Enantioselective Friedel–Crafts Aminoalkylation Catalyzed by Chiral Ammonium 1,1′-Binaphthyl-2,2′-disulfonates

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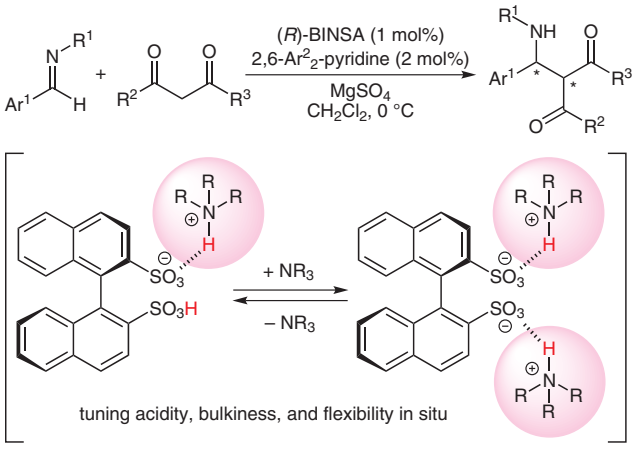
Abstract: A catalytic enantioselective Friedel–Crafts aminoalkylation between aromatic aldimines and *N*-benzylpyrrole with the use of a homogeneous chiral ammonium salt, (*R*)-BINSA–*N*,*N*-dimethylbutylamine, as a dynamic Brønsted acid–Brønsted base catalyst, is reported. Unlike the results with conventional catalysts, remarkably high reactivity was established at –78 °C within 30 minutes, and the corresponding aryl(1*H*-pyrrol-2-yl)methanamines were obtained with good to high enantioselectivities.

Key words: ammonium salt, Friedel–Crafts reaction, 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA), chiral Brønsted acid, organocatalyst

A catalytic enantioselective Friedel–Crafts aminoalkylation (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.[1,2] Over the past several years, much attention has been devoted to methods for the catalytic enantioselective Friedel–Crafts aminoalkylation using chiral metal catalysts[3] or organocatalysts.[4] In particular, chiral BINOL (1,1′-bi-2-naphthol) derived phosphoric acids have been widely used as effective chiral Brønsted acid catalysts for this reaction.[4a,c–j,l] In sharp contrast, BINSA (1,1′-binaphthyl-2,2′-disulfonic acid) and its derivatives have not yet been applied to the Friedel–Crafts aminoalkylation, although they have been recognized as attractive chiral Brønsted acid catalysts for some asymmetric catalyses.[5,6] In our initial study of BINSA-derived catalysts, we developed pyridinium 1,1′-binaphthyl-2,2′-disulfonates as effective Brønsted acid–Brønsted base catalysts[7] for the direct Mannich-type reaction of aromatic aldimines with 1,3-dicarbonyl compounds (Scheme 1).[5c] In general, acid–base combined salts have several advantages over single-molecule catalysts, with regard to flexibility in the design of their dynamic complexes. Based on the relevance of the ammonium salts of BINSA, we report here a catalytic enantioselective Friedel–Crafts aminoalkylation between aromatic aldimines and *N*-benzylpyrrole.

First, we optimized ammonium salts by tuning the achiral amines for (*R*)-BINSA (5 mol%) in the reaction between benzyl benzylidenecarbamate (**1a**) and *N*-benzylpyrrole (**2a**) in dichloromethane at –78 °C for 30 minutes in the presence of $MgSO_4$ as a drying agent (Table 1).[8] The previous homogeneous catalyst, which was optimized for the direct Mannich-type reaction and prepared in situ from (*R*)-BINSA and 2,6-diphenylpyridine (**4a**),[5c] promoted the reaction but showed only a moderate enantioselectivity of (*S*)-**3a** (45% ee, Table 1, entry 1). While a secondary amine such as diethylamine (**4b**) was less suitable (Table 1, entry 2), a tertiary aniline **4c** and tertiary aliphatic amines **4d**–**n** gave better enantioselectivities (Table 1, entries 3–16). In particular, the less sterically hindered *N*,*N*-dimethylalkylamines were effective, and the desired products were obtained in >70% yields and with >70% ee. Chirality (see **4g**–**i**) and the length of the *N*-alkyl chain (see **4j**,**k**,**m**,**n**) did not significantly affect the enantioselectivities (entries 7–10, 12, 15, and 16), although sterically demanding *N*-butyl-*N*-methylbutylamine (**4l**) was less favored (Table 1, entry 14). Next we optimized the molar amount of *N*,*N*-dimethylbutylamine (**4k**), and a 1:1 molar ratio of (*R*)-BINSA and **4k** was the most effective (Table 1, entries 11–13). Interestingly, a 1:2 molar ratio of (*R*)-BINSA and **4k** significantly decreased the catalytic activity, probably due to neutralization of the two SO_3H moieties (Table 1, entry 13). Moreover, diamines such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, **4o**) and 1,4-diazabicyclo[2.2.2]octane (DABCO, **4p**) were less effective than monoamines due to the lower solubility of the catalysts prepared in situ (Table 1, entries 17 and 18).



Scheme 1 Direct Mannich-type reaction catalyzed by (*R*)-BINSA pyridinium salts

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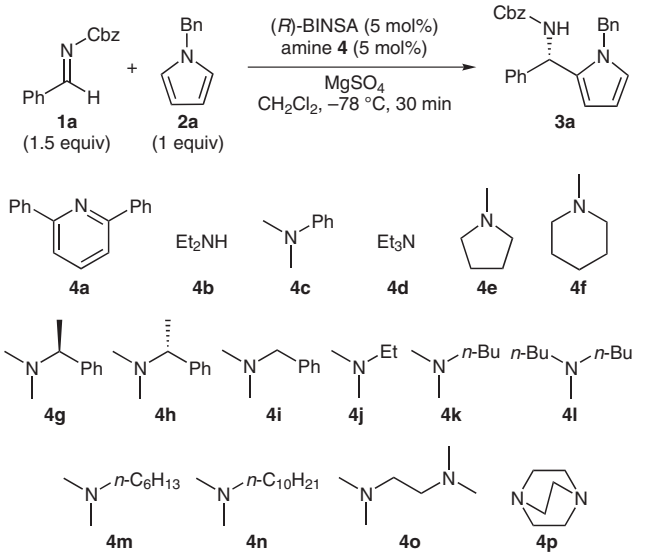
In the probe reaction between **1a** and **2a** in Table 1, we often obtained overreaction compound **5** in yields of 0–10%, which was the result of the aminoalkylation product **3a**. Therefore, we reacted **1a** (0.5 equiv) and racemic **3a** (1 equiv) in the presence of 5 mol% each of (*R*)-BINSA and **4k** to examine whether or not a kinetic resolution of **3a** would occur (Scheme 2). As a result, enantioenriched (*S*)-**3a** was recovered in 40% yield with 67% ee in addition to inseparable diastereomeric mixture **5** (39% yield, *dl*/*meso* = ca. 1:1) and other complex mixtures (<20%). This result strongly suggested that most of the enantioenriched (*S*)-**3a** would be provided by the Friedel–Crafts aminoalkylation of **1a** with **2a**, and the enantioselectivity of (*S*)-**3a** would be slightly increased by the subsequent Friedel–Crafts aminoalkylation of (*R*)-**3a** with **1a** prior to (*S*)-**3a**.

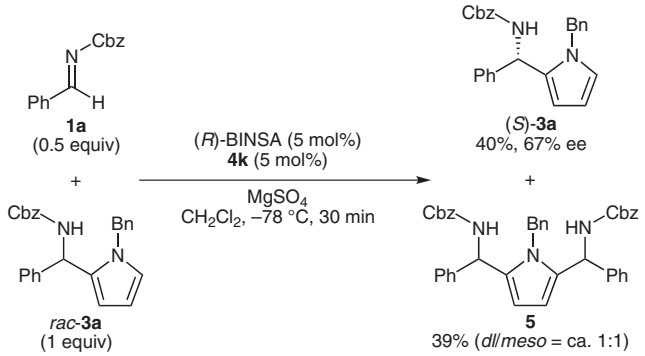
With the optimized reaction conditions in hand, we next examined the scope of aldimines **1** and pyrroles **2** (Table 2). Unfortunately, unprotected pyrrole **2b**, *N*-Boc-

Table 1 Screening of Catalysts[a]



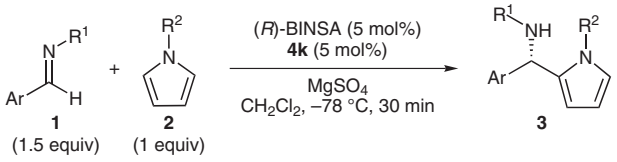
Entry	Amine (mol%)	Yield (%)	ee (%)
1	**4a** (10)	84	45
2	**4b** (5)	22	37
3	**4c** (5)	46	62
4	**4d** (5)	30	60
5	**4e** (5)	58	70
6	**4f** (5)	29	71
7	**4g** (5)	79	77
8	**4h** (5)	77	70
9	**4i** (5)	79	77
10	**4j** (5)	79	72
11	**4k** (2.5)	69	77
12	**4k** (5)	84	89
13	**4k** (10)	20	0
14	**4l** (5)	10	3
15	**4m** (5)	73	72
16	**4n** (5)	81	79
17	**4o** (2.5)	82	62
18	**4p** (2.5)	77	44

[a] The reaction of **1a** (0.30 mmol) with **2a** (0.20 mmol) was conducted in the presence of (*R*)-BINSA (0.01 mmol), amine (0.005–0.02 mmol), and $MgSO_4$ (40 mg) in CH_2Cl_2 (2 mL) at –78 °C for 30 min.



Scheme 2 Kinetic resolution of product **3a**

Table 2 Catalytic Enantioselective Friedel–Crafts Aminoalkylation with a BINSA–**4k** Salt Prepared in situ[a]



Entry	**1** Ar, R^1	**2** R^2	**3**	Yield (%)	ee (%)
1	**1b** Ph, Boc	**2a** Bn	**3b**	75	44
2	**1a** Ph, Cbz	**2b** H	**3c**	69	6
3	**1a** Ph, Cbz	**2c** Boc	**3d**	44	22
4	**1a** Ph, Cbz	**2a** Bn	**3a**	84	89 (98)[b]
5	**1c** 4-$MeOC_6H_4$, Cbz	**2a** Bn	**3e**	59	81 (96)[b]
6	**1d** 4-FC_6H_4, Cbz	**2a** Bn	**3f**	79	67 (96)[b]
7	**1e** 4-ClC_6H_4, Cbz	**2a** Bn	**3g**	82	84 (89)[b]
8	**1f** 4-BrC_6H_4, Cbz	**2a** Bn	**3h**	72	92 (>99)[b]
9	**1g** 3-BrC_6H_4, Cbz	**2a** Bn	**3i**	92	70
10	**1h** 1-naphthyl, Cbz	**2a** Bn	**3j**	85	71

[a] The reaction of **1** (0.30 mmol) with **2** (0.20 mmol) was conducted in the presence of (*R*)-BINSA (0.01 mmol), **4k** (0.01 mmol), and $MgSO_4$ (40 mg) in CH_2Cl_2 (2 mL) at –78 °C for 30 min unless otherwise noted.

[b] Enantioselectivity after a single recrystallization.

protected pyrrole **2c**, and *N*-Boc-protected aldimine **1b** gave the corresponding products in low enantioselectivities (Table 2, entries 1–3). In contrast, with optimal *N*-benzylpyrrole (**2a**), the reaction of aromatic aldimines with an electron-donating or electron-withdrawing substituent proceeded smoothly, and the desired products were obtained with good to high enantioselectivities (Table 2, entries 4–10). Fortunately, one recrystallization of the products from *n*-hexane–Et_2O–CH_2Cl_2 increased the values of enantioselectivity (89 to >99% ee) without any serious loss of yield (Table 2, entries 4–8).

To determine the absolute stereochemistry of the products, X-ray analysis of a single crystal of **3h** was conducted, and its *S*-configuration revealed that the reaction would proceed via predominant attack on the *re*-face side of **1f** (Figure 1).

Finally, ESI-MS analysis of the catalyst, which was prepared in situ from (*R*)-BINSA (1 equiv) and **4k** (1 equiv) in MeCN, was performed. Interestingly, monomeric ammonium salts of BINSA [i.e., Ar*$(SO_3H)_2$], such as [Ar*$(SO_3H)(SO_3Na)$ + **4k**]$^+$ at *m/z* = 537,[9] [Ar*$(SO_3H)_2$ + 2(**4k**) + H]$^+$ at *m/z* = 617, and [Ar*$(SO_3H)_2$+3(**4k**) + H]$^+$ at *m/z* = 718, were observed, and these species strongly support the assumed dynamic acid–base structures as illustrated in Scheme 1.[10] Although a further investigation of the actual catalysts is required to fully understand the reaction mechanism, the postulated structures of the catalyst and the substrate were considered based on theoretical calculations for a monomeric (*R*)-BINSA–**4k**–**1a** complex[11] as a working model.[10] As shown in Figure 2, **4k** is protonated by a bridged proton between the two SO_3^- moieties and oriented outward. Moreover, **1a** 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 **1a** and the electronically negative naphthyl–SO_3^- moiety. Therefore, in the possible transition state, **2a** would predominantly attack the *re*-face side of aldimines. In this preliminary stage, however, we cannot perfectly explain why **4k**, unlike other *N*,*N*-dimethylalkylamines **4g–j**,**m**,**n** or *N*-methyl cyclic amines **4e**,**f**, was critical for inducing high enantioselectivity.

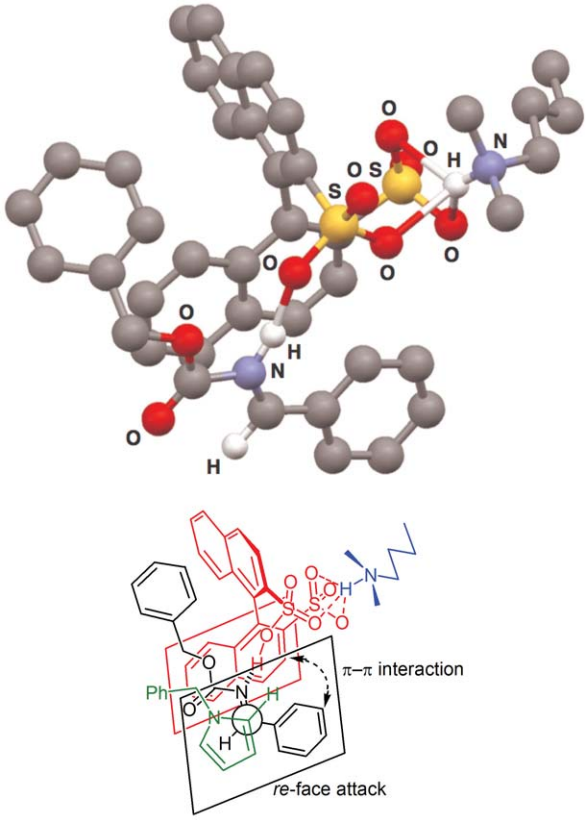


Figure 2 M05-2X/6-31G* optimized geometry of (*R*)-BINSA–**4k**–**1a** and a proposed transition state; hydrogen atoms are partially omitted for clarity.

In summary, we have developed a catalytic enantioselective Friedel–Crafts aminoalkylation between aromatic aldimines and *N*-benzylpyrrole with the use of (*R*)-BINSA–*N*,*N*-dimethylbutylamine as a dynamic Brønsted acid–Brønsted base combined salt catalyst. Unlike conventional catalysts, remarkably high reactivity was achieved even at –78 °C within 30 minutes, and the corresponding aryl(1*H*-pyrrol-2-yl)methanamines were obtained in high yields with good to high enantioselectivities. Further applications of chiral ammonium salts of BINSA to other catalytic enantioselective reactions are now under way.

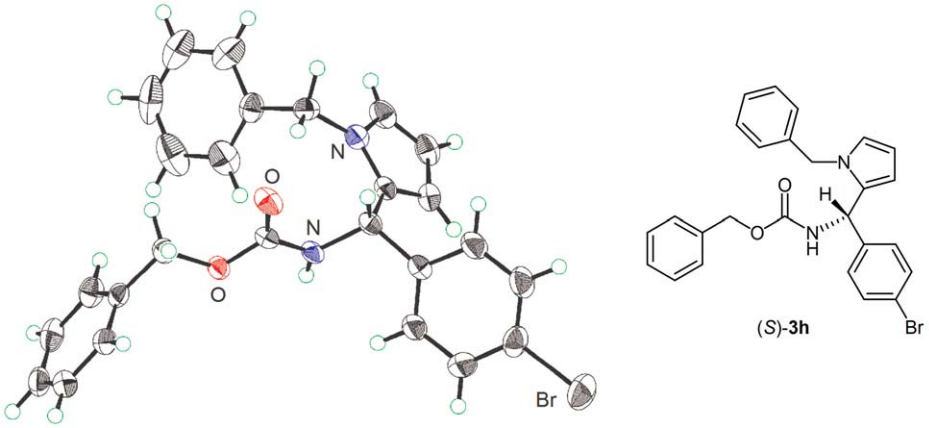


Figure 1 X-ray crystal structure analysis of the Friedel–Crafts aminoalkylation product **3h**

General Procedure for Enantioselective Friedel–Crafts Aminoalkylation

A well-dried pyrex Schlenk tube was charged with (*R*)-BINSA (4.1 mg, 0.01 mmol) and *N*,*N*-dimethylbutylamine (**4k**, 1.4 μL, 0.01 mmol) under a nitrogen atmosphere. MeCN (2 mL) was added, and the solution was stirred at r.t. for 30 min. The volatile solvent was removed in vacuo at r.t. for 1 h, and then $MgSO_4$ (40 mg, 0.33 mmol), CH_2Cl_2 (1.5 mL), and *n*-benzylpyrrole (**2a**, 30.8 μL 0.20 mmol) were added. The mixture was cooled to –78 °C and stirred for 30 min. Aldimine **1** (0.30 mmol) in CH_2Cl_2 (0.5 mL) was added via a cannula. The resultant mixture was then stirred at –78 °C for 30 min. A sat. $NaHCO_3$ aq solution (1 mL) was poured into the reaction mixture, and the product was extracted with EtOAc (2 × 15 mL). The combined extracts were washed with brine (10 mL) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane–EtOAc = 3:1 to 1:1) to give the desired products **3**. The enantiomeric purity was determined by chiral HPLC analysis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) With regard to other solvents, THF and propionitrile showed low enantioselectivities, and the catalysts showed poor solubility in Et_2O, *n*-hexane, and toluene.

(9) Naturally abundant Na^+ might be included during the analysis.

(10) See the Supporting Information for details.

(11) The optimum ratio of **4k** to (*R*)-BINSA (1:1), which was examined in entries 11–13 in Table 1, suggests that a monomeric (*R*)-BINSA–**4k**–**1a** complex is one of the most likely structures.