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# SPINOL-Derived Phosphoric Acids: Synthesis and Application in Enantioselective Friedel−Crafts Reaction of Indoles with Imines

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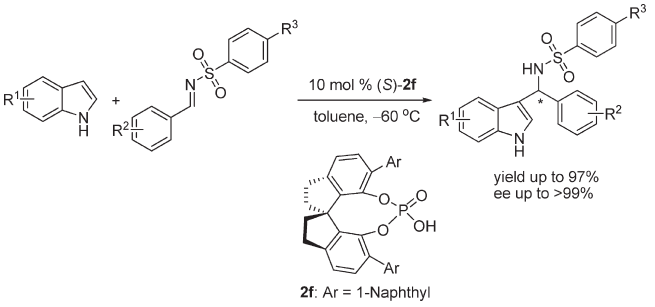


A new class of chiral phosphoric acids with spirobiindane as scaffold were conveniently synthesized from (*S*)-1,1′-spirobiindane-7,7′-diol ((*S*)-SPINOL) and employed to catalyze the asymmetric Friedel−Crafts reaction of indoles with imines to afford 3-indolyl methanamines. High yields (68−97%) and excellent enantioselectivities (up to 99% ee) were obtained.

The catalytic asymmetric Friedel−Crafts (F−C) reaction is a powerful strategy for the construction of carbon−carbon bond in organic synthesis, providing direct approach to the enantiomerically enriched arene derivatives.[1] Since indoles exhibited significant nucleophilic reactivity and extensively biological activities,[2] their asymmetric Friedel−Crafts reactions are of great value.[3] Among the published asymmetric Friedel−Crafts reactions,[4,5] the chiral phosphoric acids[6] were demonstrated to be efficient.[7] These phosphoric acid catalysts possess a biaryl backbone. Typical examples are BINOL and $H_8$-BINOL-derived phosphoric acids **1** (Figure 1). With regard to the significant works on the synthesis of enantiopure 1,1′-spirobiindane-7,7′-diol[8] (SPINOL, **3**) and catalytic applications of its derivatives,[9] we synthesized SPINOL-derived phosphoric acids **2** and investigated their application in enantioselective Friedel−Crafts reaction of indoles with imines, which furnished 3-indolyl methanamines. We herein report the results of this effort.

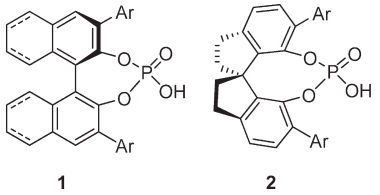


**FIGURE 1.** Chiral phosphoric acids.

As shown in Scheme 1, the SPINOL-derived phosphoric acids **2** were synthesized from (*S*)-SPINOL **3**. Initially, (*S*)-SPINOL was routinely protected with the MOM group to afford **4** in 94% yield. Compound **4** underwent lithiation and

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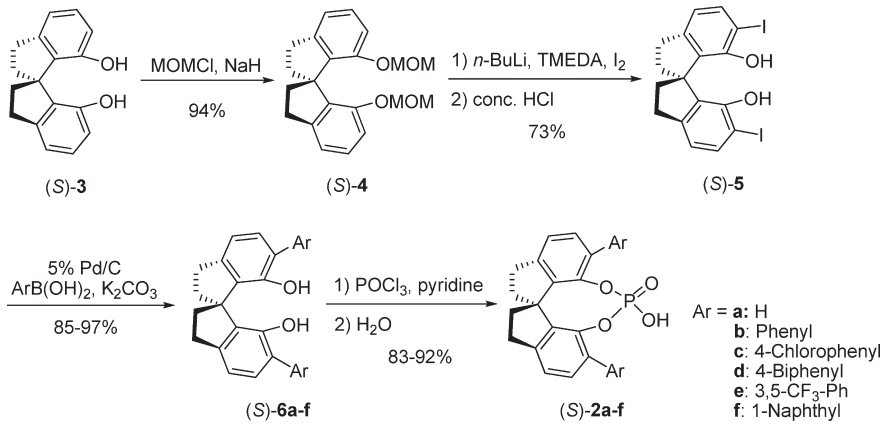
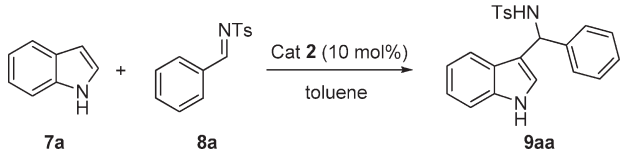
**SCHEME 1. Synthesis of SPINOL-Derived Phosphoric Acids 2**




subsequent iodination, followed by deprotection of hydroxyl groups, to gave 6,6′-diiodo compound **5** in 73% yield. Suzuki coupling reaction of **5** using 5% Pd/C as catalyst resulted in **6a**−**f** in excellent yields (85−97%) with convenient operation. Finally, phosphorylation of **6** afforded the corresponding phosphoric acids **2a**−**f** in high yields (83−92%).

**TABLE 1. Optimization for Enantioselective Friedel−Crafts Reaction**[a]




**7a** **8a** **9aa**

| entry | catalyst | temp | time | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **2a** | rt | 40 min | 80 | 11 |
| 2 | **2b** | rt | 7 h | 89 | 72 |
| 3 | **2c** | rt | 3 h | 87 | 73 |
| 4 | **2d** | rt | 4 h | 75 | 72 |
| 5 | **2e** | rt | 10 min | 100 | 56 |
| 6 | **2f** | rt | 30 min | 90 | 89 |
| 7 | **2f** | 0 °C | 75 min | 92 | 90 |
| 8 | **2f** | −40 °C | 8 h | 85 | 94 |
| 9 | **2f** | −60 °C | 36 h | 80 | 96 |

[a]The reaction was carried out with 0.5 mmol of **7a**, 0.1 mmol of **8a**, and 10 mol % of catalyst **2** in 0.5 mL toluene. [b]Isolated yield. [c]Determined by HPLC analysis on a Chiralcel OD-H column.

To test the potential applications of our catalysts, the reaction of indole (**7a**) with *N*-tosylimine **8a** was chosen as a model reaction, which has been well promoted by chiral metal complex,[4f,h] chiral thiourea,[5b] and BINOL-derived phosphoric acid catalysts.[7b] The products of this asymmetric Friedel−Crafts reaction provide easy access to the synthesis of enantiopure 3-indolyl methanamine derivatives. In our initial investigation, nonsubstituted **2a** was used as catalyst with 10 mol % loading, and the product was obtained in 80% yield with 11% ee (entry 1, Table 1), while BINOL phosphoric acid gave only racemic products.[7b] Inspired by this result, we then tested the substituent effect at the 6,6′-positions of the catalysts with various aryl groups at room temperature and found the substituent effect to be remarkable (Table 1, entries 1−6). The reactions using **2b**−**d** as catalyst proceeded in similar yields and enantioselectivities, except that **2b** took a longer reaction time (Table 1, entries 2−4). When catalyst **2e** was employed, a quantitative yield as well as a moderate ee value (56%) were obtained within 10 min (Table 1, entry 5). To our delight, the catalyst **2f**, bearing two 1-naphthyl groups at the 6,6′-positions of the SPINOL backbone, gave high yield (90%) and good enantioselectivity (89% ee) at room temperature. Further improvement of the enantioselectivity was achieved at lower reaction temperature (Table 1, entries 7−9). Up to 96% ee enantioselectivity and 80% yield were obtained when the reaction was performed at −60 °C for 36 h (Table 1, entry 9).

The substrate scope of the enantioselective Friedel−Crafts reaction of indoles **7** with imines **8** was then evaluated and is summarized in Table 2. Interestingly, both the reactivity and the enantioselectivity were enhanced by changing the tosyl group of *N*-sulfonylphenylimines to the more electron-withdrawing *p*-bromobenzenesulfonyl group (Table 2, entries 1−3). Indoles bearing different substituents were then examined for the reaction with imines **8a** or **8c**, and the result showed a good tolerance in this catalytic system (Table 2, entries 4−9), although the introduction of an electron-withdrawing group onto the indole ring led to a lower reactivity (Table 2, entries 8 and 9). For aryl imines **8d**−**i**, the reactions went smoothly to give the corresponding products in 68−93% yield and 91−>99% ee (Table 2, entries 10−16). In the case of **8i** derived from 1-naphthaldehyde, excellent enantioselectivity (97% ee) was obtained at higher temperature (0 °C) (Table 2, entry 16). In addition, heteroaryl imine **8j** also gave excellent yield (96%) and enantioselectivity (97% ee) (Table 2, entry 17). For alkyl imine **8k**, however, we obtained the adduct in lower yield (47%) and moderate enantioselectivity (79% ee) (Table 2, entry 18). The *S*-configuration adduct product **9ad** was confirmed by the X-ray crystal structure analysis (see Supporting Information).

Recently, Simon and Goodman[10] provided both data and computation models to identify the specific indolyl methamine product for Friedel−Crafts reactions of indole with *N*-tosylimines catalyzed by BINOL-phosphoric acids. On the basis of this result, we propose a possible model for the asymmetric induction of our catalytic system as shown in Scheme 2. Phosphoric acid (S)-**2** as a bifunctional catalyst combines two substrates through hydrogen bonding. In this model, indole attacks *N*-tosylimine from the *re* face preferentially, leading to a *S*-configuration adduct.

In conclusion, we have synthesized a new class of chiral phosphoric acids with a spirobiindane backbone, which could efficiently promote the enantioselective Friedel−Crafts reaction of indoles with imines to afford 3-indolyl methanamines. Up

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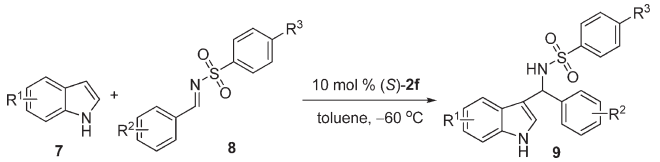
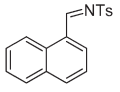
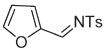
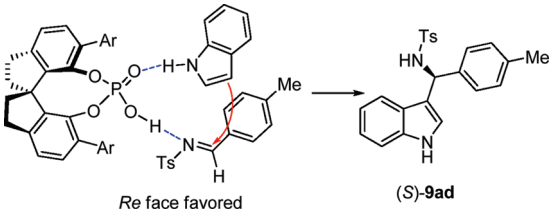
**TABLE 2. Enantioselective Friedel−Crafts Reaction Catalyzed by 2f[a]**




| entry | 7 ($R^1$) | 8($R^2$/$R^3$) | time (h) | product | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **7a** (H) | **8a** (H/Me) | 36 | **9aa** | 80 | 96 |
| 2 | **7a** | **8b** (H/H) | 24 | **9ab** | 85 | 96 |
| 3 | **7a** | **8c** (H/Br) | 18 | **9ac** | 89 | 99 |
| 4 | **7b** (2-Me) | **8a** | 12 | **9ba** | 97 | 91 |
| 5 | **7b** | **8c** | 8 | **9bc** | 93 | 93 |
| 6 | **7c** (5-OMe) | **8a** | 24 | **9ca** | 85 | 97 |
| 7 | **7c** | **8c** | 28 | **9cc** | 81 | 99 |
| 8[d] | **7d** (5-Br) | **8a** | 36 | **9da** | 85 | 93 |
| 9[d] | **7d** | **8c** | 24 | **9dc** | 79 | 94 |
| 10 | **7d** | **8d** (4-Me/Me) | 24 | **9dd** | 81 | >99 |
| 11 | **7a** | **8d** | 20 | **9ad** | 92 | >99(S)[f] |
| 12 | **7a** | **8e** (3,4-$Me_2$/Me) | 40 | **9ae** | 77 | 98 |
| 13 | **7a** | **8f** (4-OMe/Me) | 48 | **9af** | 76 | 97 |
| 14 | **7a** | **8g** (4-Cl/Me) | 60 | **9ag** | 68 | 91 |
| 15 | **7a** | **8h** (3-OMe/Br) | 26 | **9ah** | 93 | 97 |
| 16[e] | **7a** | **8i**:  | 12 | **9ai** | 85 | 97 |
| 17 | **7a** | **8j**:  | 9 | **9aj** | 96 | 97 |
| 18 | **7a** | **8k**:  | 10 | **9ak** | 47 | 79 |

[a]Unless otherwise noted, reactions were carried out with 0.5 mmol of **7**, 0.1 mmol of **8**, and 10 mol % of **2f** in 0.5 mL of toluene at −60 °C. [b]Isolated yield. [c]Determined by HPLC analysis on a Chiralcel OD-H column. [d]Reaction at −40 °C. [e]Reaction at 0 °C. [f]Absolute configuration determined by X-ray single-crystal analysis.

**SCHEME 2. Proposed Reaction Model**




to 97% yield and up to 99% ee enantioselectivity were obtained. Further catalytic applications of the SPINOL-derived phosphoric acids in other enantioselective reactions are in progress.

## Experimental Section

**Synthesis of (*S*)-6,6′-Diiodo-1,1′-spirobiindane-7,7′-diol (5).** To a solution of (*S*)-**4**[9d] (0.81 g, 2.4 mmol) and TMEDA (0.75 mL, 5 mmol) in $Et_2O$ (15 mL) was added *n*-BuLi (2.5 M in hexane, 2.88 mL, 7.2 mmol) at −78 °C. After being stirred at room temperature for 6 h, the mixture was cooled to −78 °C, and a solution of iodine (1.83 g, 7.2 mmol) in $Et_2O$ (20 mL) was carefully added. The resulted suspension was warmed to room temperature, stirred overnight, quenched by saturated $Na_2SO_3$, and stirred for an additional 1 h. The organic layer was separated, and the aqueous layer was extracted by ether. The combined organic layer was washed with brine, dried over $Na_2SO_4$, passed through a pad of silica, and concentrated in vacuo, giving the crude (*S*)-6,6′-diiodo-7,7′-bis(1-methoxymethoxy)-1,1′-spirobiindane as brown solid, which was used without further purification in the next step. The crude (*S*)-6,6′-diiodo-7,7′-bis(1-methoxymethoxy)-1,1′-spirobiindane was dissolved in $CHCl_3$ (12 mL) and MeOH (18 mL), and conc HCl (12 mL) was added. After being refluxed for 3 h, the mixture was poured into water and extracted by $CH_2Cl_2$. The organic layer was washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:10) to give the product **5** (0.88 g, 73% yield) as white solid. Mp 149−150 °C; $[\alpha]^{20}_D = -187.2$ (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.18−2.24 (m, 2 H), 2.29−2.37 (m, 2 H), 2.94−3.06 (m, 4 H), 5.11 (s, 2H), 6.65 (d, $J$ = 8.0 Hz, 2 H), 7.52 (d, $J$ = 7.6 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 31.1, 37.7, 59.8, 83.2, 119.2, 133.0, 137.7, 146.7, 151.1; ATR-FTIR 3479, 2935, 1571, 1436, 1323, 1290, 1233, 1188, 1061, 1000, 796,

754 $cm^{-1}$; HRMS (ESI) calcd for $C_{17}H_{13}I_2O_2^-$ ($[M - H]^-$): 502.9005. Found: 502.8989.

**Typical Synthesis of (*S*)-6,6′-Diphenyl-1,1′-spirobiindane-7,7′-diol (6b).** A solution of (*S*)-**5** (151 mg, 0.3 mmol), phenylboronic acid (128 mg, 1.05 mmol), $K_2CO_3$ (0.145 g, 1.05 mmol), and 5% Pd/C (13 mg; 0.006 mmol) in dioxane/water (1:1, 6 mL) was stirred at 80 °C for 2 h and then diluted with ethyl acetate and 3 N HCl. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:15) to give the product **6b** (117 mg, 97% yield) as white solid. Mp 203−204 °C; $[\alpha]^{20}_D = -281.5$ (*c* 0.9, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.34−2.46 (m, 4 H), 3.02−3.15 (m, 4 H), 5.07 (s, 2H), 6.93 (d, $J$ = 7.6 Hz, 2 H), 7.19 (d, $J$ = 7.6 Hz, 2 H), 7.30 (t, $J$ = 7.2 Hz, 2 H), 7.39 (t, $J$ = 7.2 Hz, 4 H), 7.47 (d, $J$ = 7.6 Hz, 4 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 31.1, 37.7, 58.4, 117.4, 126.9, 127.2, 128.6, 129.3, 130.5, 132.0, 137.4, 145.2, 149.4; ATR-FTIR 3510, 2943, 1616, 1580, 1499, 1472, 1420, 1253, 1228, 1180, 1074, 998, 814, 753, 698 $cm^{-1}$; HRMS (ESI) calcd for $C_{29}H_{23}O_2^-$ ($[M - H]^-$): 403.1698. Found: 403.1683.

**Typical Synthesis of (*S*)-1,1′-Spirobiindane-7,7′-diyl phosphate (2f).** To a solution of (*S*)-**6f** (252 mg, 0.5 mmol) in pyridine (3 mL) was added $POCl_3$ (92 $\mu$L, 1.0 mmol) dropwise at 0 °C, and the resulting mixture was heated to 70 °C and stirred for 3 h. After the mixture cooled to 0 °C, 3 mL of water was carefully added, and the resulting suspension was stirred at 110 °C for an additional 4 h. Dichloromethane was added, and the pyridine was removed by reverse extraction with 4 N HCl. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 1:20 to 1:10) to give the product **2f** (257 mg, 91% yield) as a foamy solid. Mp > 300 °C; $[\alpha]^{20}_D = -362.2$ (*c* 0.50, $CHCl_3$); $^1$H NMR (400 MHz, $CHCl_3$) $\delta$ 2.34−2.51 (m, 4H), 2.90−2.97 (m, 2H), 3.19−3.25 (m, 2H), 6.95−7.02 (m, 2H), 7.19−7.25 (m, 6H), 7.36−7.49 (m, 4H), 7.56−7.61 (m, 2H), 7.70−7.81 (m, 4H); $^{13}$C NMR (100 MHz, $CHCl_3$) $\delta$ 30.3, 39.1, 59.9, 120.7, 121.9, 125.2, 125.8, 126.5, 127.8, 129.8, 131.3, 131.7, 132.5, 132.7, 133.4, 137.4, 140.5, 144.4, 145.6; $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$ −9.9; ATR-FTIR 3668, 2982, 2902, 1612, 1398, 1249, 1059, 871, 802, 777 $cm^{-1}$; HRMS (ESI) calcd for $C_{37}H_{26}O_4P^-$ ($[M - H]^-$): 565.1569. Found: 565.1541.

**Typical Procedure for the Enantioselective Friedel−Crafts Reaction.** To a mixture of *N*-sulfonyl imine **8** (0.1 mmol) and catalyst **2f** (0.01 mmol) was added toluene (0.5 mL). Then the mixture was stirred for 10 min at room temperature. Indole **7** (0.5 mmol) was subsequently added in one portion at −60 °C. After the reaction was complete, it was quenched by 2 M NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:3) to give the corresponding product **9**. Product **9ac** was obtained in 89% yield after chromatography and 99% ee as determined by HPLC [Daicel Chiralcel OD-H, *n*-hexane/*i*-propanol = 70:30, 0.8 mL/min, $\lambda$ = 254 nm, $t_R$ (minor) = 15.69 min, $t_R$ (major) = 35.37 min]. Mp 135−136 °C; $[\alpha]^{20}_D = -88.3$ (*c* 0.80, Acetone); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.24 (d, $J$ = 7.2 Hz, 1 H), 5.91 (d, $J$ = 7.2 Hz, 1H), 6.65 (s, 1 H), 7.06 (t, $J$ = 7.6 Hz, 1 H), 7.18−7.22 (m, 6 H), 7.30−7.38 (m, 4 H), 7.42 (d, $J$ = 8.0 Hz, 2 H), 7.99 (br, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.2, 111.4, 115.8, 119.3, 120.1, 122.6, 123.8, 125.3, 126.9, 127.2, 127.5, 128.38, 128.44, 131.6, 136.5, 139.4, 139.6; ATR-FTIR 3669, 3411, 2982, 2902, 1399, 1323, 1249, 1157, 1071, 896, 740 $cm^{-1}$; HRMS (ESI) calcd for $C_{21}H_{17}BrN_2O_2SNa^+$ ($M + Na^+$): 463.0092. Found: 463.0072.

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**Supporting Information Available:** Detailed experimental procedures, characterization data, CIF file, and copies of $^1$H and $^{13}$C NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.