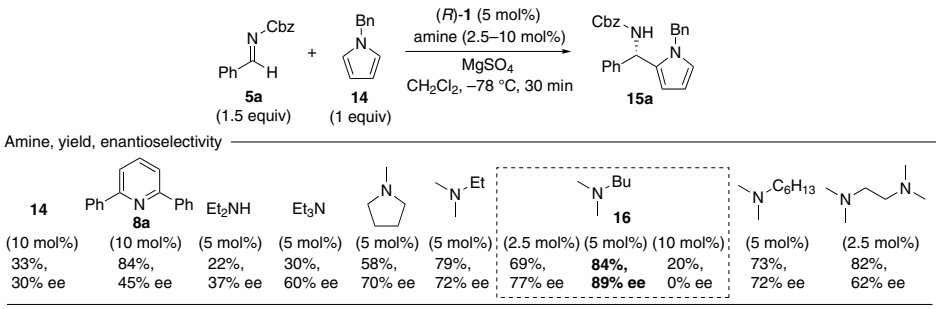
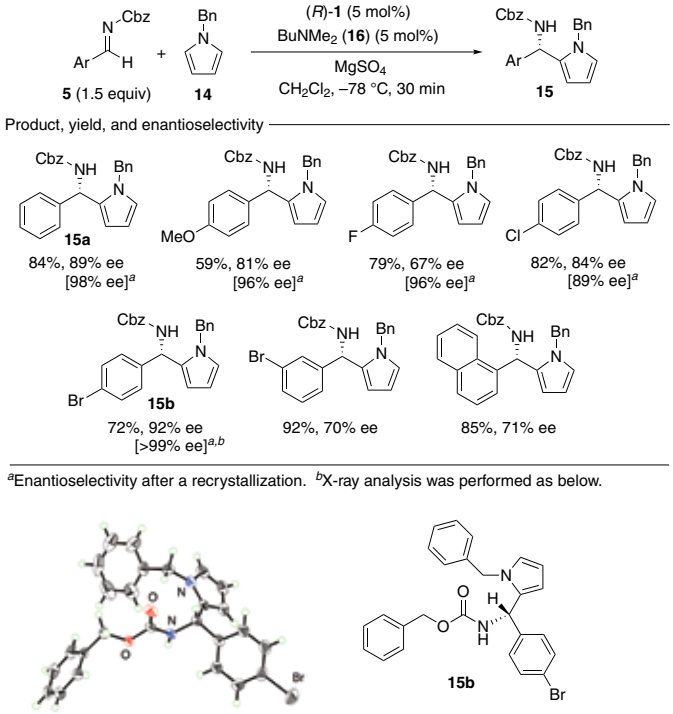


Table 5. Catalytic enantioselective aza-Friedel–Crafts reaction with (*R*)-BINSA ammonium salt.



[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).

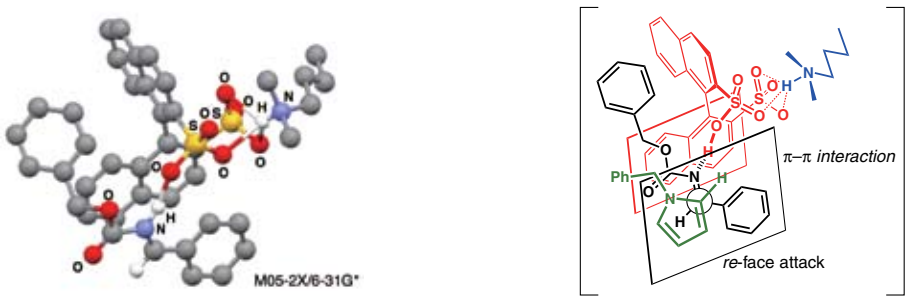


Figure 2. M05-2X/6-31G* optimized geometry of (*R*)-**1•16** and a proposed transition state.

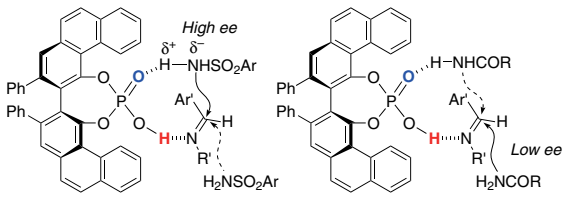
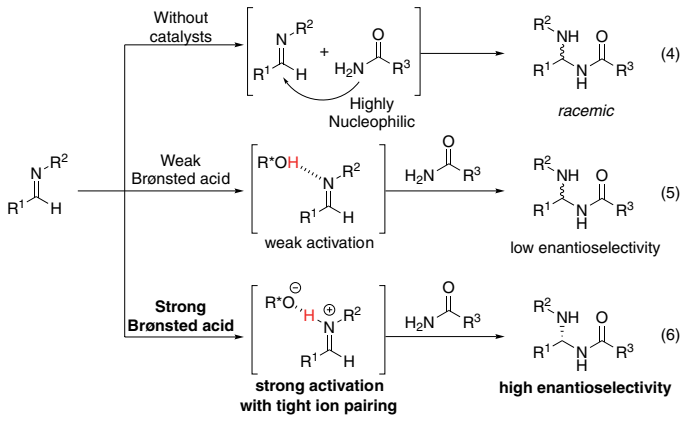


Figure 3. Assumed activation mechanism by the phosphoric acid catalyst.



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.

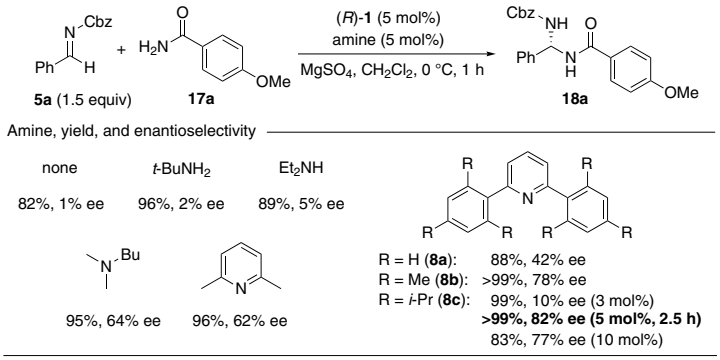
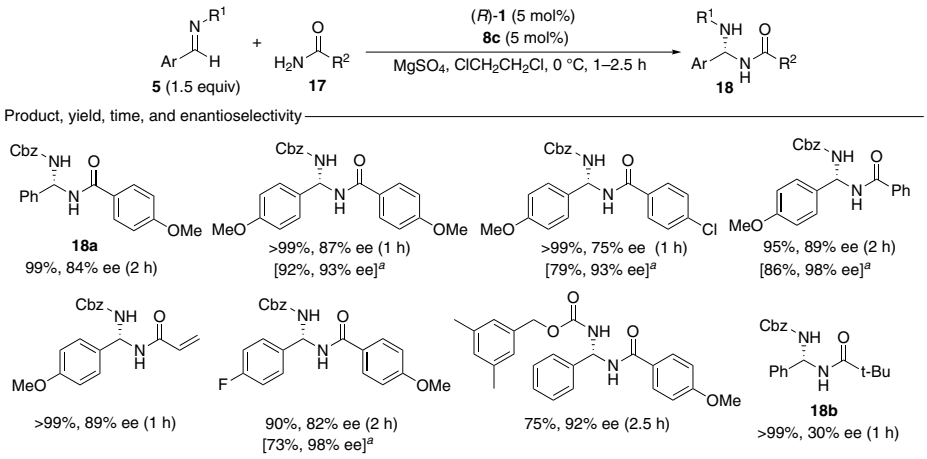
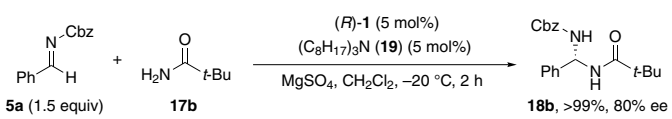


Table 7. Catalytic enantioselective direct aminal synthesis with the use of (*R*)-BINSA ammonium salt.



[a]Yield and enantioselectivity after a recrystallization.



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

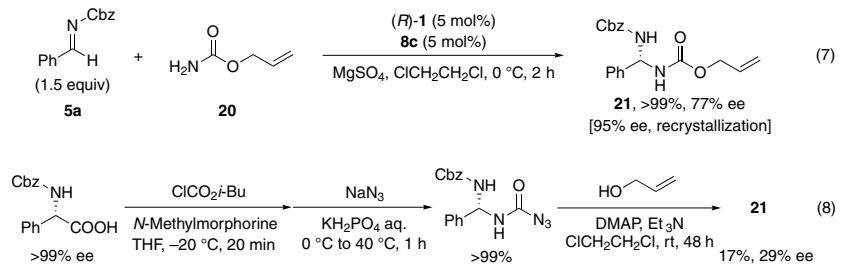
used in the reaction of **5a**. Fortunately, the reaction proceeded smoothly, and the corresponding product **21** was obtained in >99% yield with 77% ee (Scheme 10, eq 7). Moreover, a single recrystallization increased the enantiopurity up to 95% ee. In sharp contrast, the conventional synthesis of **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]

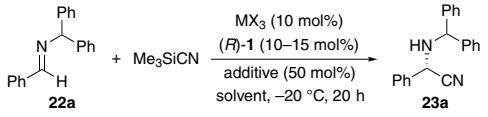
First, we examined the metal tuning for (*R*)-**1** (10–15 mol%) in the reaction of aldimine **22a** with trimethylsilyl cyanide (TMSCN) (1.5 equiv) at –20 °C for 20 h (Table 8). As expected, trivalent precursors promoted the reaction moderately. In particular, La(O*i*-Pr)$_3$ gave the product (**23a**) 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.

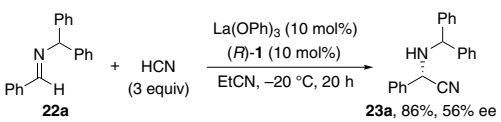


Scheme 10. Catalytic enantioselective direct aminal synthesis from allyl carbamate (**20**).

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



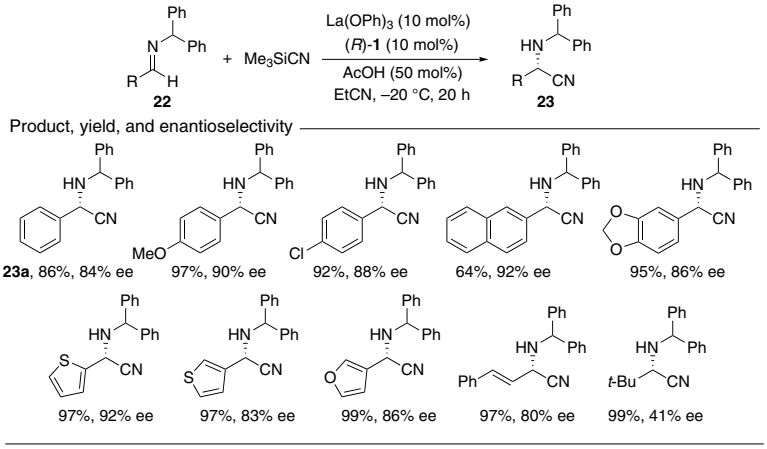
Scheme 11. Reaction with HCN.

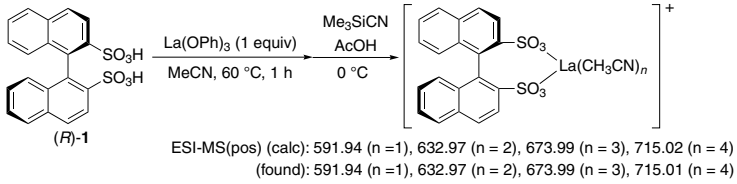
Next, we examined the scope of the aldimines (**22**) in the presence of (*R*)-**1** (10 mol%), La(OPh)$_3$ (10 mol%), AcOH (50 mol%), and TMSCN (1.5 equiv) in EtCN at –20 °C (Table 9). The reactions of aromatic and heteroaromatic aldimines bearing an electron-withdrawing or electron-donating group proceeded 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.

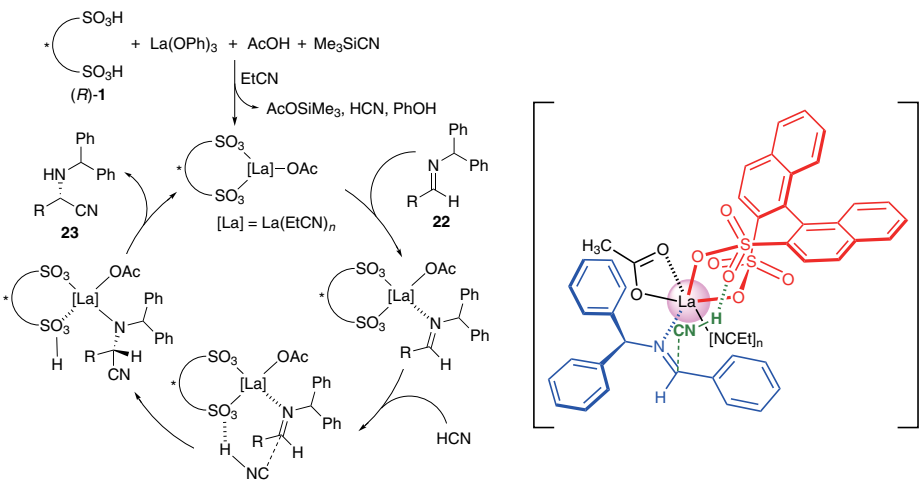


Figure 4. Postulated catalytic cycle and transition state.

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

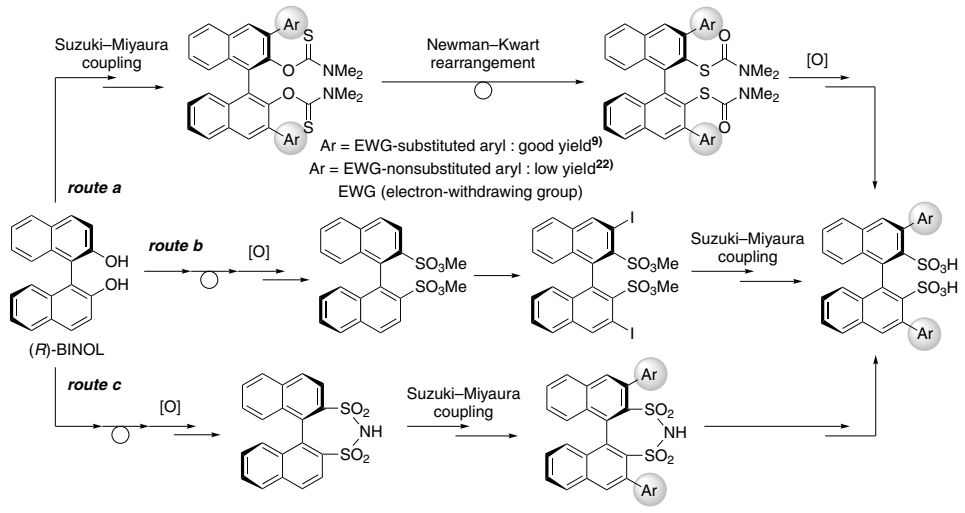
The introduction of 3,3′-disubstituents has not been well established for chiral 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA), due to synthetic difficulties, unlike for chiral binaphthyl phosphoric acid, dicarboxylic acid, etc. In particular, the key to synthesizing chiral 3,3′-Ar_2-BINSAs from chiral 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).

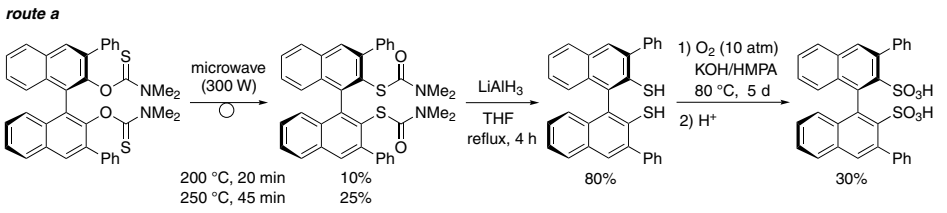
As a third synthetic route to chiral 3,3′-Ar_2-BINSAs, the deprotection of 3,3′-diaryl-1,1′-binaphthyl-2,2′-sulfonimides may be possible (Scheme 13, **route c**). Remarkably, Lee reported a practical synthesis of (*R*)-3,3′-diaryl-1,1′-binaphthyl-2,2′-sulfonimides from the parent (*R*)-3,3′-dibromo compound 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**,



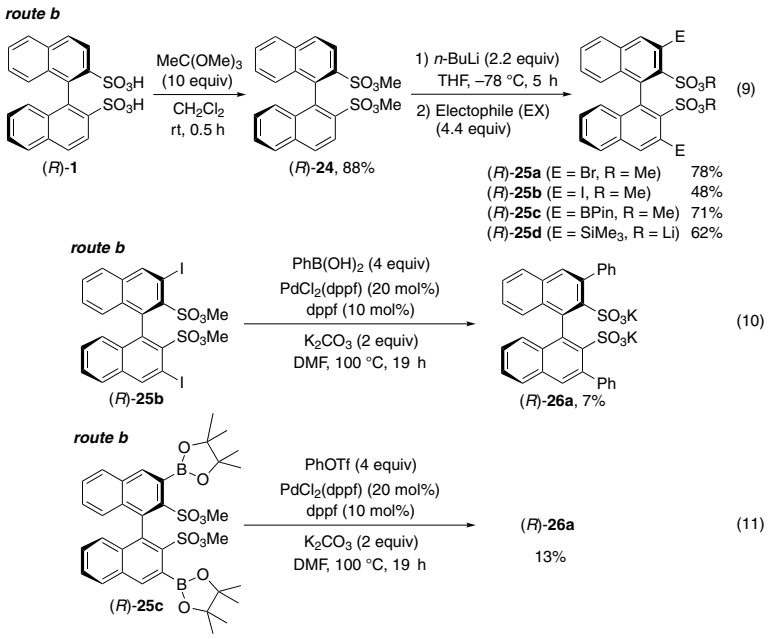
Scheme 13. Synthesis of (*R*)-3,3′-Ar_2-BINSAs.



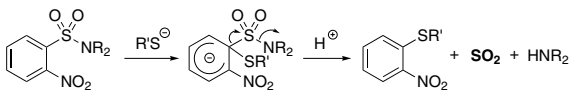
Scheme 14. Synthesis of (*R*)-3,3′-Ph_2-BINSA *via* **route a**.

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.

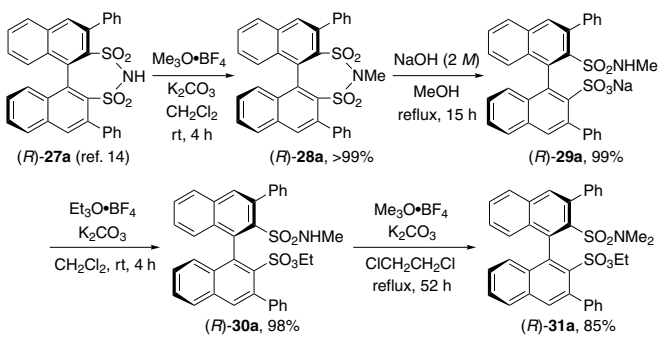
Finally, we examined reductive cleavage of the *N*–*S* bond of sulfonamides with aluminum hydride reagents, which has scarcely been developed since the products would be a mixture of unstable sulfinic acids, sulfenic acids, thiols, and disulfides. We expected that the desired sulfonic acids could be 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**.



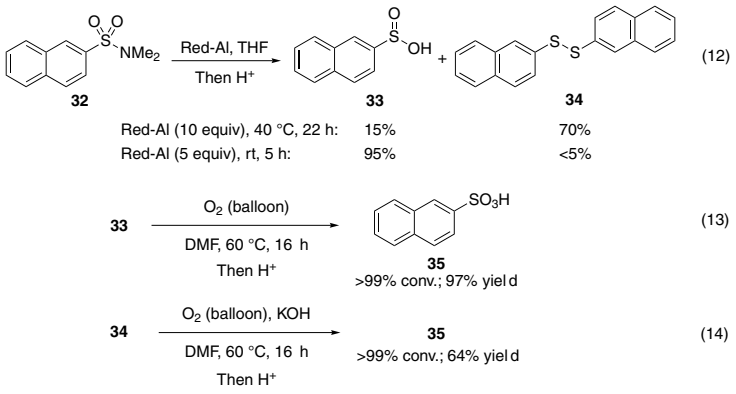
Scheme 16. Deprotection of nitrobenzenesulfonamide (Ns amide) with the release of SO_2.



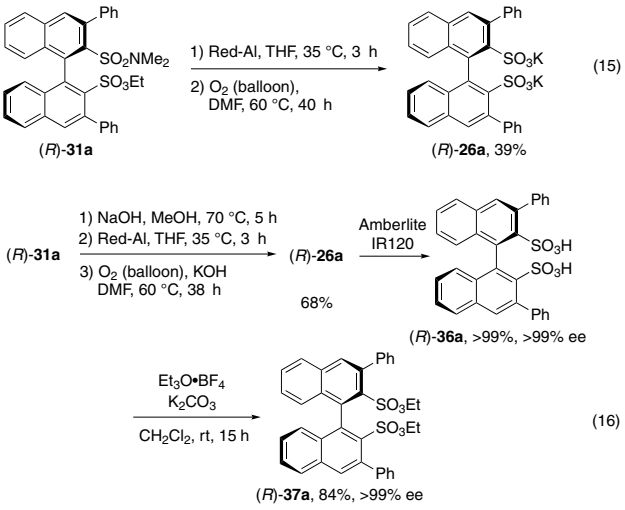
Scheme 17. Cleavage of the *N*–*S* bond of sulfonimide (*R*)-**27a**.

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.

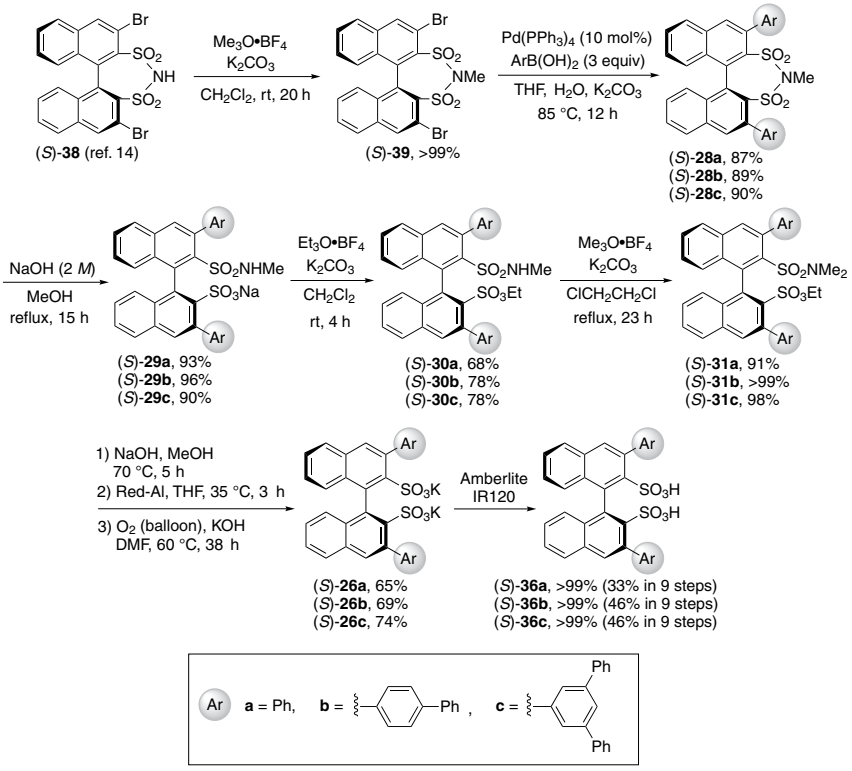
This method was effective for the synthesis of bulky (*R*)- and (*S*)-3,3′-Ar_2-BINSAs (**36**). We could use *N*-Me sulfonimide (*S*)-**39** as a common intermediate after the *N*-methylation of (*S*)-**38**[14] in the initial step (Scheme 20). Overall, we demonstrated that (*S*)-compounds with phenyl, 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.



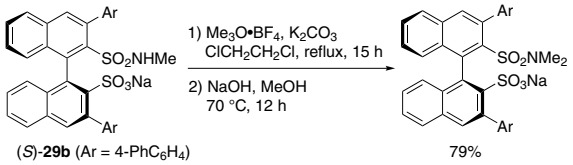
Scheme 18. Transformation of sulfonamide to sulfonic acid *via* stepwise reduction and oxidation.



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



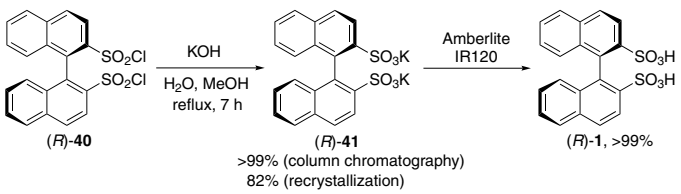
Scheme 20. Synthesis of (*S*)-3,3′-Ar$_2$-BINSAs ((*S*)-**36a–c**) (**a**: Ar = Ph, **b**: Ar = 4-biphenyl, **c**: Ar = 3,5-terphenyl).



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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Manabu Hatano received his Ph.D. from the Tokyo Institute of Technology in 2003 under the direction of Prof. K. Mikami. He joined Prof. Ishihara's group at Nagoya University as an assistant professor in 2003, and promoted associate professor in 2007. He has received the Tejima Research Award for Young Scientists in 2004, the TORAY Award in Synthetic Organic Chemistry, Japan in 2006, the Encouragement Prize from the Tokai Branch of the Society of Synthetic Organic Chemistry, Japan in 2007, the Banyu Chemist Award in 2011, the Incentive Award in Synthetic Organic Chemistry, Japan in 2012, the Nippon Shokubai Award in Synthetic Organic Chemistry, Japan in 2012, and The Young Scientists' Prize of the Commendation for Science and Technology by the MEXT in 2013.
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Graduate School of Engineering, Nagoya University

Keisuke Nishikawa received his Ph.D. from University of Fukui in 2013 under the direction of Prof. Y. Yoshimi. Then he became a postdoctoral fellow of Prof. Ishihara's group at Nagoya University in 2013. He received the Best Student Presentation Award in the annual meeting of photochemistry in 2009 and the Student Presentation Award in the Hokuriku Seminar in the Synthetic Organic Chemistry, Japan in 2010.
[Specialties] Synthetic Organic Chemistry, Organic Photochemistry

Kazuaki Ishihara
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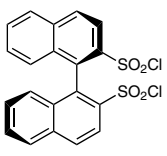
Kazuaki Ishihara received his Ph.D. from Nagoya University in 1991 under the direction of Prof. H. Yamamoto. After he completed his postdoctoral studies with Prof. E. J. Corey at Harvard University (15 months beginning in 1991), he returned to Japan and joined Prof. H. Yamamoto's group at Nagoya University as an assistant professor in 1992, and promoted associate professor in 1997. In 2002, he was appointed to his current position as a full professor at Nagoya University. He has received the Inoue Research Award for Young Scientists, the Chemical Society of Japan Award for Young Chemists, the Green and Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science and Technology, the JSPS Prize, the BCSJ Award, the IBM Japan Science Prize, the Mukaiyama Award, the Inoue Prize for Science, Fellow of the Royal Chemical Society, the SSOCJ Daiichi–Sankyo Award for Medicinal Organic Chemistry 2012, the Yazaki Academic Award, and the Ichimura Prizes in Technology–Contribution Prize.
[Specialties] Synthetic Organic Chemistry, Stereochemistry, Chemical Catalysis
[E-mail] ishihara@cc.nagoya-u.ac.jp
[Homepage] http://www.ishihara-lab.net/

TCI Related Compound



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

Chemistry Chat -Focusing on the Elements-

Colors and Chemical Names (1)

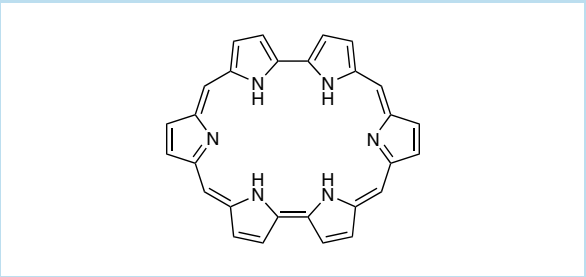
Kentaro Sato

Vivid, diverse, and changeable colors of chemicals lured many of us stepping into the field of chemistry as young students. There are indeed a number of elements and compounds that display beautiful colors. Some of them are used as synthetic dyes and were a major part of the early development of chemical industry. From litmus paper to state-of–the-art bioimaging technologies, color and chemical research always go hand in hand.

So not surprisingly, there are quite a few chemicals with names derived from their colorful appearances. In this article, let us look at some of the interesting examples.

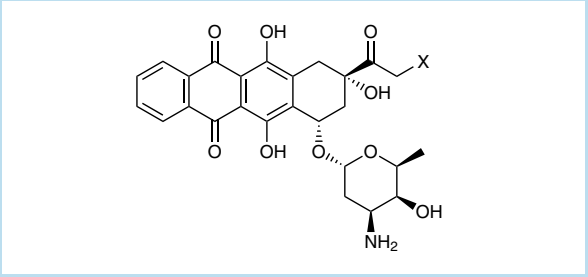
Red

In the periodic table, the element whose name is derived from red is the thirty seventh rubidium. This name was coined because the color of rubidium's emission spectrum was rubidus, meaning red in Latin. The ruby gemstone has the same name origin. As for organic compounds, there is a compound called rubyrin. A relative of porphyrin, rubyrin is composed of six pyrrole rings and shows beautiful red color.



Rubyrin

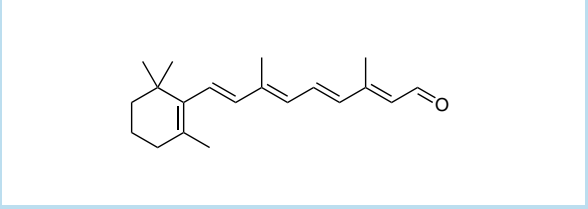
Some members of anthracycline antibiotics family show red colors such as aunorubicin and doxorubicin, where the *rubi* in thier names is derived from the color.



X=H: Daunorubicin, X=OH: Doxorubicin

There are several types of redness. For example, rosy color is rhodon in Latin and rhodeos in Greek. These words became the origin of the name of the forty fifth element rhodium since solutions containing rhodium metal appeared rosy red.

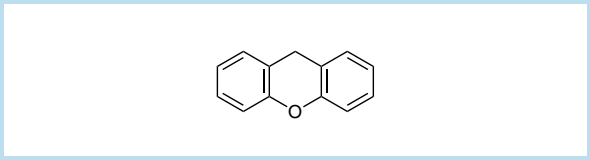
Around 1876, it was discovered that the animal photoreceptor cells contain a reddish substance that are responsible for sensing of light. The substance was named rhodopsin by combining rhodo and opsis (which means vision). The redness is actually a result of the chemically bonded compound called retinal, which produces visual signals in the form of double bond isomerization upon photo irradiation.



Retinal

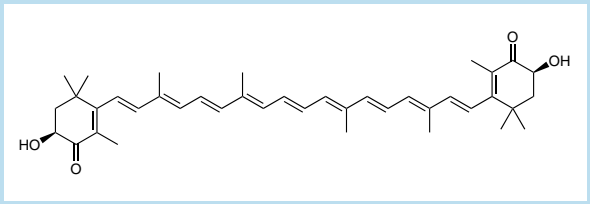
Yellow

Yellow in Greek is xanthon and there are lots of compounds named after it. Xanthene has a structure composed of two benzene rings fused with a pyran and is literally a yellow solid.



Xanthene

Xanthophyll compounds are yellow pigments containing a long chain of conjugated double bonds and are involved in photosynthesis. This group includes compounds such as lutein, zeaxanthin, neoxanthin, violaxanthin, and cryptoxanthin. Some compounds that appear more red than yellow like astaxanthin are also found in the group.

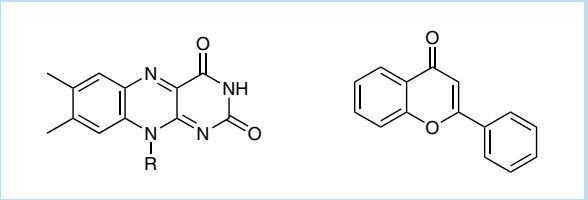


Astaxanthin

Xanthic acids have a formula of RO-C(=S)SH and xanthate salts indeed show yellowish colors. In organic synthesis, xanthate esters are used in the Chugaev elimination reaction (a type of dehydrative olefination) and the Barton-McCombie radical deoxygenation reaction mediated by stannanes.

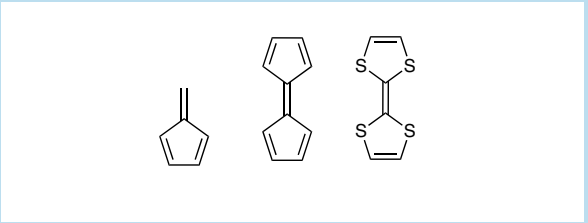
It is probably a common experience for many of us that accidently touching nitric acid during an experiment turns the affected part of the skin yellow. The reaction is known as the xanthoproteic reaction and is used as a test to determine the amount of protein in the sample. The term *xantho* in this case is also derived from the same origin. The color change is due to the nitration of aromatic rings such as the one contained in tyrosine residues.

On the other hand, the Latin translation of yellow is *flavum* and there are compounds known that are named based on it. One of them is flavines, whose derivatives act as coenzymes, the shortage of which causes various disorders such as inflammation. Flavones sound very similar and are derived from the Latin *flavus* but are unrelated to flavines structurally.



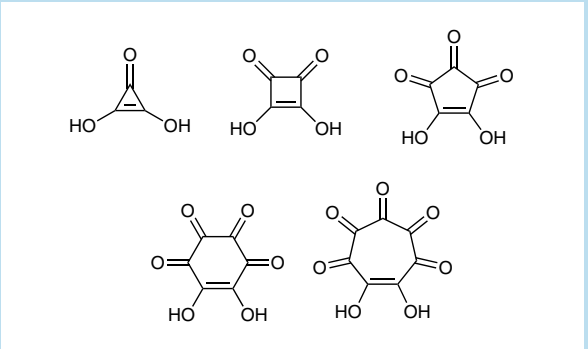
Flavines and flavones

In a similar context, the word fulvous (dull brownish yellow) can be found as part of the names of some compounds. For instance, the hydrocarbon compound shown on the left in the figure below is fulvene, which is an isomer of benzene. The compound in the middle composed of two cyclopentadienes is called fulvalene, but the one on the right, tetrathiafulvalene (TTF) with four sulfur atoms replacing the methine hydrogens, is far more well-known. TTF works as the electron donor of a charge transfer complex and is an iconic compound in the field of organic electronics materials.



Fulven, fulvalen, and tetrathiafulvalene

There is a group of cyclic compounds called oxocarbonic acids. Three- to seven-membered ring compounds are known and all of them show strong acidity. Among these, the five-membered ring compound is yellow and called croconic acid after the Greek *krokos*, which means saffron or egg yolk. The six-membered ring compound appears rosy red so it is called rhodizonic acid. However, the three, four, and seven-membered ring members are called deltic, squaric, and haptagonic acids, respectively, after their shapes rather than colors. Scientific nomenclature usually stresses consistency, but this is a rather unusual exception.

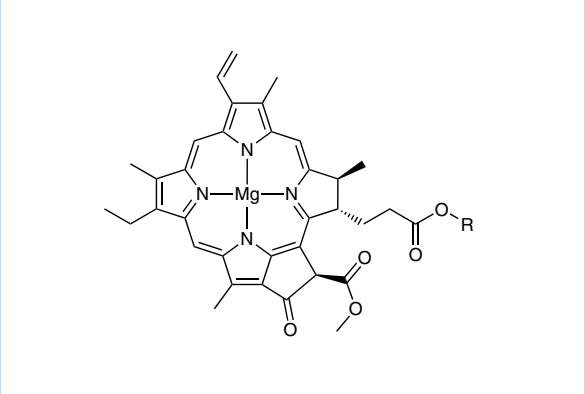


From the upper left, deltic acid, squaric acid, croconic acid, rhodizonic acid, and haptagonic acid

Green

As for elements named after the color of green, there is praseodymium with the atomic number 59 whose name origin is the Greek *prasios*, meaning bluish green. Pr(III) ions indeed appear green. Similarly, the eighty first element thallium was named after the Greek *thallos*, which means green twig, since the spectroscopic spectrum of the element was green.

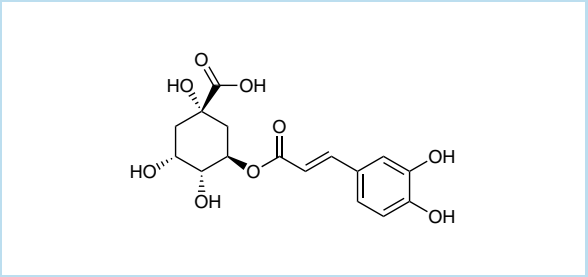
I once thought that chlorophyll contained chlorine atoms because of how the name sounded. But needless to say, the molecule of chlorophyll is made up of C, H, O, N, and Mg, having nothing to do with Cl.



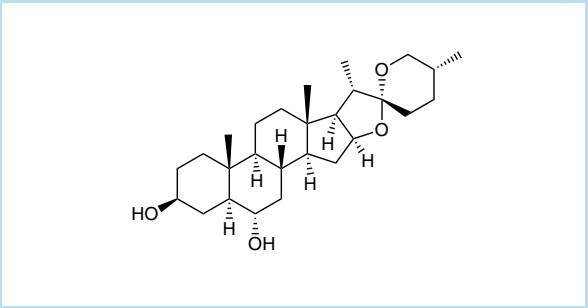
Chlorophyll a

In fact, the name chlorophyll is a portmanteau based on the Greek *chloros* (green) and *phyllon* (leaf). Chlorine has the same name origin as it is a yellowish green gas in an elemental form, but is not directly related.

Chlorogenic acid, a type of polyphenol found in coffee, doesn't contain any chlorine atoms either. The acid was given the name meaning "green generating" because it turns green when it is oxidized. In addition, the steroid compound found in a species of lily *Chlorogalum pomeridianum* is called chlorogenin even though it neither has any chlorines nor structural similarities to chlorogenic acid. This is such a confusing case.



Chlorogenic acid



Chlorogenin

There are more than a few cases where structurally unrelated compounds share the same central component in their names. They are a cause of confusions but it is nonetheless interesting to learn where the names originated. Let us go over more examples for other colors next time.

Introduction of the author :

Kentaro Sato

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2007-Present Freelance science writer. 2009-2012 Project assinstant professor of the graduate school of Science, the University of Tokyo.
[Specialty] Organic chemistry
[Website] The Museum of Organic Chemistry <http://www.org-chem.org/yuuki/MOC.html>

Chemistry Chat -Visit to a School Science Lab-

Visit to a Science Club

Chemistry Club at Shibuya Kyoiku Gakuen Makuhari Junior and Senior High School

Introduction

On this occasion, we would like to turn a spotlight on the chemistry club at Shibuya Makuhari Junior and Senior High School, which has received multiple awards such as the Golden Award in the Chemistry Club Presentation 2011 hosted by the Chemical Society of Japan, Kanto Branch. We visited the club on July 30, 2013, just after the summer vacation had started. The school encourages the idea of "Self-thinking, Self-awareness" as an educational goal, and is very active in cross-cultural experiences to nurture internationally-minded individuals. At the laboratory where we were invited, the club members were preparing demonstration experiments for the school cultural festival in September. A student counseling room and teachers' office are located nearby, and it could be seen that the school has been providing a quality education in chemistry, which is rich in personal attention.

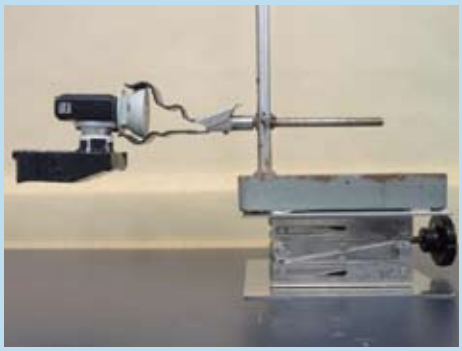
Members of the chemistry club with TCI pens and notes in hand. Four teachers Mr. Toya (back row left), Mr. Murakami (middle row left), Mr. Iwata (middle row right), Ms. Sahara (front row right), and the captain Ryoichi Yabuki (front row center).

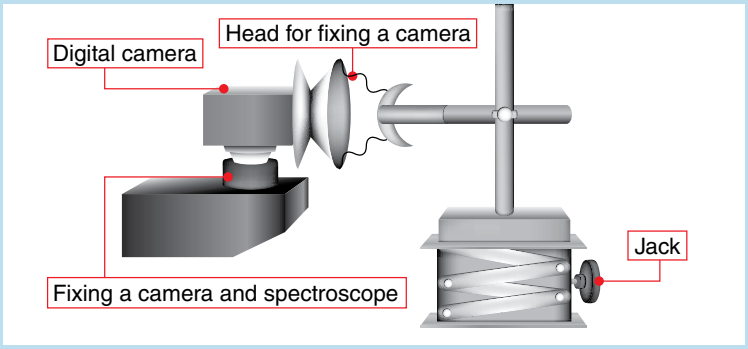
Chemistry Club at Shibuya Makuhari Junior and Senior High School

This year, the chemistry club consists of 31 students (16 junior high and 15 senior high, including 5 female students) and 5 teachers (Mr. Iwata, Mr. Toya, Mr. Murakami, Mr. Oki and Ms. Sahara), and meets four times a week. The club activities begin with learning about experiments of interest by self-study, which are performed with proper guidance after much consultation with teachers. Students seek a study theme from questions and topics raised through this process to work on over time.

The results obtained from these experiments are sent out to the Science Research Presentation hosted by Chiba University (September), the Japan Student Science Awards (November, consecutively since 1991) and the Chemistry Club Presentation hosted by the Chemical Society of Japan, Kanto Branch (March). In December 2012, they also took part in the Japan Science and Engineering Challenge (JSEC). Aki Kitaori, the former captain and JFE Steel Award winner, was chosen to represent Japan at the Intel International Science and Engineering Fair (ISEF) in the U.S. in May, 2013. For school events, they perform demonstration experiments in the welcome festival for new students (April) and the annual cultural festival (September).

The chemistry club has already adopted a self-constructed DVD spectroscope for use in experiments, similar to the one described in the Rikkyo school article in TCIMAIL No. 159[1]. A photo of the real object is given below. The tool is of course hand-made and height-adjustable with a jack. For the spectrum analysis of images, Makali`i, a free image processing software distributed by the National Astronomical Observatory of Japan, is used. This software is able to display a graph of RGB and brightness values for a line segment on the active image. They analyze the spectral color information from the brightness values.





1) M. Makino "The creation of a simple discharge device using an aspirator" Minister of Education Award in Japan Student Science Award 2007, First Award in Coalition of Plasma Science in Intel ISEF 2008.
http://event.yomiuri.co.jp/jssa/works/works_prize51.htm (Japanese); http://www.sciserv.org/document.doc?id=75 (Page 26): http://www.plasmacoalition.org/plasma_pages/P_pages_Jun2008.pdf
2) Makali`i, SUBARU Image Processing software (National Astronomical Observatory of Japan)
http://makalii.mtk.nao.ac.jp/index.html.en

Here, students are performing various experiments. We had the opportunity to interview the club captain, Ryoichi Yabuki (11th grade).

- *How do you like the activities of the science club?*
  It is hard for junior and senior high school students to acquire college-level knowledge and experimental techniques, but it's a lot of fun. We cannot do without teachers with specialized knowledge. Experimental techniques, however, have been passed down from students in upper-grades to students in lower-grades. I believe that experience in the chemistry club will be helpful in my future.
- *What are your plans for the future?*
  I am interested in fields relating to chemistry and biology so I am taking a biology class, too, at my school. I would like to go to a college where I can study pharmaceutical sciences.

Award winning results (school grade at the time of award receipt.)

Academic year 2012:

10th Japan Science and Engineering Challenge (JSEC, hosted by the Asahi Shimbun, supported by multiple government agencies including the Cabinet Office)
http://www.asahi.com/shimbun/jsec/jsec2012/winner.html (Japanese)
JFE Steel Award (A. Kitaori, 12th grade): Formation and Behavior of a Suspension Membrane

A suspension membrane of calcium hydroxide is formed in a striped pattern when calcium metal reacts with water. In this study, the forming conditions and behavior of the membrane are examined from experimental results, and its fundamental rule is considered. It is also demonstrated that the viscosity of a solution and surface tension are influential in forming a liquid membrane.

30th Chemistry Club Presentation (hosted by Chemical Society of Japan, Kanto Branch)
http://kanto.csj.jp/?page_id=177 (Japanese)
Idea Award (A. Funamoto, 11th grade): Study on the Flame Reaction of Copper Using a Self-constructed Spectroscope

This study examines the effect of anions contained in ionic substances by analyzing emission spectra of the flame light reaction when mixing various inorganic copper compounds and ionic substances. The self-made spectroscope described above and Makali`i for the spectrum analysis are used.

Idea Award (R. Nakamura, 10th grade): Effects of Microwave Irradiation on Ionic Crystals and Their Hydrates

This study observes the effects of microwave irradiation on ionic crystal hydrates. A microwave oven (700W) is used for the experiment.

6th Science Research Presentation (hosted by Chiba University)
http://koudai.cfs.chiba-u.ac.jp/n1_kr_houkoku24.htm (Japanese)
First Prize (R. Yabuki, 10th grade): A Method to Promote a Copper Dendrite Growth

Metal dendrites, crystals with a tree-like branching structure, can be separated from a metal having a smaller ionization tendency by making use of the differences among metals. In this study, Ryoichi Yabuki focuses on copper and examines various conditions to promote the dendrite growth. The shape of a zinc plate is reported to be the most influential on the growth.

Second Prize (K. Shimomura, 11th grade): Forming Condition and Behavior of a Polyaniline Membrane

Polyaniline membrane, a conductive polymer, is produced by mixing ammonium peroxodisulfate and a saturated aniline aqueous solution. This study aims to investigate the forming conditions of a membrane and the connection between its electrical conductivity and color. Kai Shimomura has found that the electrical conductivity and color are changed by adding acids and bases when a membrane is formed, and also reports that addition of metal ions causes an increase in membrane intensity and alteration of electrical conductivity.

Second Prize (S. Masuda, 10th grade): A New Method for the Synthesis of Esters

This study reports on the synthesis of esters with silica gel as an acid catalyst. This reaction proceeds efficiently even at 30 ºC.

Academic year 2011:

29th Chemistry Club Presentation (hosted by Chemical Society of Japan, Kanto Branch)
http://kanto.csj.jp/?page_id=168 (Japanese)
Golden Award (K. Miyamoto, 11th grade): Study on Luminol Chemiluminescence
Best Poster Award (K. Teranishi, 10th grade, S. Nakamura, 8th grade): Origin of Life, Part VI
Best Poster Award (K. Shimomura, 10th grade): Effects of Amines on Aniline Oxidation
Best Poster Award (Y. Misawa, 8th grade): Preparation of a Fluorescent Material Glowing Three Colors

5th Science Research Presentation (hosted by Chiba University)
http://koudai.cfs.chiba-u.ac.jp/n1_kr11_houkoku23.htm (Japanese)
First Prize (A. Kitaori, 11th grade): Formation of a Suspension Membrane Containing Calcium Ions
Second Prize (S. Nitta, 11th grade): Silver Mirror Reaction with Common Drinking Water

Closing Remarks

We had opportunities to talk with the 11th-grade club members during this visit. Each one of them talked about chemistry in their own words, and from this, we are sure that the school's educational policy "Self-thinking, Self-awareness" is not just a written slogan. We wish continued success and future growth for the chemistry club of Shibuya Makuhari Junior and Senior High School. We will continue our visits to school science labs to meet new people and to make new discoveries.

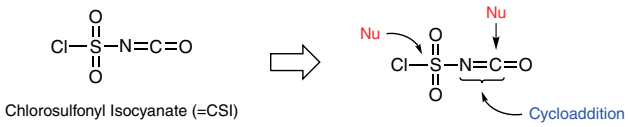
Organic Syntheses Utilizing the Chemical Properties of Chlorosulfonyl Isocyanate

Haruhiko Taguchi

Tokyo Chemical Industry, Co. Ltd.

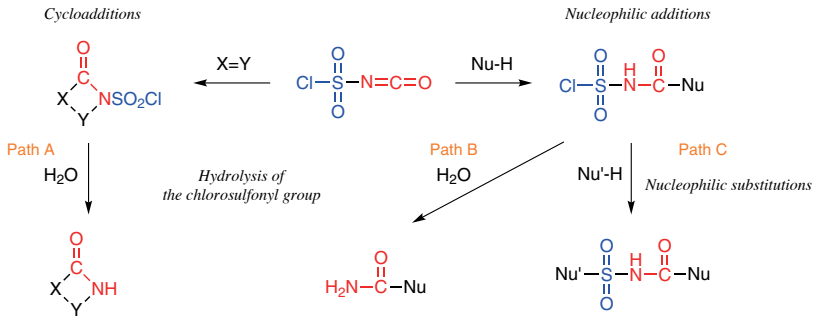
In this column, we focus on another usage of reagents from the viewpoint of a reagent company. In this issue, we introduce a reagent having some probable reactive sites. In general, organic synthetic reagents have a certain reactive site and this chemical property is utilized for organic synthesis. Reagents having some active reactive sites such as dihalogen compounds and haloalcohols are available from reagent companies and these chemical properties can be used for design and synthesis of compounds with more complex structures.

However, there are some unusual reagents in organic chemistry and some of them are available from reagent companies. Now, we pick chlorosulfonyl isocyanate (CSI) and focus on its unique reactivities.



The reactivities of chlorosulfonyl isocyanate

CSI has been well used for organic syntheses due to its unique reactivities. CSI is composed of two functional groups, the isocyanate portion and the chlorosulfonyl group. In “Encyclopedia of Reagents for Organic Synthesis”, it is written that CSI has three reactive sites.[1)] The isocyanate portion of CSI shows two reactivities: the cycloaddition at the carbon-nitrogen double bond and the nucleophilic addition at the carbon-oxygen double bond. The chlorosulfonyl group of CSI proceeds with nucleophilic substitution. How can each reactivity of CSI be successfully controlled? In fact, these three reactivities can be successfully controlled.



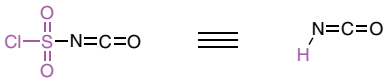
The reactions using chlorosulfonyl isocyanate

We understand that the isocyanate portion is the higher reactive functional group compared with the reactivity of the chlorosulfonyl group based upon accumulated experiments. Actually, in the reactions using CSI, the isocyanate portion generally reacts prior to the chlorosulfonyl group, thereby allowing the CSI reactivities to be controlled even with having three reactive sites.

Especially, the β-lactam moiety formed by the cycloaddition of unsaturated compounds to the carbon-nitrogen double bond of CSI, is the essential part to synthesize the β-lactam antibiotics (Path A). Then, how to utilize the chlorosulfonyl group of CSI in organic synthesis? As shown in Path A, B, and C in the above scheme, there are some usages. The residual chlorosulfonyl group after the reaction of CSI with nucleophiles is available for further reactions, and one of the typical reactions of it is with other nucleophiles (Path C).

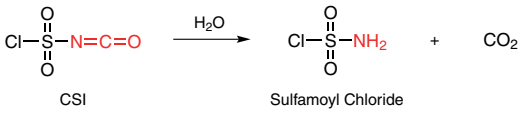
One example reaction through the Path C route is the preparation of Burgess reagent, an efficient reagent converting alcohols to the related amines or olefins, which is synthesized from CSI.[3] On the other hand, other methods to use the chlorosulfonyl group of CSI like Path A or Path B are the aqueous hydrolyses.[1,2]

As shown in Path A and Path B in above scheme, the chlorosulfonyl group of the intermediates is hydrolyzed by the addition of water to afford the desired *N*-free amines. In these reactions, we recognize that chemically same products can be obtained even when using isocyanic acid instead of CSI, and CSI can be also used as an isocyanic acid equivalent. Isocyanic acid is a highly toxic and volatile liquid with a low boiling point. Thus, CSI is an efficient reagent as an alternative to using isocyanic acid.



The usage of CSI as an isocyanic acid equivalent

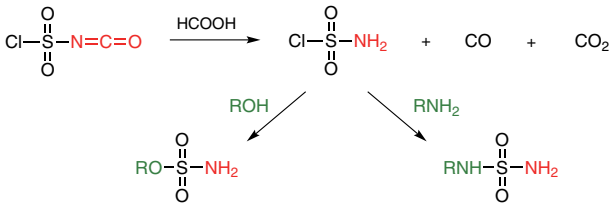
As mentioned above, the reactivity of CSI is quite high. How much toxicity and chemical stability does CSI show? CSI is toxic and hygroscopic due to one of isocyanate derivatives and reacts easily with water to decompose. It seems difficult to store CSI without decomposition. If CSI is partially decomposed by moisture, will it be able to be used as a reagent anymore? In a case of CSI, the reaction shown in the scheme below occurs as hygroscopic decomposition.



Hydrolysis of CSI to generate sulfamoyl chloride

The isocyanate portion of CSI is hydrolyzed by moisture and crystalline sulfamoyl chloride is formed. In experiments, CSI has formed some solids in a bottle and a cap with use. It has been caused by the hygroscopic decomposition of CSI to form crystalline sulfamoyl chloride. However, even when CSI is partially decomposed and crystalline sulfamoyl chloride precipitates appear in a bottle, the supernatant liquid of CSI has kept the purity sufficiently high and it can be still used as a reagent.

By the way, sulfamoyl chloride can be also used for a sulfonamide bond forming reaction, which enables CSI to be used as the precursor of sulfamoyl chloride. Actually, in situ preparation of sulfamoyl chloride by the treatment of CSI with water is not safe, so the same equivalent of formic acid toward CSI is better used instead of water to generate sulfamoyl chloride more gently.[4]



Preparation of sulfamoyl chloride from CSI and its use for organic synthesis

When preparing sulfamoyl chloride according to above mentioned method, we find that crystalline sulfamoyl chloride is being formed as a precipitate by the decomposition of liquid CSI. The reactivities of formed sulfamoyl chloride to alcohols and amines are excellent and the desired sulfonamide derivatives are given. This synthetic manner is especially efficient to produce *N*-free terminal sulfonamide derivatives.

The usage of CSI as a reagent is very unique because of having three different reactive sites. In addition, it can be also used as an isocyanic acid equivalent and the precursor of sulfamoyl chloride. Furthermore, CSI would be a powerful tool to construct the sulfonamide structure which is often seen in bioactive compounds. As one method to synthesize the bioactive compounds, chlorosulfonyl isocyanate is recommended for your organic synthesis.

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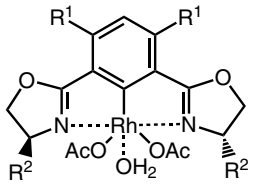
Related Compounds

C0886	Chlorosulfonyl Isocyanate (= CSI)	25, 500g
M1279	Burgess Reagent	1g, 5g, 25g

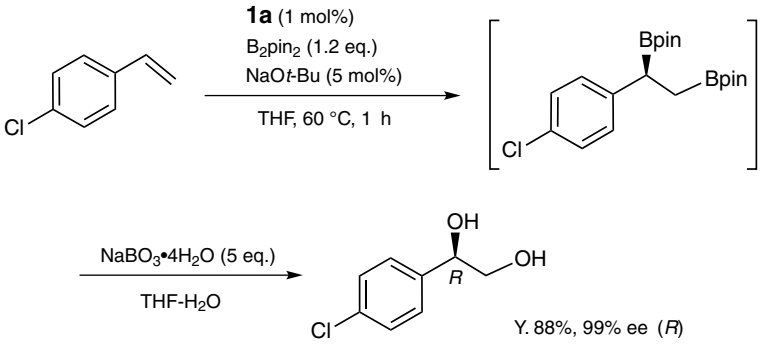
Pincer Type Rh Complexes Catalyzed Asymmetric Diboration of Terminal Alkenes and Their Conversion to the Optically Active 1,2-Diols

B4195 Bis(acetato)aqua[(*S*,*S*)-4,6-bis(4-isopropyl-2-oxazolin-2-yl)-*m*-xylene]rhodium (1a) 10mg



1
Rh(Phebox)

R^1 = Me, R^2 = *i*-Pr (**1a**)
R^1 = H, R^2= *i*-Pr, Ph, Bn, *t*-Bu



Nishiyama *et al*. have reported that optically active 1,2-diols are given by the pincer type Rh complexes [Rh(Phebox), **1**] catalyzed asymmetric 1,2-diboration of terminal alkenes and subsequent oxidation. According to their results, the asymmetric diboration of 4-chlorostyrene with a diboron ester proceeds with high enantioselectivity by using a rhodium complex coordinated with a pincer type ligand (**1a**), and the desired 1,2-diborylated product is formed. Subsequent oxidation of it with sodium peroxoborate in THF-water gives the corresponding 1,2-diol. In this reaction, allyl ethers and allyl anilines can be transformed into the related optically active 1,2-diols. In addition, when using *trans* 1,3-dienes as reactants, terminal alkene moieties are selectively reacted and the optically active allylic alcohols are given. Thus, this asymmetric diboration using **1** is an efficient synthetic method to produce the optically active 1,2-diols.

Reference

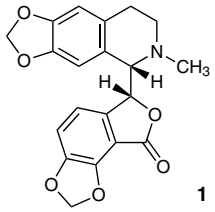
Asymmetric diboration of terminal alkenes with a rhodium catalyst and subsequent oxidation: enantioselective synthesis of optically active 1,2-diols
K. Toribatake, H. Nishiyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 11011.

Related Compounds

B4196	(*S*,*S*)-4,6-Bis(4-isopropyl-2-oxazolin-2-yl)-*m*-xylene			20mg
B1964	Bis(pinacolato)diboron	1g	5g	25g
S0450	Sodium *tert*-Butoxide	25g	100g	500g
S0887	Sodium Perborate Tetrahydrate		25g	500g

GABA Receptor Antagonist

B1890 (+)-Bicuculline (1) 25mg, 100mg



1

GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter in the mammalian central nerve system and $GABA_A$, $GABA_B$, and $GABA_C$ receptors have been identified as the major receptors.[1] $GABA_A$ and $GABA_C$ receptors are members of transmitter-gated ion channels, and $GABA_B$ receptors are the receptors that are coupled to G-protein and activate secondary messenger systems and Ca^{2+} and K^+ ion channels.[1]

Bicuculline (**1**) is a phthalide isoquinoline alkaloid isolated from a variety of plants, *Dicentra, Corydalis*, and *Adlumia*, genera of the *Fumariaceae* family. $GABA_A$ receptors are selectively blocked by **1**.[1-3] Affinity of **1** and the receptors have been studied by using mutational forms of recombinant receptor proteins.[3] **1** and its quaternary salts also have actions other than as GABA-receptor antagonists including inhibition of cholinesterase, effects on $5\text{-}HT_3$, nicotinic, and *N*-methyl-D-aspartate (NMDA) receptors.[2,3]

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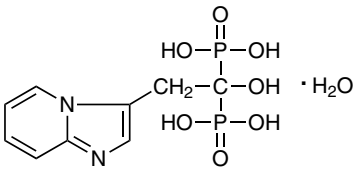
Bone Resorption Inhibitor

M2360 Minodronate Monohydrate (1) 25mg



1

Bisphosphonates (BPs), including minodronate, ibandronate, *etc.*, are very effective inhibitors of bone resorption *in vivo* and *in vitro*. Minodronate monohydrate (**1**) is one of BPs.[1,2] These compounds are characterized by two C-P bonds which are located on the same carbon atom, *i.e.* geminal BPs, and have been used for many research studies regarding bone metabolism.[1,2]

According to differences in the side chain, BPs can be divided into two groups, non-nitrogen containing BPs (non-N-BPs) and nitrogen-containing BPs (N-BPs). **1** is a N-BP and is classified as a third-generation heterocyclic N-BP.[2,3] N-BPs inhibit farnesyl pyrophosphate synthetase, a key enzyme in the mevalonate pathway, which affects cellular activity and survival.[1,2] Regarding inhibition of bone resorption, **1**, as well as zoledronic acid, is more effective than other BPs.[4]

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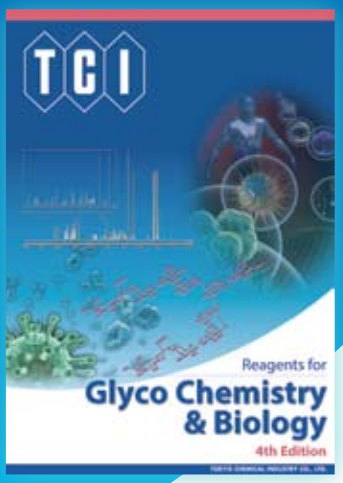

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