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Highly Enantioselective Friedel–Crafts Reaction of 4,7-Dihydroindoles with β,γ-Unsaturated α-Keto Esters by Chiral Brønsted Acids

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Dedicated to Prof. Xiyan Lu on the occasion of his 80th birthday.

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Abstract: A highly efficient Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters by a chiral *N*-triflyl phosphoramide was realized, affording the 2-substituted 4,7-dihydroindoles with up to 98% *ee* for a wide range of substrates. The Friedel–Crafts alkylation together with a subsequent oxidation of the product with *p*-benzoquinone led to a 2-alkylated indole derivative in 98% *ee*.

Keywords: asymmetric catalysis; chiral Brønsted acids; conjugate addition; enantioselectivity; Friedel–Crafts reaction; indoles

Indoles are probably the most widely distributed heterocyclic compounds in nature and exist extensively as the structure core of biologically active natural products and pharmaceutical compounds.[1] Therefore the synthesis of optically pure indole derivatives is one of the most intense research areas in organic synthesis.[2] In this regard, the enantioselective Friedel–Crafts reaction of indole represents one of the most important reactions for the direct access to optically pure indoles.[3] Although the enantioselective Friedel–Crafts reaction has attracted considerable interest and witnessed significant progress recently,[4] the highly enantioselective synthesis of 2-substituted indole derivatives is still a challenge since enantioselective Friedel–Crafts reactions of indole always lead to 3-substituted indole derivatives.[5]

Just recently, following the protocol of Saraçoğlu,[6] Evans and co-workers have realized the Lewis acid-catalyzed asymmetric Friedel–Crafts reaction of α,β-unsaturated 2-acylimidazoles with 4,7-dihydroindoles.[7] This elegant protocol provides an easy access to 2-substituted indole derivatives after a simple oxidation of the products generated therefrom. Similarly, Pedro and co-workers reported a catalytic Friedel–Crafts alkylation at the 2-position of indole with simple enones, giving moderate *ee*s in the presence of a zirconium(IV)-BINOL complex.[8] Interesting as the optically pure 2-substituted indole derivatives are, their catalytic asymmetric synthesis is still rather limited. For instance, the alkylation of β,γ-unsaturated α-keto esters at the 2-position of indole has not been reported yet although both the ketone and ester groups in the products would offer facile conversions to versatile functionalities.[9] Taking advantage of Brønsted acid catalysis,[10–11] we recently realized the chiral phosphoric acid-catalyzed Friedel–Crafts reaction of 4,7-dihydroindoles with imines, affording the 2-indolylmethanamine derivatives after a subsequent oxidation.[11a] Moreover, Yamamoto and co-workers have recently introduced the chiral *N*-triflyl phosphoramide as a stronger acid compared with the chiral phosphoric acid, and the former enables the activation of carbonyl groups and highly extends the reaction type catalyzed by chiral Brønsted acids.[12] We envisaged that the chiral *N*-triflyl phosphoramide might be able to activate the β,γ-unsaturated α-keto ester to realize the Friedel–Crafts alkylation of indole at the 2-position (Figure 1). It should be noted that, very recently, Rueping and co-workers reported the chiral *N*-triflyl phosphoramide-catalyzed enantioselective Friedel–Crafts alkylation of indole with β,γ-unsaturated α-keto esters with up to 92% *ee*.[12c] In this paper, we report a highly enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters catalyzed by the chiral *N*-triflyl phosphoramide,

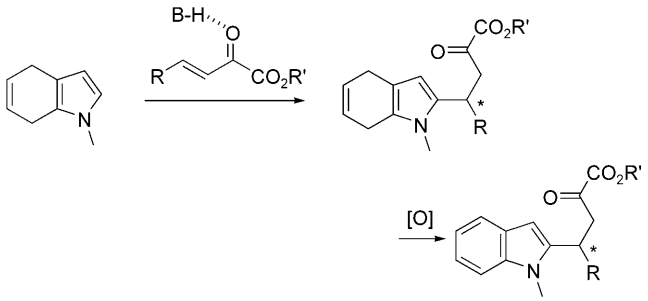


Figure 1. Route to 2-substituted indoles *via* Friedel–Crafts alkylation of 4,7-dihydroindoles.

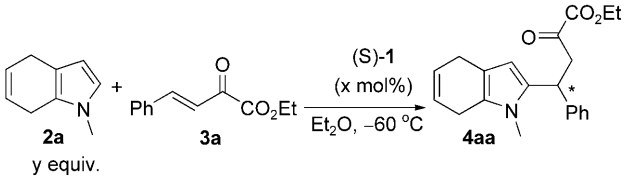
giving the 2-substituted indole derivatives with up to 98% *ee*.

We first examined the reaction between 4,7-dihydroindole **2a** and β,γ-unsaturated α-keto ester **3a** catalyzed by different chiral *N*-triflyl phosphoramides (see the Supporting Information for details). In the presence of 5 mol% of the chiral *N*-triflyl phosphoramides in toluene at −78 °C, reactions of **3a** with 2 equivalents of **2a** all gave the desired product **4aa** smoothly together with 1,2-addition byproduct, and the best *ee* (89% *ee*) was obtained using catalyst **1** bearing the bulky 2,4,6-(i-Pr)$_3$C$_6$H$_2$ groups (entry 5, Table 1).

With 5 mol% of (*S*)-**1** as the catalyst, reaction temperatures and solvents have been examined, and the results are summarized in Table 1. Interestingly, the reaction at −60 °C gave a higher *ee* (92%) with a reasonable yield (84%) (entry 4, Table 1). Several common solvents such as dichloromethane (CH_2Cl_2), THF, diethyl ether (Et_2O), and EtOAc have been tested. All the solvents led to excellent enantiomeric excess values, and reaction in diethyl ether (Et_2O) gave the optimal result, 96% yield and 98% *ee* (entry 8, Table 1).

As listed in Table 2, the catalyst loading and the equivalents of 4,7-dihydroindole have been examined.

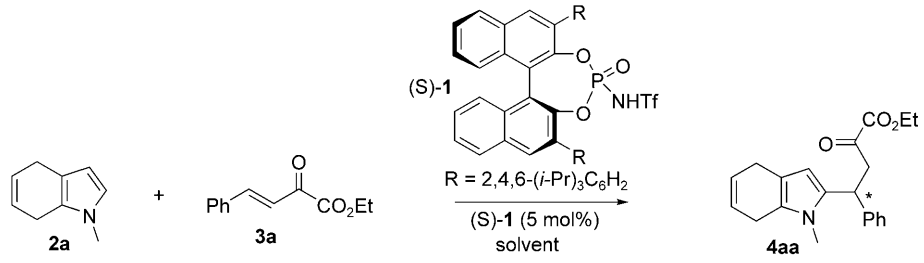
Table 2. Optimization of the reaction conditions.[a]



Entry	y (equiv)	x (mol%)	Time (h)	Yield [%][b]	*ee* [%][c]
1	2.0	5	1.0	96	98
2	1.5	5	1.0	84	98
3	1.1	5	2.0	74	94
4	2.0	2	1.0	89	97
5	2.0	1	2.0	85	94

[a] *Reaction conditions:* y equiv of **2a**, x mol% **1**, −60 °C, 0.20 mol/L of **3a** in ether.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).

Table 1. Optimization of the reaction conditions for enantioselective Friedel–Crafts reactions.[a]



Entry	Temperature [°C]	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	25	toluene	0.25	52	64
2	0	toluene	1.0	80	84
3	−40	toluene	1.0	77	90
4	−60	toluene	1.5	84	92
5	−78	toluene	2.5	87	89
6	−60	dichloromethane (CH_2Cl_2)	1.0	70	87
7	−60	tetrahydrofuran (THF)	8.0	48	86
8	−60	diethyl ether (Et_2O)	1.0	**96**	**98**
9	−60	EtOAc	1.0	80	90

[a] *Reaction conditions:* 2.0 equiv. of **2a**, 5 mol% of **1**, 0.20 mol/L of **3a**.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).

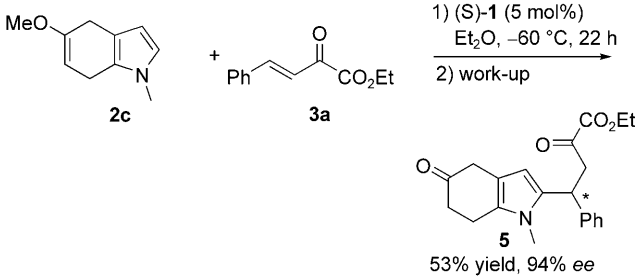
With 1.5 or 1.1 equivalents of dihydroindole **2a**, the reaction proceeded smoothly to give the alkylation product in 98% and 94% *ee*, respectively. Gratifyingly, even with 1 mol% of the catalyst, alkylation product **4aa** was also obtained in 85% yield with 94% *ee* (entry 5, Table 2).

Under the above optimized reaction conditions (2.0 equivalents of 4,7-dihydroindole, 5 mol% of **1**, −60 °C, and Et_2O as the solvent), Friedel–Crafts reactions between a wide range of β,γ-unsaturated α-keto esters **3** and substituted 4,7-dihydroindoles have been carried out to test the generality of the reaction. The results are summarized in Table 3.

The chiral phosphoramide-catalyzed Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters was found to be general with keto esters bearing different substituents. Several substituted keto esters **3b–g**, containing electron-donating groups at the *para*- or *meta*-position of the phenyl ring, have been tested in the reaction with 4,7-dihydroindole **2a**. In all cases, moderate to high yields and excellent enantioselectivities could be achieved for the desired alkylation products (59 to 82% yield, 87 to 97% *ee*, entries 2–7, Table 3). The chemistry went also well with substituted keto esters **3h–l**, containing electron-withdrawing groups at the *para*- or *meta*-position of the phenyl ring, and the desired alkylation products were obtained in 66 to 85% yield with 91 to 97% *ee* (entries 8–12, Table 3). When γ-heteroaryl-substituted α-keto esters **3m**, **n** were used, the reaction also gave excellent results, 89% yield with 96% *ee* (2-furyl), and 75% yield with 98% *ee* (2-thienyl), respectively (entries 13 and 14, Table 3). 5-Fluoro-4,7-dihydroindole **2b** has been tested in the reaction with keto ester **3a**, the alkylation product **4ba** was obtained in 84% yield with 96% *ee* (entry 15, Table 3).

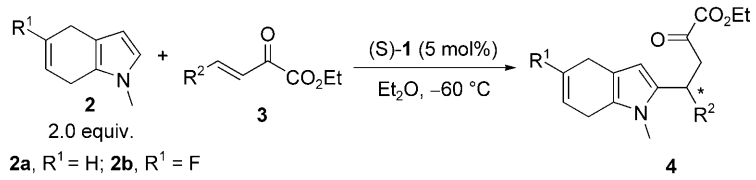
Interestingly, when 5-methoxy-4,7-dihydroindole **2c** was tested in the reaction with keto ester **3a**, product **5** was obtained in 53% yield with 94% *ee* due to the hydrolysis of the enol methyl ether (Scheme 1).

To demonstrate the suitability of the current methodology for the synthesis of 2-substituted indole derivatives, the oxidation of the 2-substituted 4,7-dihydroindole derivative has been tested. As shown in Scheme 2, after a quick work-up of the Friedel–Crafts



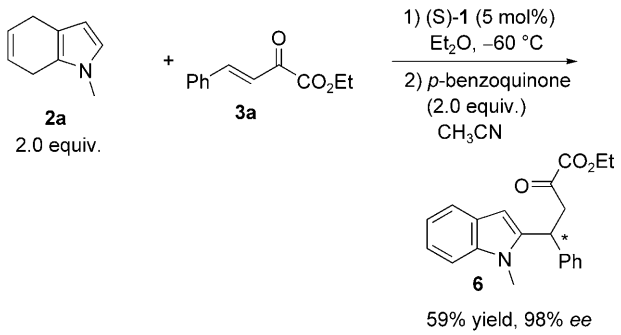
Scheme 1. Friedel–Crafts reaction of 5-methoxy-4,7-dihydroindole **2c** with keto ester **3a**.

Table 3. Enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters.[a]



Entry	**2**	**3**, R^2	Time (h)	**4**, Yield [%][b]	*ee* [%][c]
1	**2a**	**3a**, C_6H_5	1.0	**4aa**, 96	98
2	**2a**	**3b**, 4-Me-C_6H_4	12	**4ab**, 59	87
3	**2a**	**3c**, 3-Me-C_6H_4	2.5	**4ac**, 82	97
4	**2a**	**3d**, 3-MeO-C_6H_4	1.5	**4ad**, 80	96
5	**2a**	**3e**, 4-MeO-C_6H_4	1.0	**4ae**, 75	97
6	**2a**	**3f**, piperonyl	1.0	**4af**, 82	97
7	**2a**	**3g**, 2-naphthyl	30	**4ag**, 74	93
8	**2a**	**3h**, 3-NO_2-C_6H_4	24	**4ah**, 66	93
9	**2a**	**3i**, 4-Cl-C_6H_4	2.5	**4ai**, 83	91
10	**2a**	**3j**, 4-Br-C_6H_4	1.0	**4aj**, 85	96
11	**2a**	**3k**, 4-F-C_6H_4	3.0	**4ak**, 80	91
12	**2a**	**3l**, 3-Br-C_6H_4	2.0	**4al**, 85	96
13	**2a**	**3m**, 2-furyl	1.0	**4am**, 89	96
14	**2a**	**3n**, 2-thienyl	2.5	**4an**, 75	98
15	**2b**	**3a**, C_6H_5	12	**4ba**, 84	96

[a] Reaction conditions: 2.0 equiv. of **2**, 5 mol% **1**, −60 °C, 0.20 mol/L of **3** in ether.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.



Scheme 2. Friedel–Crafts reaction of **2a** with keto ester **3a** and *p*-benzoquinone oxidation.

reaction of 4,7-dihydroindole **2a** with keto ester **3a**, the reaction mixture was subjected to 2 equivalents of *p*-benzoquinone in acetonitrile. The desired 2-indolyl compound **6** was obtained smoothly in an overall 59% yield with 98% *ee*, which indicated the perfect retention of the stereochemistry during the oxidation process (entry 1, Table 3).

In summary, we have developed the enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters by utilizing chiral *N*-triflyl phosphoramide **1** as an efficient catalyst. The reaction features a metal-free approach, high efficiency of the catalyst, mild reaction conditions, high yields, and excellent enantioselectivities, providing a practical method to synthesize highly enantiopure 2-substituted 4,7-dihydroindole and 2-indole derivatives.

Experimental Section

General Procedure for the Catalytic Asymmetric Friedel–Crafts Reaction

In a dry Schlenk tube, β,γ-unsaturated α-keto ester **3** (0.20 mmol) and *N*-triflyl phosphoramide **1** (8.8 mg, 0.010 mmol) were dissolved in Et_2O (1 mL) under argon. The solution was stirred for 5 min at room temperature and then for another 5 min at −60 °C. Subsequently, *N*-methyl-4,7-dihydroindole **2** (0.40 mmol) was added in one portion at −60 °C. After the reaction was complete (monitored by TLC), saturated aqueous $NaHCO_3$ (3 mL) was added to quench the reaction. The mixture was allowed to warm to room temperature and was then extracted with CH_2Cl_2. 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 = 1/5–1/20) to afford the product.

Supporting Information

Full experimental details with characterization data are available as Supporting information.

Acknowledgements

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