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Enantioselective Synthesis of Fluorene Derivatives by Chiral Phosphoric Acid Catalyzed Tandem Double Friedel–Crafts Reaction

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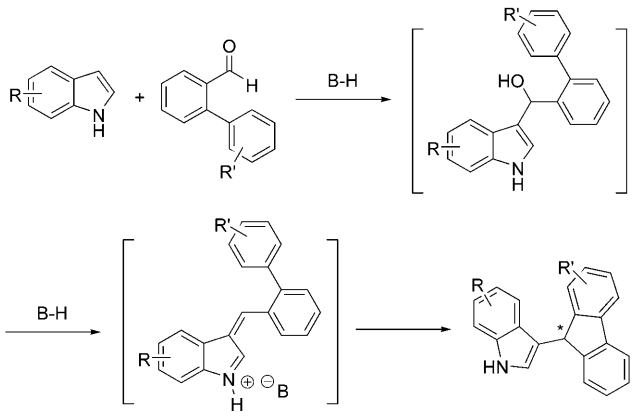
The asymmetric Friedel–Crafts reaction is one of the most powerful methods to synthesize optically active aromatic compounds,[1] and chiral Brønsted acids have recently emerged as efficient catalysts.[2] Chiral phosphoric acids, first introduced by Akiyama et al. and Terada and Uraguchi as organocatalysts,[3] were shown to be effective in the Friedel–Crafts alkylation reactions of indoles and pyrroles by several groups. However, electrophilic partners that can be activated by chiral phosphoric acids in Friedel–Crafts reactions have, so far, been limited to imines,[4] enamides,[5] α,β-unsaturated carbonyls,[6] and nitroolefins.[7] Developing new, suitable electrophilic partners and novel catalytic models for chiral phosphoric acid catalyzed reactions are extremely desirable. In this regard, vinyl ether[8] and nitroso compounds[9] have recently been developed successfully.[10] Alcohols are among the most abundant chemicals and synthetic intermediates, however, their use in enantioselective Friedel–Crafts reactions has only appeared recently.[11] To the best of our knowledge, the only example involving the use of alcohols in the Brønsted acid catalyzed asymmetric Friedel–Crafts reaction was carried out by Rueping et al., in which chiral *N*-triflylphosphoramide was used and a moderate enantiomeric excess (*ee*) value was obtained.[6a]

During our recent study on the chiral Brønsted acid catalyzed Friedel–Crafts reaction, we found that a chiral phosphoric acid could catalyze the Friedel–Crafts reaction of indole with 2-formylbiphenyl derivatives. Interestingly, this reaction proceeded through a double Friedel–Crafts alkylation process,[12] providing the 9-(3-indolyl)fluorene derivatives with high *ee* values (Scheme 1).[13] To the best of our knowledge, despite their significant applications in organic synthesis,[14] this represents the first asymmetric synthesis of fluorene derivatives. More interestingly, the current reaction proceeds with the activation of both carbonyl and hydroxy groups by a chiral phosphoric acid. The enantiocontrol is likely to be made possible through the close proximity of the chiral phosphate counterion to the 3-benzylidene-3*H*-indolium ion.[15] Herein, we report a tandem double Friedel–Crafts reaction of indoles with 2-formylbiphenyls, leading to 9-(3-indolyl)fluorene derivatives with up to 96% *ee*.



Scheme 1. Chiral phosphoric acid catalyzed tandem double Friedel–Crafts reaction.

We first examined the reaction between 3′,5′-dimethoxybiphenyl-2-carbaldehyde (**2a**) and 2-methyl indole (**3a**) catalyzed by different, readily available, chiral phosphoric acids.[16] To our delight, reaction of **2a** and **3a** in the presence of (*S*)-**1** (5 mol%) and 5 Å molecular sieves (MS), in toluene at room temperature, proceeded smoothly to afford fluorene **4aa** in 70% yield with 75% *ee* (Table 1, entry 1). Optimization of the reaction conditions was carried out and the results are summarized in Table 1. Lowering the temperature to 0°C resulted in an increase of enantioselectivity (81% *ee*; Table 1, entry 2). Several solvents, namely, benzene, dichloromethane, and carbon tetrachloride, were screened and the use of carbon tetrachloride resulted in an excellent 92% *ee* (Table 1, entries 2–5). Further screening of

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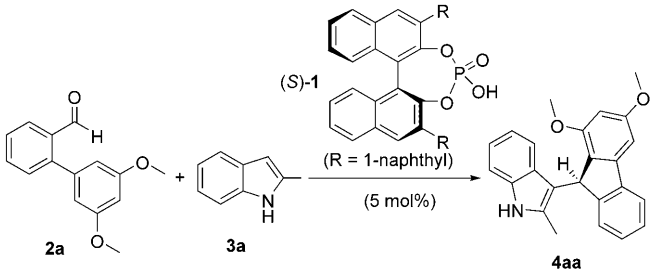
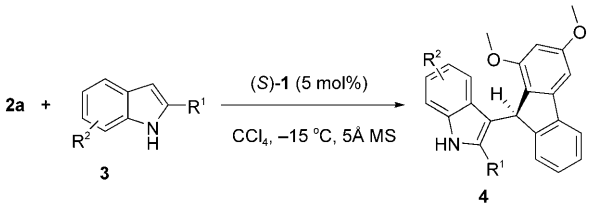
Table 1. Screen of the reaction conditions.



Entry[a]	Solvent	Additive	T [°C]	t	Yield [%][b]	*ee* [%]
1	toluene	5 Å	20	30 min	70	75
2	toluene	5 Å	0	30 min	66	81
3	benzene	5 Å	0	10 min	85	80
4	CH_2Cl_2	5 Å	0	4 h	95	85
5	CCl_4	5 Å	0	10 min	90	92
6	CCl_4	5 Å	−15	20 min	90	96
7	CCl_4	4 Å	−15	3 h	85	90
8	CCl_4	3 Å	−15	30 min	51	88
9	CCl_4	–	−15	40 min	50	83

[a] Reaction conditions: **2a** (0.1 mmol), (*S*)-**1** (5 mol%), **3a** (0.15 mmol), and molecular sieves (70 mg) in 2 mL of solvent. [b] Yield of the isolated product.

Table 2. Substrate scope of indoles in the tandem double Friedel–Crafts reaction.



Entry[a]	R^1	R^2	t	Product	Yield [%][b]	*ee* [%]
1	Me	H	20 min	**4aa**	92	96
2	Me	5-Me	30 min	**4ab**	90	91
3	Me	5-Br	30 min	**4ac**	94	93
4	Me	5-Cl	20 min	**4ad**	96	93
5	Me	5-F	30 min	**4ae**	91	77
6	Me	5-CH_3O	30 min	**4af**	66	90
7	Me	7-Br	70 min	**4ag**	84	81[c]
8[d]	H	H	3 h	**4ah**	37	89
9	Et	H	30 min	**4ai**	85	89
10	Ph	H	24 h	**4aj**	86	73

[a] Reaction conditions: **2a** (0.2 mmol), (*S*)-**1** (5 mol%), **3** (0.3 mmol), and 5 Å molecular sieves (150 mg) in CCl_4 (3 mL) at −15 °C. [b] Yield of the isolated product. [c] An X-ray structure of the enantiopure *N*-Boc derivative of **4ag** disclosed the *S* configuration. [d] The reaction was carried out at room temperature.

the reaction temperature led to 96% *ee* at −15 °C (Table 1, entry 6). Replacement of the 5 Å MS with 4 or 3 Å MS led to a slight decrease of the enantioselectivity. In general, the presence of molecular sieves increases the enantioselectivity because water is generated during the second Friedel–Crafts reaction with the hydroxy group (Table 1, entries 6–9).

Various indoles were treated with 2-formylbiphenyl **2a** under the optimized reaction conditions ((*S*)-**1** (5 mol%) with 5 Å MS in CCl_4 at −15 °C). The results are summarized in Table 2.

For the 2-methylindole derivatives, different substituents, such as 5-Me, 5-Br, 5-Cl, 5-F, 5-OMe, and 7-Br, were all tolerated to afford the fluorene products with good to excellent yields (66–96%). Enantioselectivities of over 90% *ee* were obtained for most of the substrates except those with 5-F (77% *ee*) and 7-Br (81% *ee*) (Table 2, entries 2–7). Protection of the indole NH of the bromo-containing compound **4ag** by treatment with Boc_2O led to the formation of **5** without loss of optical purity. An X-ray structure of enantiopure **5** was obtained, which enabled the absolute configuration of the product to be assigned as *S* (Figure 1).[17]

Indoles with different substituents at the 2-position were also examined. Excellent *ee* values were obtained for indole (89%) and 2-ethylindole (89%), however, the use of indole resulted in a relatively low yield due to the formation of a bisalkylated byproduct (Table 2, entries 8–9). The reaction also tolerated 2-phenylindole as a substrate, giving the desired product in 86% yield with 73% *ee* (Table 2, entry 10).

The substrate scope of the reaction was further explored by subjecting various 2-formylbiphenyls to the optimized reaction conditions with 2-methyl indole (**3a**) (Scheme 2). The desired fluorene derivatives were formed in good to excellent yields and with excellent *ee* values (92–96%) except for the fluorene **4da**, which was formed with 74% *ee*.

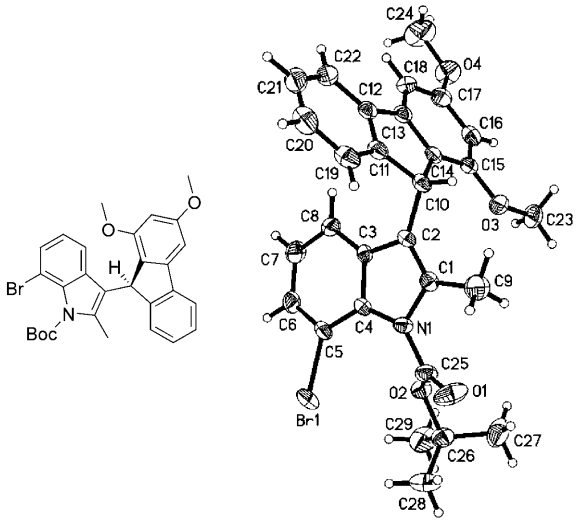
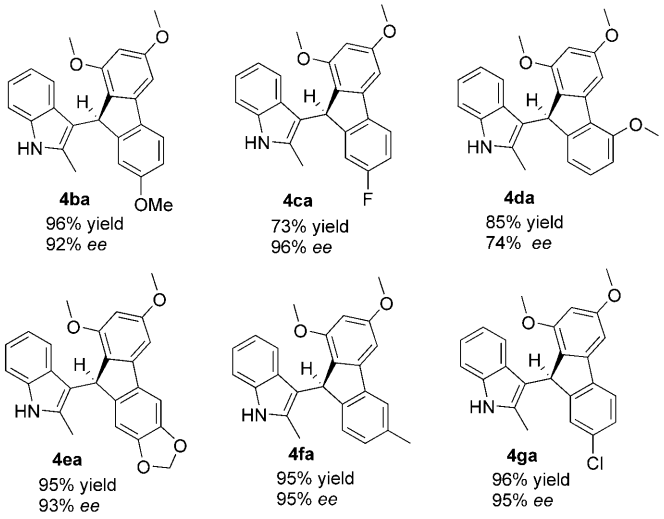
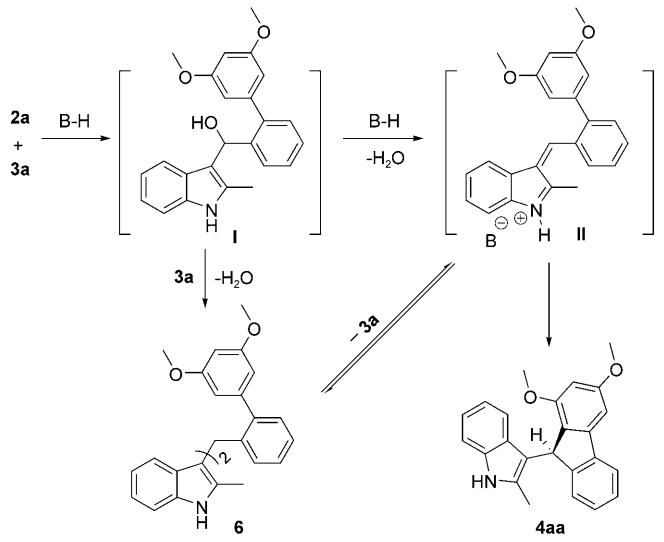


Figure 1. X-ray structure of enantiopure (*S*)-**5**. Ellipsoids at 30% probability.

The reaction mechanism proposed is depicted in Scheme 3. The first Friedel–Crafts reaction between **2a** and **3a** is catalyzed by phosphoric acid to afford the secondary alcohol **I**. Intermediate **I** is unstable under the reaction conditions and attempts to isolate this alcohol from the reaction mixture have, so far, been unsuccessful. The exposure of alcohol **I** to the chiral phosphoric acid leads to the formation of the close counterion **II**, in which the chiral phosphate anion creates a chiral environment to control the enantioselectivity of the second Friedel–Crafts reaction. Interestingly,



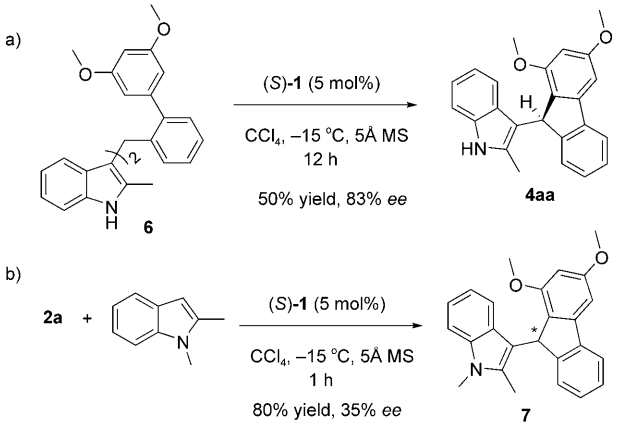
Scheme 2. Substrate scope of the 2-formylbiphenyl partner for the tandem double Friedel–Crafts reaction.



Scheme 3. Reaction pathways for the tandem double Friedel–Crafts reaction of **2a** with **3a**.

since bisindole **6** can be observed during the reaction, an alternative pathway involving the transformation of **6** to the intermediate **II** is included in the catalytic cycle. As evidence for the two coexistent pathways, when bisindole **6** was isolated and subjected to the optimized reaction conditions, product **4aa** was isolated in 50% yield with 83% *ee* (Scheme 4a). In addition, when the *N*-methyl-2-methylindole was used, the product was obtained in 35% *ee* (Scheme 4b). The dramatic decrease of both the *ee* value and the reaction time (1 h), compared with those of 2-methylindole, indicates that the reaction might proceed preferentially through intermediate **II**, in which the enantiocontrol is realized through a 3-benzylidene-3*H*-indolium intermediate.

In summary, we have developed a chiral phosphoric acid catalyzed tandem double Friedel–Crafts reaction of indoles



Scheme 4. Friedel–Crafts reaction of bisindole **6** and *N*-methylindole.

with 2-formylbiphenyl derivatives, affording the fluorene derivatives with up to 96% *ee*. This represents the first enantioselective synthesis of fluorene derivatives. In addition, the activation of both carbonyl and hydroxy groups by chiral phosphoric acid and the high enantiocontrol through the close proximity of the chiral phosphate counterion to the 3-benzylidene-3*H*-indolium ion provides a new reaction model for chiral phosphoric acid catalysis. Ongoing efforts in our laboratory focus on mechanistic study and further application of this novel catalytic model.

Experimental Section

General procedure for the catalytic asymmetric Friedel–Crafts reaction: In a dry Schlenk tube, biphenyl-2-carbaldehyde **2** (0.20 mmol), 5 Å molecular sieves (150 mg), and phosphoric acid (*S*)-**1** (6.0 mg, 0.01 mmol) were dissolved in CCl_4 (1.5 mL) at −15 °C under argon. The solution was stirred for 5 min, then substituted indole **3** (0.3 mmol) in CCl_4 (1.5 mL) was added slowly for 15 min at −15 °C. After the reaction was complete (monitored by TLC), saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/petroleum ether 1:10→1:5) to afford the product.

Acknowledgements

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Keywords: asymmetric catalysis · chiral Brønsted acids · fluorenes · Friedel–Crafts reaction · organocatalysis

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[16] See the Supporting Information for details.

[17] CCDC-725911 contains the supplementary crystallographic data for **5**. These 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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