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Chiral Brønsted Acid-Catalyzed Enantioselective Friedel–Crafts Reaction of 4,7-Dihydroindoles with Trifluoromethyl Ketones

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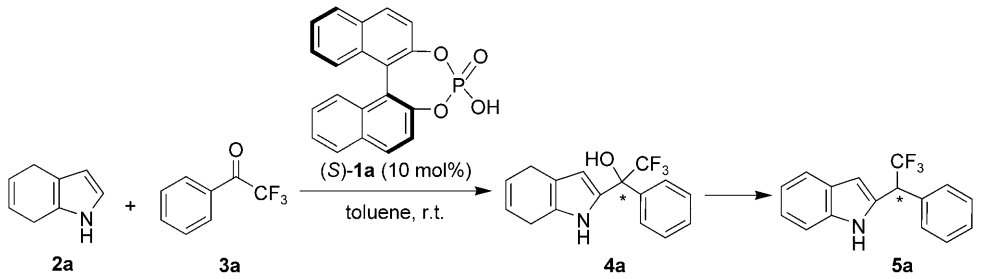
Abstract: In the presence of chiral phosphoric acid, an enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with aromatic trifluoromethyl ketones and ethyl 4,4,4-trifluoroacetoacetate has been realized. A series of 2-substituted 4,7-dihydroindoles with a trifluoromethylated tertiary alcohol moiety were obtained in 45–95% yields with 60–93% *ee*. Furthermore, 2-functionalized indole derivatives could be produced through a one-pot process.

Keywords: Brønsted acids; 4,7-dihydroindoles; enantioselectivity; Friedel–Crafts reaction; trifluoromethyl-substituted compounds

Chiral compounds with a trifluoromethyl-substituted tertiary alcohol moiety have a considerable importance in the field of biological and medicinal chemistry.[1] In particular, the application of Mosher's acid[2a] and some drugs such as Efavirenz (anti-HIV)[2b] or CJ-17,493 (NK-1 receptor antagonists),[2c] chiral trifluoromethyl tertiary alcohols in which the CF_3 moiety is located at a stereogenic tetrasubstituted carbon atom, has stimulated investigations in this area. One of the methods to synthesize chiral trifluoromethylated alcohols is by asymmetric addition of various nucleophiles to trifluoromethyl ketones.[3] We have demonstrated that chiral phosphoric acids[4] can efficiently promote the enantioselective additions of indoles to trifluoroacetaldimines and trifluoromethyl ketones.[5] However, due to the dramatic difference in reactivity between the 2- and 3-positions of indole, these successful examples are limited to the formation of 3-substituted indoles with a trifluoromethyled amine or alcohol moiety. Therefore, we have an interest in developing a suitable protocol for the synthesis of trifluoromethylated 2-indolylmethanol derivatives.

On the other hand, considerable advancement has been made during the past decades for catalytic asymmetric Friedel–Crafts reactions of pyrroles at the 2-position.[6] Recently, Saraçoğlu and co-worker reported that the Friedel–Crafts reaction of 4,7-dihydroindole (2,3-disubstituted pyrrole) with enones, followed by a *p*-benzoquinone oxidation, gave 2-substituted indoles in moderate yields.[7] Subsequently, two research groups developed the asymmetric version of this reaction by utilizing chiral Lewis acid catalysts, providing easy access to enantioenriched 2-substituted indole derivatives.[8] More recently, enantioselective Friedel–Crafts reactions of 4,7-dihydroindoles with imines and α,β-unsaturated carbonyl compounds activated by chiral organocatalysts have been described by You[9a,b] and Wang.[9c] In contrast, little progress has been made in the development of trifluoromethyl ketones as electrophilic reagents in the Friedel–Crafts reaction of 4,7-dihydroindoles, and only one example by Pedro and co-workers has addressed 2,2,2-trifluoroacetophenone as an electrophilic species.[8d] We were delighted to find that chiral Brønsted acids **1** serve as efficient organocatalysts in the Friedel–Crafts reaction of 4,7-dihydroindoles with aromatic trifluoromethyl ketones and ethyl 4,4,4-trifluoroacetoacetate for the synthesis of 2-substituted indoles with a trifluoromethyl-substituted tertiary alcohol moiety.

We initially investigated the reaction of 4,7-dihydroindole (**2a**) with 2,2,2-trifluoroacetophenone (**3a**) in the presence of readily available BINOL-derived phosphoric acid **1a** (10 mol%) in toluene (Scheme 1). The starting material **2a** disappeared almost completely within 30 h (detected by TLC), however, the desired adduct **4a** was obtained only in moderate yield (48%) with poor enantioselectivity. Interestingly, the racemic by-product **5a** was observed (43%). A kinetic profile was then obtained for these transformations (Figure 1). Accompanied by a slow drop in the concentration of 4,7-dihydroindole **2a**, an increase in the concentration of the desired product **4a** occurs gradually. A significant increase in the concentration



Scheme 1. Brønsted acid **1a**-catalyzed Friedel–Crafts reaction of 4,7-dihydroindole **2a** with 2,2,2-trifluoroacetophenone **3a**.

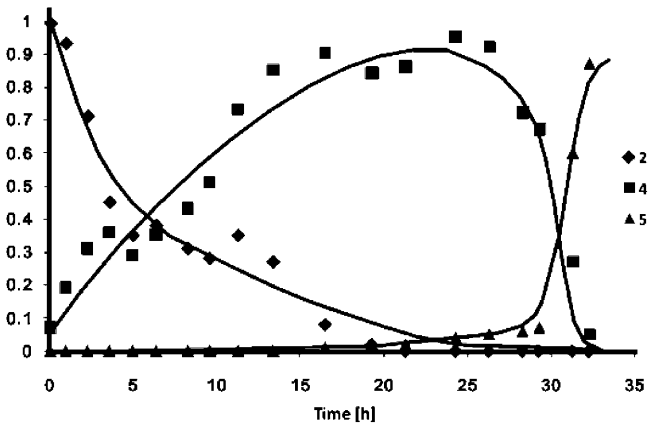
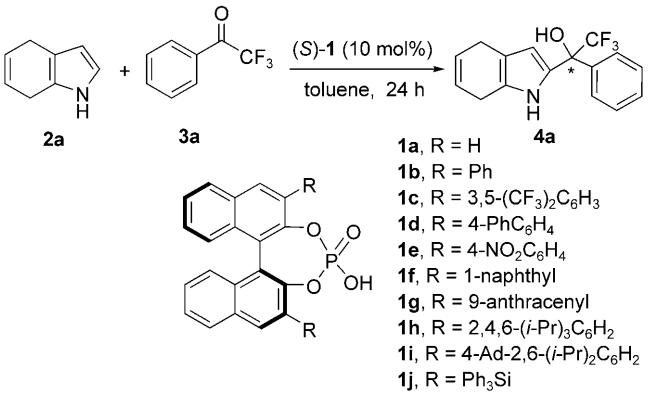


Figure 1. In the graph, the relative concentrations, monitored by HPLC, of **2a** (◆), product **4a** (■), and by-product **5a** (▲) under standard conditions are compared to the relative concentrations of the same compounds.

Table 1. Optimization of the reaction conditions.



Entry	Catalyst (mol%)	Solvent	*T* [°C]	Yield [%][a]	*ee* [%][b]
1	**1a** (10)	toluene	25	86	<5
2	**1b** (10)	toluene	25	62	<5
3	**1c** (10)	toluene	25	67	<5
4	**1d** (10)	toluene	25	56	<5
5	**1e** (10)	toluene	25	56	<5
6	**1f** (10)	toluene	25	76	6
7	**1g** (10)	toluene	25	52	<5
8	**1h** (10)	toluene	25	55	48
9	**1i** (10)	toluene	25	58	60
10	**1j** (10)	toluene	25	45	<5
11	**1i** (15)	toluene	25	40	60
12	**1i** (10)	benzene	25	47	50
13	**1i** (10)	xylene	25	68	85
14[c]	**1i (10)**	**xylene**	**25**	**53**	**93**
15	**1i** (10)	mesitylene	25	43	67
16	**1i** (10)	CH_2Cl_2	25	61	48
17	**1i** (10)	$ClCH_2CH_2Cl$	25	74	50
18	**1i** (10)	$CHCl_3$	25	42	40
19	**1i** (10)	xylene	15	58	80
20	**1i** (10)	xylene	0	67	60
21	**1i** (10)	xylene	40	75	79

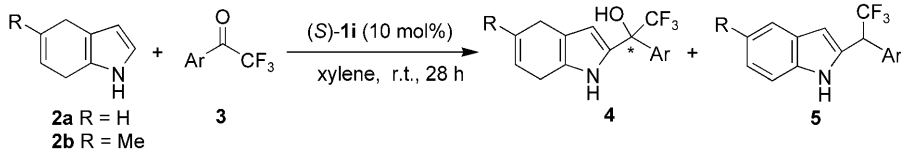
[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Reaction time: 28 h.

of the undesired product **5a** was observed with prolonged reaction times. In the control reaction, the isolated adduct **4a** was rapidly converted into **5a** with a catalytic amount of **1a** (10 mol%). This is a strong indication that by-product **5a** could be formed through dehydration and oxidation of the alkylation product **4a**. Thus, screening experiments were carried out for 24 h with respect to the yield of the desired adduct.

A further screening of catalysts has been carried out and the results are shown in Table 1 (entries 1–11). It was found that phosphoric acid **1i**, with bulky 4-adamantanyl-2,6-diisopropylphenyl groups at the 3,3′-positions of the binaphthyl scaffold, gave the highest enantioselectivity (60% *ee*) (entry 9). Subsequently, an optimization of the reaction solvents was undertaken (entries 12–18). Among the solvents tested, xylene was found to be the best with respect to catalytic activity and asymmetric induction (entries 13 and 14). Substantial changes in reaction temperature had s significant effect on the enantioselectivity (entries 19–21 *vs.* 14). Good results were attained when the reaction were carried out at room temperature for 28 h.

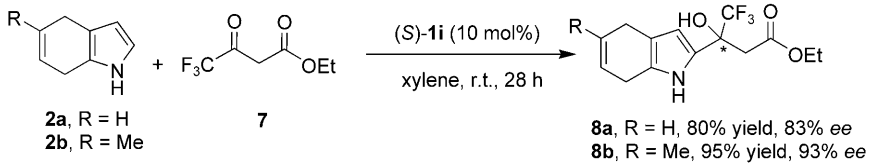
With the optimal conditions established, the scope of the Friedel–Crafts reaction between trifluoromethyl ketones and substituted 4,7-dihydroindoles has been examined in the presence of **1i**. The results are summarized in Table 2. A series of aromatic trifluoro-

Table 2. Enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with aromatic trifluoromethyl ketones.

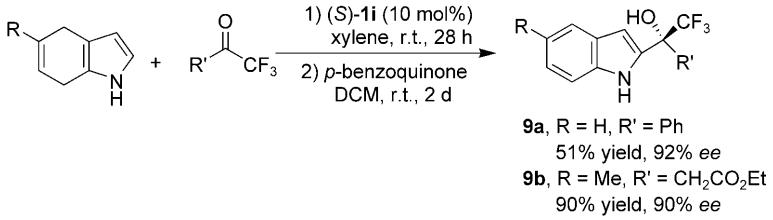


Entry	R	Ar	Product **4** Yield [%][a]	*ee* [%][b]	Product **5** Yield [%][a]
1	H	C_6H_5 (**3a**)	53 (**4a**)	93	46 (**5a**)
2	H	4-FC_6H_4 (**3b**)	45 (**4b**)	66	45 (**5b**)
3	H	4-ClC_6H_4 (**3c**)	54 (**4c**)	61	42 (**5c**)
4	H	4-BrC_6H_4 (**3d**)	54 (**4d**)	61	43 (**5d**)
5	H	4-MeC_6H_4 (**3e**)	57 (**4e**)	73	30 (**5e**)
6	H	3,5-$Me_2C_6H_3$ (**3f**)	69 (**4f**)	65	–[c]
7	H	4-PhC_6H_4 (**3g**)	47 (**4g**)	72	50 (**5g**)
8	H	2-naphthyl (**3h**)	55 (**4h**)	60	–[c]
9	Me	C_6H_5 (**3a**)	55 (**4i**)	90	43 (**5i**)
10	Me	4-MeC_6H_4 (**3e**)	45 (**4j**)	67	51 (**5j**)

[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] No isolation.



Scheme 2. Organocatalytic enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with ethyl trifluoroacetoacetate **7**.



Scheme 3. Friedel–Crafts reaction of 4,7-dihydroindoles with trifluoromethyl ketones and *p*-benzoquinone oxidation. The absolute configuration of **9a** was determined by comparison of retention time and specific rotation with those reported in the literature.[8d] The absolute configuration of adduct **9b** was assigned on the basis of an analogy with the study of **9a**.

methyl ketones has been tested in the reaction with 4,7-dihydroindole **2a**. Moderate yields and good to high enantioselectivities were achieved for the adduct **4a–h** (entries 1–8). When 5-methyl-4,7-dihydroindole **2b** was used as a substrate, the desired products **4i** and **8j** were also obtained with 90% *ee* and 67% *ee*, respectively (entries 9 and 10). Accordingly, in most cases the by-products **5** were isolated in moderate yields. It was noteworthy that the reaction of 4,7-dihydroindoles **2a** and **2b** with ethyl trifluoroacetoacetate **7** proceeded well under our current reaction conditions to afford the adducts **8a** and **8b** in high yields and enantioselectivities (Scheme 2).

Subsequently, we developed a one-pot procedure including the Friedel–Crafts reaction of 4,7-dihydroindoles with trifluoromethyl ketones and further oxidation of the resulting adducts with *p*-benzoquinone. The corresponding trifluoromethyl-substituted 2-indolyl compounds **9a** and **9b** were obtained smoothly with high enantioselectivities (92% *ee* for **9a** and 90% *ee* for **9b**, respectively) (Scheme 3). This is a strong indication that the current methodology is suitable for

the synthesis of 2-indolyl derivatives with a trifluoromethyl-substituted tertiary alcohol moiety.

In summary, we have developed a catalytic enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with trifluoromethyl ketones by employing BINOL-derived phosphoric acids as organocatalysts. The reaction takes place with good to high enantioselectivities (up to 93% *ee*). Furthermore, the resulting 4,7-dihydroindole products could be readily transformed into 2-functionalized indoles in one-pot by the oxidation of *p*-benzoquinone with high enantioselectivity. Further applications of these trifluoromethylated compounds are ongoing in our laboratory.

Experimental Section

Typical Procedure

In a dry Schlenk tube, a mixture of phosphoric acid **1i** (9.4 mg, 0.01 mmol), 4,7-dihydroindole **2a** (11.9 mg, 0.1 mmol), and 2,2,2-trifluoroacetophenone **3a** (26.1 mg, 0.15 mmol) in xylene (0.5 mL) under argon was stirred at room temperature for 28 h. Then, the reaction solution was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography (petroleum ether/AcOEt: 20/1) to give the desired product **4a** (yield: 15.5 mg, 53%, 93% *ee*) and by-product **5a** (yield: 12.6 mg, 46%, $<5\%$ *ee*).

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