Enantioselective Brønsted Acid Catalysis in the Friedel–Crafts Reaction of Indoles with Secondary *ortho*-Hydroxybenzylic Alcohols

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Abstract: The reaction of indole and various methyl-substituted indoles with the title compounds was studied in the presence of chiral phosphoric acids, which act as Brønsted acid catalysts. While yields were generally high (>90%), significant enantioselectivities (up to 77% ee) were only achieved for certain substrate–catalyst combinations. In addition, a kinetic resolution of the starting material was observed, which led to an enrichment of one chiral alcohol to up to 68% ee after 76% conversion. The Friedel–Crafts reaction is not stereospecific (no direct S_N2-type substitution), but rather is likely to proceed via a cation, which is bound to the chiral Brønsted acid or its anion in a close contact ion pair.

Key words: carbocations, stereoselective synthesis, electrophilic aromatic substitutions, alkylations, enantioselectivity, organocatalysis

The cationic carbon atom of benzylic cations is frequently prostereogenic and can be attacked by suitable carbon nucleophiles to form new carbon–carbon bonds.[1] If arenes are employed as nucleophiles, products of a Friedel–Crafts reaction are obtained.[2] Studies with α-chiral benzylic carbocations of general structure **A** have revealed that the Friedel–Crafts reactions of these electrophiles can be highly diastereoselective leading to the respective *syn*- or *anti*-products (Figure 1).[3] Facial stereocontrol is exerted by the adjacent stereogenic center (*) due to 1,3-allylic strain.[4] In continuation of this work we wondered whether facial stereocontrol could also be possible by a chiral counterion $*X^-$ of a benzylic cation **B** thus rendering the reaction of this cation with a given nucleophile enantioselective. Inspired by the tremendous success of chiral 1,1′-bi-2-naphthol (BINOL) based phosphoric acids,[5] which have been introduced into enantioselective organocatalysis by M. Terada et al.[6] and by T. Akiyama et al.,[7] we initiated a study, in which the asymmetric induction of chiral phosphoric acids was probed in Friedel–Crafts reactions of secondary alcohols. Our preliminary results are disclosed in this Letter.

Previous work on the generation of cations related to **B** with chiral phosphoric acids has been mostly concerned with 3-indolyl-substituted cations.[8] It has been postulated that the phosphate counterion forms close ion pairs with these cations, which are in turn responsible for the observed enantioselectivities. Other relevant work, in which 3-indolyl-substituted cations have been postulated to form ion pairs with chiral phosphoric acids, include enantioselective alkylation[9] and rearrangement[10] reactions.[11] Initial studies in our laboratories were conducted with 1-phenyl-2,2-dimethyl-1-propanol as immediate precursor for the parent cation **B** (R = H) and with standard arenes previously employed.[3,4] However, no reactions were observed in the presence of chiral phosphoric acids or the related more acidic *N*-triflyl phosphoramides.[12] We therefore turned to precursor alcohols, which were suspected to form more stable cations capable of coordination to chiral phosphate counterions. To this end, the *para*-substituted aldehydes **1** (Y = OMe) and **2** ($Y = NMe_2$)[13] were treated with *tert*-butyllithium generating the 1-aryl-2,2-dimethyl-1-propanols **3** and **4** in high yields. The known secondary alcohols **5**[14] and **6**[15] (vide infra) were prepared for comparison (Scheme 1).

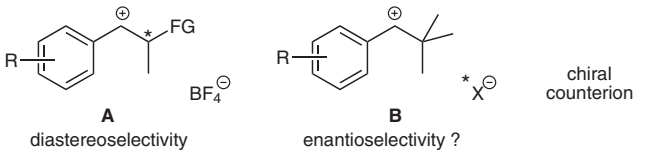
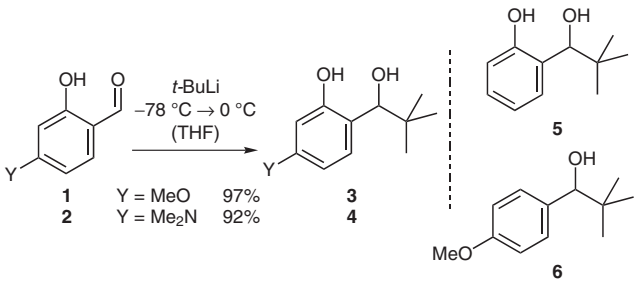


Figure 1 Structure of benzylic cations **A** and **B** with different elements of chirality present either in the cation (**A**) or in the counterion (**B**)



Scheme 1 Preparation of starting materials **3** and **4** from the respective aldehydes **1** and **2** and structures of the known alcohols **5** and **6**

The phosphoric acids **7** (Figure 2) employed as catalysts in this study were synthesized according to literature procedures[6,16] starting from commercially available (*R*)-BINOL. The phosphoric acids were washed with HCl before use to ensure that they were present in their free acid form.[17] Compound **7g** was purchased from a commercial supplier.

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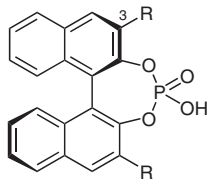
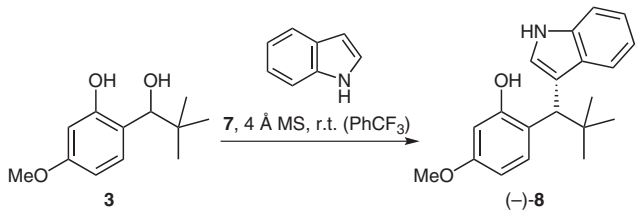


7a R = H
7b R = $SiPh_3$
7c R = Ph
7d R = 9-phenanthryl
7e R = *p*-$O_2NC_6H_4$
7f R = 2-Naphthyl
7g R = 2,4,6-(*i*-Pr)$_3C_6H_2$

Figure 2 Structures of phosphoric acids **7** used in this study

We were pleased to note that compound **3** indeed underwent a reaction in the presence of chiral phosphoric acid **7a**. *N*-Methylindole[18] was used as the electrophile, and the respective Friedel–Crafts alkylation product at substrate carbon atom C3 was obtained. Other regioisomers were not detected. The reaction was complete upon stirring the reagents for 72 hours in the presence of 5 mol% catalyst and 4 Å molecular sieves in CH_2Cl_2 as the solvent. In CH_2Cl_2, there was no enantioselectivity, however. Improved selectivities were obtained in toluene and most notably in trifluorotoluene (vide infra). A screening of different phosphoric acids **7** was performed for the reaction of substrate **3** with indole in trifluorotoluene as the solvent (Table 1). It revealed that the 2,4,6-tris(isopropyl)phenyl-substituted acid **7g** was the best catalyst in terms of product ee (Table 1, entry 7). All phosphoric acids **7b–g** (Table 1, entries 2–7) except for the parent compound **7a** (Table 1, entry 1) led to the preferred formation of the levorotatory product (–)-**8**.[19] A reaction conducted at –15 °C with 20 mol% of catalyst **7g** delivered product (–)-**8** in a yield of 87% and with 57% ee.

Table 1 Enantioselective Friedel–Crafts Reaction of Indole with Substrate **3** Catalyzed by the Chiral Brønsted Acids **7**



Entry[a]	Catalyst	Yield (%)[b]	(–)-**8**/(+)-**8**[c]	ee (%)[d]
1	**7a**	quant.	39:61	22
2	**7b**	91	67:33	34
3	**7c**	quant.	60:40	20
4	**7d**	quant.	62:38	24
5	**7e**	quant.	58:42	16
6	**7f**	quant.	63:37	26
7	**7g**	quant.	75:25	50

[a] All reactions were conducted at r.t. with 4 equiv of indole and 10 mol% of the catalyst at a substrate concentration of 0.07 M in trifluorotoluene as the solvent.
[b] Yield of isolated product.
[c] The er of (–)-**8**/(+)-**8** was determined by HPLC (Daicel Chiralcel OD, 250 × 4.6, hexane–*i*-PrOH = 70:30).
[d] The ee was calculated from the er.

The absolute configuration of the major enantiomer (–)-**8** could be elucidated by single-crystal X-ray analysis. The quality of the anomalous X-ray diffraction data was sufficient to assign the absolute configuration at the stereogenic center as shown in Figure 3.[20]

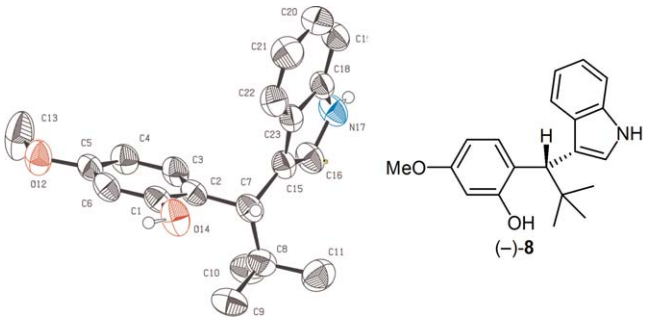
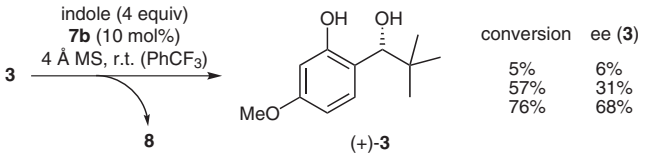


Figure 3 Structure of enantiomerically pure product (–)-**8** in the crystal and molecular formula

In experiments, which were not run to completion, it was noted that the recovered starting material was optically active.[21] Regarding enantioselectivity, the best result was recorded when using chiral phosphoric acid **7b**. In this case the starting material was recovered after 76% conversion in a yield of 24% and with 68% ee. The absolute configuration of the major enantiomer (+)-**3** was elucidated by anomalous X-ray diffraction (see Supporting Information).[22] In the very same experiment, which resulted in the formation of (+)-**3**, the respective indole derivative (–)-**8** was produced as major enantiomer (17% ee after 76% conversion).



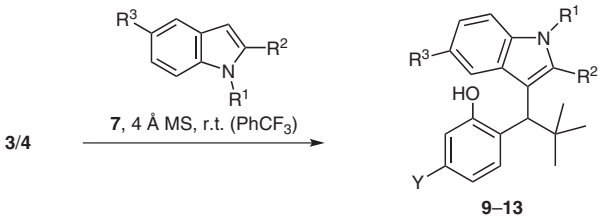
Scheme 2 Kinetic resolution of compound **3** in the course of the enantioselective Friedel–Crafts reaction with indole

The enantiomerically pure substrate (+)-**3** when employed in the reaction with indole in the presence of a racemic phosphoric acid delivered the substitution product **8** as a racemate (Scheme 2). The latter result proves that the substitution is not stereospecific and that the resolution is not due to the selective reaction of one substrate enantiomer in a S_N2-type fashion.

When attempting the enantioselective Friedel–Crafts-type reaction with other indole nucleophiles and with substrate **4**, it was found that there was no consistently superior phosphoric acid for all reactions (Table 2).

N-Methylindole delivered with substrate **3** the best ee if the reaction was catalyzed by phosphoric acid **7e** (Table 2, entry 1) indicating that an interaction of the phosphate anion with the indole NH is not crucial for the success of the reaction. The reaction with phosphoric acids **7a** and **7g**

Table 2 Optimum Results from the Enantioselective Friedel–Crafts Reaction of Various Indoles with Substrates **3** and **4** Catalyzed by the Chiral Brønsted Acids **7**



Entry[a]	Substrate	Catalyst	R^1	R^2	R^3	Product	Yield (%)[b]	ee (%)[c]
1	**3**	**7e**	Me	H	H	**9**	90	37
2	**3**	**7g**	H	Me	H	**10**	96	8
3	**3**	**7g**	H	H	Me	**11**	87	53
4	**4**	**7c**	H	H	H	**12**	23[d]	77
5	**4**	**7g**	H	H	H	**12**	99[d]	46
6	**4**	**7a**	Me	H	H	**13**	95	28

[a] All reactions were conducted at r.t. with 4 equiv of the respective indole and 10 mol% of the catalyst at a substrate concentration of 0.07 M in trifluorotoluene as the solvent.
[b] Yield of isolated product.
[c] The ee was calculated from the er. The er was determined by HPLC (for specific conditions see Supporting Information).
[d] The reaction was incomplete, and the yield is based on recovered starting material.

under otherwise identical conditions turned out to lead to the opposite enantiomer of product **9** (15% and 22% ee, respectively). The introduction of a methyl group at C2 atom of indole resulted in a complete loss of enantioselectivity in the Friedel–Crafts reactions. With phosphoric acids **7a–f** only racemic product **10** was formed. The use of acid **7g** gave a low, but detectable ee (Table 2, entry 2). Not surprisingly, it was observed that the influence of a distal methyl group at C5 of the indole is marginal. The best selectivity was recorded with chiral phosphoric acid **7g** (Table 2, entry 3), which delivered the enantiomerically enriched product **11** in 53% ee. The reactions of indoles with the *N*,*N*-dimethylamino-substituted substrate **4** were significantly slower than with the methoxy-substituted benzylic alcohol **3**. Even after a prolonged reaction time of 72 hours the conversion to substitution product **12** was incomplete, irrespective what phosphoric acid was employed. The best results were obtained with acid **7c** (Table 2, entry 4) and with acid **7g** (Table 2, entry 5). A similar trend was recorded in the reaction with *N*-methylindole. The reaction catalyzed by phosphoric acid **7a** was complete after five days delivering product **13** in 95% yield and with 28% ee (Table 2, entry 6). Reactions performed in other solvents but trifluorotoluene delivered lower enantioselectivities under otherwise identical conditions. In CH_2Cl_2 product **13** was isolated with 11% ee, in toluene with 14% ee.

Mechanistically, there is no observation that contradicts the formation of cations **B** and their association to the chiral counterion. Both the *para*- and the *ortho*-substituent are mandatory to achieve an enantioselective reaction. With substrate **5** there was no conversion and with substrate **6** there was no enantioselectivity in all reactions we attempted with phosphoric acids and the respective *N*-triflyl phosphoramides. Future work is directed towards a better understanding of the parameters governing the selectivity of this process. In addition, it is planned to extend the scope of potential nucleophiles, which react with cations of type **B**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are procedures and analytical data for all new compounds, selected HPLC traces, and crystal structure data.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0011th. FIDs and associated files for the ^1H and ^{13}C NMR spectra for compounds **3**, **4**, **8**, **9**, **10**, **11**, **12**, and **13** are summarized.

Acknowledgment

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(19) **Representative Procedure (8)**
A Schlenk flask containing 250 mg of 4 Å MS was charged with benzylic alcohol **3** (21.0 mg, 100 μmol) and indole (46.9 mg, 400 μmol) in dry trifluorotoluene (1.5 mL). Catalyst **7g** (7.53 mg, 10 μmol) was added, and the resulting mixture was stirred at r.t. until the starting material was completely consumed (monitored by TLC). The crude reaction mixture was purified directly by flash column chromatography on silica gel (eluent: pentane–Et_2O = 4:1 to 2:1) yielding compound **8** (30.9 mg, 100 μmol, quant., 50% ee) as a light-brown solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.15 (s, 9 H), 3.71 (s, 3 H), 4.51 (s, 1 H), 5.30 (s, 1 H), 6.28 (d, ^4J = 2.3 Hz, 1 H), 6.44 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1 H), 7.04 (virt. t, ^3J = ca. 7.5 Hz, 1 H), 7.15 (virt. t, ^3J = ca. 7.6 Hz, 1 H), 7.26 (d, ^3J = 8.5 Hz, 1 H), 7.29 (d, ^3J = 8.1 Hz, 1 H), 7.36 (d, ^3J = 1.9 Hz, 1 H), 7.52 (d, ^3J = 8.0 Hz, 1 H), 8.02 (br s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 28.9, 35.8, 45.4, 55.1, 101.6, 105.8, 110.8, 117.3, 119.4, 119.5, 121.2, 121.5, 122.2, 128.7, 132.1, 135.5, 154.9, 158.6 ppm. HRMS: *m/z* calcd for $C_{20}H_{23}NO_2$: 309.1723; found: 309.1724.

(20) An analysis of the absolute structure based on Bayesian statistics and Friedel pairs with a coverage of 99% resulted in a probability of 1.00.
Crystal Data
Formula: $C_{20}H_{23}NO_2 \cdot C_4H_{10}O$; M_r = 383.51; crystal color and shape: colorless fragment, crystal dimensions: 0.13 × 0.23 × 0.69 mm; crystal system: monoclinic; space group: $P2_1$ (no. 4); a = 10.2950 (4), b = 7.7382 (3), c = 15.1602 (5) Å, β = 104.737 (2)°; V = 1168.00(8) Å^3; Z = 2; $\mu_{MoK\alpha}$ = 0.071 mm^{-1}; ρ_{calcd} = 1.090 g cm^{-3}; c range = 1.39–25.33°; data collected: 27134; independent data [$I_o > 2\sigma(I_o)$/all data/R_{int}]: 3857/4255/0.027; data/restraints/parameters: 4255/1/267; $R1$ [$I_o > 2\sigma(I_o)$/all data]: 0.0376/0.0419; $wR2$ [$I_o > 2\sigma(I_o)$/all data]: 0.1086/0.1119; GOF = 1.089; $\Delta\rho_{max/min}$: 0.11/–0.13 e Å^{-3}; Flack parameter; x = –0.6 (13); 'Flack Equivalent' Hooft parameter y = –0.3 (3). For detailed information see Supporting Information. CCDC 808871 [(–)-**8**] contains the supplementary crystallographic data for this compound. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(22) **Crystal Data**
Formula: $C_{12}H_{18}O_3$; M_r = 210.26; crystal color and shape: colorless fragment, crystal dimensions: 0.46 × 0.51 × 0.61 mm; crystal system: orthorhombic; space group: $P2_12_12_1$ (no. 19); a = 6.6950 (1), b = 9.1455 (2), c = 19.2531 (4) Å; V = 1178.85 (4) Å^3; Z = 4; $\mu_{CuK\alpha}$ = 0.680 mm^{-1}; ρ_{calcd} = 1.185 g cm^{-3}; c range = 4.59–66.30°; data collected: 27197; independent data [$I_o > 2\sigma(I_o)$/all data/R_{int}]: 1984/1995/0.027; data/restraints/parameters: 1995/0/209; $R1$ [$I_o > 2\sigma(I_o)$/all data]: 0.0215/0.0216; $wR2$ [$I_o > 2\sigma(I_o)$/all data]: 0.0582/0.0582; GOF = 1.111; $\Delta\rho_{max/min}$: 0.13/–0.12 e Å^{-3}; Flack parameter; x = 0.03 (15); 'Flack Equivalent' Hooft parameter y = 0.05 (3). For detailed information see Supporting Information. CCDC 808870 [(+)-**3**)] contains the supplementary crystallographic data for this compound. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.