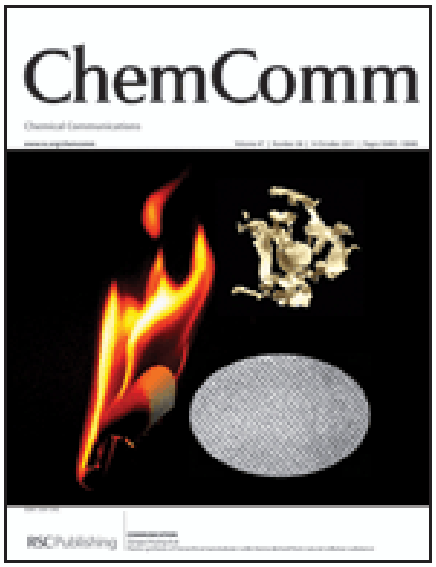

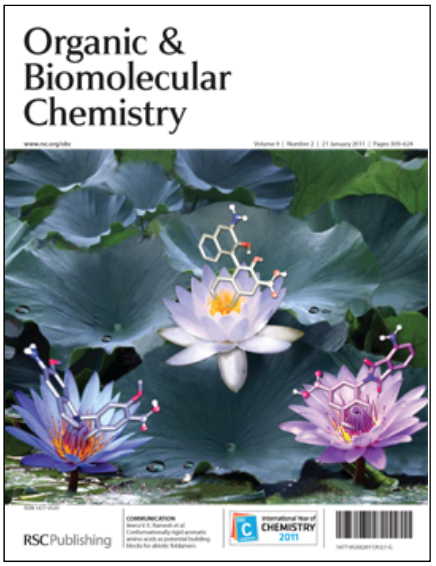

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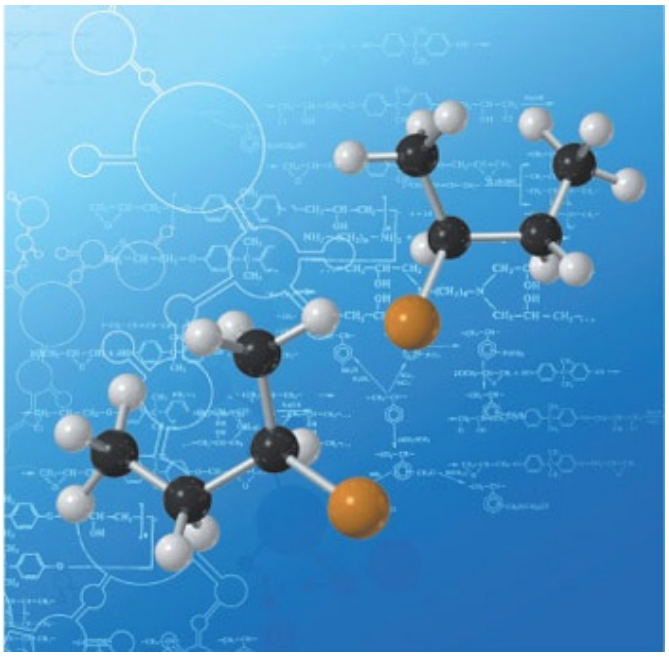

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COMMUNICATION

Enantioselective direct aminalization with primary carboxamides catalyzed by chiral ammonium 1,1′-binaphthyl-2,2′-disulfonates†‡

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A highly effective catalytic enantioselective direct aminal synthesis was developed. Chiral ammonium 1,1′-binaphthyl-2,2′-disulfonates, which were prepared *in situ* from (*R*)-BINSA and achiral amines, promoted the enantioselective addition of primary amides to aromatic aldimines.

Aminals, which are nitrogen equivalents of acetals, are synthetically and medicinally useful compounds in natural products and pharmaceuticals.[1] In particular, acyclic *N*-protected chiral aminals have often been designed in retro-inverso pseudopeptides, by virtue of various biochemical processes through their intra- and extracellular functions such as antibacterial, antimycotic, antioxidant, antitumor, antiviral, sweetening, and other properties.[2,3] Nevertheless, practical catalytic methods for the synthesis of chiral 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 serious loss of optical purity is sometimes observed by epimerization.[2] In this context, Antilla *et al.* recently reported a catalytic enantioselective aminal synthesis by the direct amidation of aldimines in the presence of a chiral VAPOL-derived phosphoric acid as a Brønsted acid catalyst (Fig. 1).[4–6] According to their reports, acidic sulfonamides and phthalimides could be used successfully, but the use of simple primary carboxamides, which are less acidic and strong nucleophiles, showed unsatisfactory enantioselectivities (21–34% ee).[4] We assumed that a 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 (Fig. 1a). In sharp contrast, since carboxamides are basically more nucleophilic and less acidic, they cannot be easily activated through deprotonation with the phosphoric acid catalyst. In this case, carboxamides may directly react with aldimines through an extended transition state (Fig 1b). Therefore, the enantiofacial stereocontrol of aldimines with chiral acid catalysts should be very important for the enantioselective reaction with carboxamides. To overcome this synthetic problem, a stronger Brønsted acid catalyst might be able to activate aldimines more effectively. In this regard, (*R*)-1,1′-binaphthyl-2,2′-disulfonic acid (BINSA, **1**)[7,8] should be attractive, since both its Brønsted acidity and bulkiness can be easily controlled by complexation with achiral amines (**2**) without substitutions at the 3,3′-position in the binaphthyl skeleton (Fig. 2). According to the theoretical calculation for the (*R*)-BINSA ammonium salt in our previous work,[8e] it is expected that SO_3 moieties strongly coordinate to the ammonium proton through three hydrogen bonds, and the bulky achiral amine moiety is effective to construct a chiral reaction field around the other SO_3H moiety. We report here a catalytic enantioselective aminal synthesis from aryl aldimines (**3**) and primary carboxamides or carbamates (**4**) based on the use of chiral ammonium 1,1′-binaphthyl-2,2′-disulfonates as acid–base combination catalysts.[9]

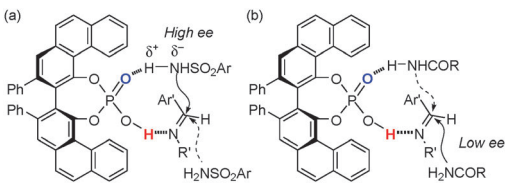

Fig. 1 Assumed activation mechanism by the phosphoric acid catalyst.

In the course of our study on asymmetric catalysis using chiral ammonium 1,1′-binaphthyl-2,2′-disulfonate catalysts, which are prepared *in situ* from (*R*)-BINSA (1,1′-binaphthyl-2,2′-disulfonic acid, **1**) and achiral amines (**2**), *N*-Cbz aryl aldimines were suitable substrates in the direct Mannich reaction and aza-Friedel–Crafts reaction.[8c,e] By taking advantage of this fact, we envisioned the catalytic enantioselective addition of aryl carboxamide **4a** to aldimine **3a** with the catalytic use of

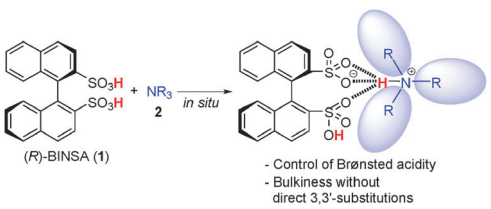

Fig. 2 BINSA (**1**) ammonium salts *in situ*.

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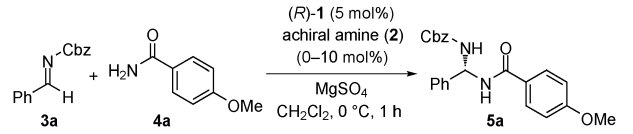
Table 1 Screening of catalysts[a]



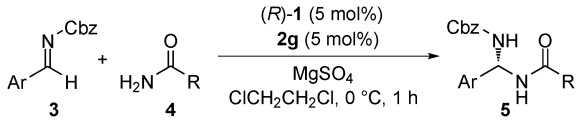
Entry	**2** [mol%]	Yield (%)	ee (%)
1[b]	—	96	—
2[c]	—	0	—
3[d]	—	82	1
4	*t*-BuNH$_2$ (**2a**) [5]	96	2
5	Et$_2$NH (**2b**) [5]	89	5
6	Me$_2$NBu (**2c**) [5]	95	64
7	2,6-Ph$_2$-pyridine (**2d**) [5]	88	42
8	2,6-(3,5-*t*-Bu$_2$C$_6$H$_3$)$_2$pyridine (**2e**) [5]	84	43
9	2,6-(2,4,6-Me$_3$C$_6$H$_2$)$_2$pyridine (**2f**) [5]	>99	78
10	2,6-(2,4,6-*i*-Pr$_3$C$_6$H$_2$)$_2$pyridine (**2g**) [3]	99	10
11	**2g** [5]	>99	82
12	**2g** [10]	83	77
13[e]	**2g** [5]	>99	84

[a] Unless otherwise noted, the reaction was conducted with **3a** (0.75 mmol), **4a** (0.5 mmol), (*R*)-**1** (0.025 mmol), and **2** (0.015–0.05 mmol) in the presence of MgSO$_4$ as a drying agent in dichloromethane at 0 °C for 1 h. [b] Without both (*R*)-**1** and **2** at room temperature. [c] Without both (*R*)-**1** and **2** at 0 °C. [d] Without **2**. [e] 1,2-Dichloroethane was used in place of dichloromethane. The reaction time was 2 h.

(*R*)-**1** and **2** in the presence of MgSO$_4$ as a drying agent (Table 1). Since **4a** is highly nucleophilic than sulfonamides and phthalimides,[10] this reaction easily proceeded without catalysts at room temperature (entry 1). However, the reaction did not proceed without catalysts at 0 °C (entry 2). Therefore, the strong activation of aldimines with the chiral BINSA salts should be effective at 0 °C without the competitive thermodynamic racemic pathways. First, we optimized the catalysts by screening **2** (5 mol%) for (*R*)-**1** (5 mol%). Poor enantioselectivities (<5% ee) were observed for the product (**5a**) when the reaction was conducted in the absence of **2** (entry 3) or in the presence of primary and secondary amines (**2a** and **2b** in entries 4 and 5). In sharp contrast, Me$_2$NBu (**2c**)[8e] and 2,6-diphenylpyridine (**2d**)[8c] as tertiary amines improved the enantioselectivity of **5a** (64% ee in entry 6 and 42% ee in entry 7, respectively). We eventually found that more sterically hindered 2,6-dimesitylpyridine (**2e**) and 2,6-(2,4,6-*i*-Pr$_3$C$_6$H$_2$)$_2$pyridine (**2g**) were effective (78% ee in entry 9 and 82% ee in entry 11, respectively), although 2,6-(3,5-*t*-Bu$_2$C$_6$H$_3$)$_2$pyridine (**2e**) was less effective (entry 8). Therefore, we decided to use **2g** as an optimal achiral amine for (*R*)-**1** in further examinations. For this catalysis, more or less than a 1 : 1 molar ratio of (*R*)-**1** and **2g** was not effective (entries 10–12). With regard to other solvents, 1,2-dichloroethane gave better enantioselectivity (84% ee) (entry 13), while low enantioselectivity (0–<50% ee) was observed when other common solvents, such as toluene, diethyl ether, THF, and propionitrile, were used.

Next, we examined the scope of the aryl aldimine and primary carboxamide under the optimum reaction conditions (Table 2). When aryl aldimines with an electron-donating or electron-withdrawing group were used with **4a**, the desired products (**5b–d**) were obtained with high enantioselectivity (81–87% ee) (entries 2–4). Other benzamides were also used and the corresponding products (**5e–h**) were obtained in almost

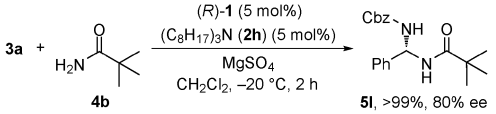
Table 2 Catalytic enantioselective aminal synthesis[a]



Entry	Ar	R	Product	Yield (%)	ee (%)
1[b]	Ph	*p*-MeOC$_6$H$_4$	**5a**	99	84
2	1-Naph	*p*-MeOC$_6$H$_4$	**5b**	80	81
3[b]	*p*-FC$_6$H$_4$	p-MeOC$_6$H$_4$	**5c**	90 [73][c]	82 [98][c]
4	*p*-MeOC$_6$H$_4$	*p*-MeOC$_6$H$_4$	**5d**	>99 [92][c]	87 [93][c]
5	Ph	Ph	**5e**	98	87
6[b]	*p*-MeOC$_6$H$_4$	Ph	**5f**	95 [86][c]	89 [98][c]
7	Ph	*p*-ClC$_6$H$_4$	**5g**	>99	80
8	*p*-MeOC$_6$H$_4$	*p*-ClC$_6$H$_4$	**5h**	>99[d] [79][c]	75 [93][c]
9	Ph	CH=CH$_2$	**5i**	>99	74
10	*p*-MeOC$_6$H$_4$	CH=CH$_2$	**5j**	>99[d]	89
11	Ph	C(CH$_3$)=CH$_2$	**5k**	87	71
12	Ph	*t*-Bu	**5l**	>99	30

[a] Unless otherwise noted, the reaction was conducted with **3** (0.75 mmol) and **4** (0.5 mmol) in the presence of MgSO$_4$ as a drying agent in 1,2-dichloroethane at 0 °C for 1 h. [b] The reaction time was 2 h. [c] After purification of the crude mixture by washing and recrystallization without silica gel column chromatography. [d] Conversion yield determined by ^{1}H NMR.

quantitative yields with high enantioselectivity (75–89% ee) (entries 5–8). Moreover, when aliphatic conjugate carboxamides, acrylamide and methacrylamide were also used, good to high enantioselectivity was observed (71–89% ee) (entries 9–11). As a more nucleophilic non-conjugate carboxamide, pivalamide (**4b**) gave the corresponding aminal **5l** with low enantioselectivity (30% ee) when the (*R*)-**1–2g** catalyst was used (entry 12). However, another optimization of achiral amines for (*R*)-**1** proved that more basic trioctylamine (**2h**) was effective in dichloromethane at −20 °C, and the enantioselectivity was greatly improved up to 80% ee (eqn (1)). Acyclic aminals, unlike cyclic aminals, are often unstable, epimerize, and are not isolable. However, the acyclic *N*-protected aminals (**5**) obtained here were highly stable in a solid state and in general solvents. Therefore, **5** could be thoroughly purified by silica gel column chromatography without decomposition and/or epimerization. Moreover, since many of the products were highly crystalline, washing of the crude mixture with water and ethyl acetate and subsequent recrystallization from chloroform–hexane was a practical alternative to silica gel column chromatography for purification. Water and ethyl acetate can dissolve and thus remove (*R*)-**1** and the starting materials, respectively. For example, the enantioselectivity values of **5c**, **5d**, **5f**, and **5h** increased to 93–98% ee without any serious loss of yield after this simple purification (Table 2, brackets in entries 3, 4, 6, and 8).



(1)

Unfortunately, *N*-protecting groups other than *N*-Cbz did not give better results in these reactions. However, one improved result was observed in the synthesis of **5m** with

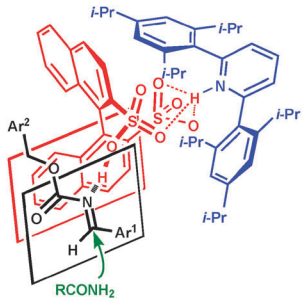
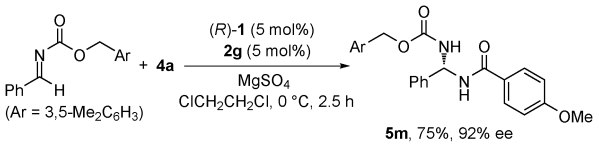


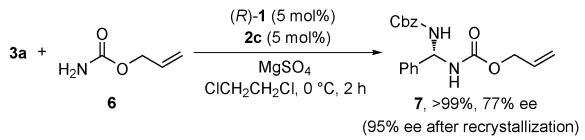
Fig. 3 Possible extended transition state.

3,5-dimethylbenzyl carbamate (92% ee) in place of benzyl carbamate (eqn (2)).

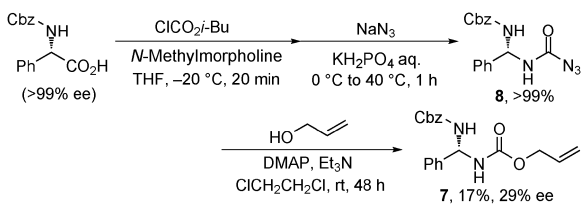


(2)

In place of carboxamide (**4**), allyl carbamate **6** was used in the reaction of **3a**. Fortunately, the reaction proceeded smoothly in 1,2-dichloroethane at 0 °C within 2 h, and the corresponding product **7** was obtained in >99% yield with 77% ee (eqn (3)). Moreover, a single recrystallization increased the enantiopurity up to 95% ee. In sharp contrast, the conventional synthesis of **7** from *N*-Cbz-L-phenylglycine *via* the Curtius rearrangement to azide carbonyl compound **8**[11] failed (eqn (4)). Compound **7** was obtained in 17% yield with a significant loss of enantiopurity (29% ee) in addition to the generation of racemic *N*,*O*-acetal **9**, since **8** is unstable under basic conditions. Therefore, direct enantioselective aminal synthesis with such a chiral Brønsted acid catalyst under mild reaction conditions is highly useful.



(3)



(4)

Based on the absence of a nonlinear effect between the enantioselectivity of (*R*)-**1** and that of aminal product **5a** (see the ESI†) and the theoretical calculation for the **3a**–(*R*)-BINSA ammonium salt,[8e] a postulated extended transition state is shown in Fig. 3 as a working model.[12] The predominant attack to the *re*-face of the aldimine by carboxamide can explain the absolute *S*-configuration of the products.

In summary, we have developed a highly effective catalytic enantioselective direct aminal synthesis. A chiral ammonium 1,1′-binaphthyl-2,2′-disulfonate, which was prepared *in situ* from (*R*)-BINSA and bulky 2,6-(2,4,6-*i*-$Pr_3C_6H_2)_2$pyridine as an achiral amine, promoted the direct addition of primary carboxamides to aromatic aldimines. The corresponding optically active peptidomimetic non-cyclic *N*-protected aminals were obtained without decomposition or epimerization in high yields with high enantioselectivities after simple purification by recrystallization without silica gel column chromatography.

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10 Interestingly, the reaction between **3a** and phthalimide did not proceed with (*R*)-**1–2** catalysts, while the reaction between **3a** and *p*-toluenesulfonamide proceeded with (*R*)-**1–2** catalysts (<50% ee). These results strongly suggest that (*R*)-**1–2** might act as a strong Brønsted acid catalyst with low Brønsted basicity, which can anionically activate *p*-toluenesulfonamide (pK_a = 10.2) but not phthalimide (pK_a = 10.4) and **4a** (pK_a = 16.0). Estimated pK_a values were reported by SciFinder with ACD Software V11.02.

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12 Preliminary analysis of the catalysts from (*R*)-**1** (1 equiv.) and **2** (0–2 equiv.) by ^{1}H NMR ($CDCl_3$) also suggested the generation of a 1 : 1 complex *in situ*. See the ESI†.

