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Asymmetric Friedel–Crafts Reaction of 4,7-Dihydroindoles with Nitroolefins by Chiral Brønsted Acids under Low Catalyst Loading

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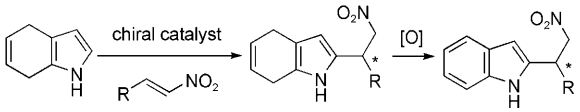
Dedicated to Professor Li-Xin Dai on the occasion of his 85th birthday.

The enantioselective Friedel–Crafts reaction has attracted considerable interest and witnessed significant progress recently.[1] Indoles are the most widely distributed heterocyclic compounds in nature and exist extensively as the structure core of biologically active natural products and pharmaceutical compounds.[2] The asymmetric Friedel–Crafts reaction of indoles has stimulated intense activity and has become an efficient tool for the synthesis of optically pure indole derivatives.[3] In particular, the asymmetric Friedel–Crafts reaction employing a nitroolefin as the electrophilic partner is very attractive, since the nitro group of the products allows subsequent versatile transformations.[4] Successful catalytic systems for this asymmetric reaction include the SalenAlCl complex,[5] bis-sulfonamides,[6] thioureas,[7] copper complexes,[8] zinc complexes,[9] and recently chiral phosphoric acids.[10] The latter were successfully introduced by Akiyama and co-workers, and, for the first time, chiral phosphoric acid was used to activate nitroolefins. Despite all the progress made in this area, most of the current catalytic systems still require the use of a substoichiometric amount of catalyst (5–20 mol%) and long reaction time (days) for the maximum yields and enantiomeric excesses.[11] A highly efficient catalytic system that addresses both these issues would certainly improve the practicality of the asymmetric Friedel–Crafts reaction of nitroolefins. In addition, to our knowledge, to date, there is no report on the asymmetric synthesis of products from the alkylation of nitroolefins at the 2-position of indoles. As part of our continuing interest in exploring the synthesis of 2-substituted indoles,[12] we recently found that chiral phosphoric acids were efficient catalysts for the asymmetric Friedel–Crafts reaction of nitroolefins with 4,7-dihydroindoles, providing 2-substituted indole derivatives after a subsequent oxidation (Scheme 1). More interestingly, all the reactions proceeded to completion in 2 h at room temperature with excellent yields and *ee* values with only 0.5 mol% of the catalyst.[13] Herein, we report our preliminary results.



Scheme 1. Route to 2-substituted indole by Friedel–Crafts alkylation.

We first examined the reaction between 4,7-dihydroindole (**2a**) and nitroolefin **3a** catalyzed by different chiral phosphoric acids.[14] After the screening of the chiral phosphoric acids, we found that (*S*)-**1** bearing 9-anthryl groups is the optimal catalyst. Notably, the acid bearing Ph_3Si groups, the best one in the Friedel–Crafts reaction between indoles and nitroolefins,[10a] afforded **4aa** with only moderate *ee* and reversed optical rotation. Different molecular sieves (MS) were tested as the additive (Table 1). In the presence of 5 mol% of (*S*)-**1** in dichloromethane/benzene (1/1) at room temperature, 4 Å MS were found to be the best ones, leading to the 2-substituted alkylation product **4aa** in 95% yield with 80% *ee* (entries 1–3, Table 1). Lowering the reaction temperature to 0 °C and −20 °C did not show any effects on the reaction outcomes, but the *ee* values decreased when the reactions were carried out at lower temperatures (entries 4–7, Table 1). To our delight, all the reactions proceeded to completion within 1 h.

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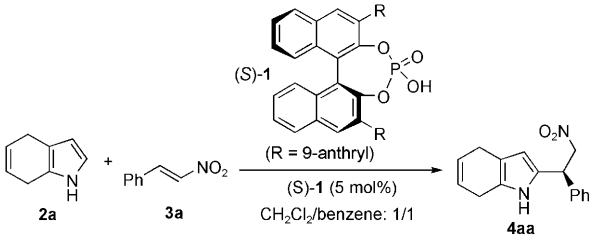
Table 1. Optimization of the reaction conditions for enantioselective Friedel–Crafts reaction.

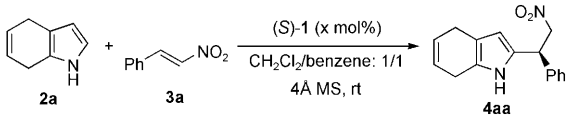


Entry[a]	Additive	Temp [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	3 Å MS	rt	1.0	95	49
2	4 Å MS	rt	1.0	95	80
3	5 Å MS	rt	1.0	95	57
4	4 Å MS	0	1.0	94	80
5	4 Å MS	−20	1.0	94	80
6	4 Å MS	−50	1.0	93	54
7	4 Å MS	−78	1.0	93	13

[a] Reaction conditions: 1.5 equiv of **2a**, 5 mol% of **1**, 0.25 mol L^{-1} of **3a** in CH_2Cl_2/benzene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (Chiralcel OD-H column).

A parallel reaction without the catalyst was set up and disclosed a severe background reaction. We hypothesized that a slow addition of the nitroolefin substrate would maximize the ratio between the catalyst and the nitroolefin in the reaction mixture and therefore afford the product with better *ee* and possibly allow the reduction of the catalyst loading. As expected, by using a syringe pump to slowly add the nitroolefin substrate over 1 h and 2 h, the *ee* of **4aa** increased to 90% and 91%, respectively (entries 1–3, Table 2). To our great delight, the same level of yield and *ee*

Table 2. Screening the catalyst loading and the slow addition.



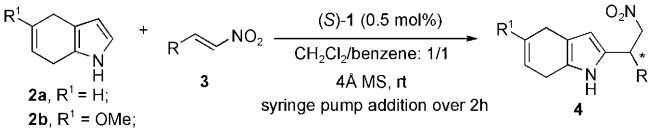
Entry[a]	Syringe pump	*x* [mol%]	Time [h]	Yield [%][b]	*ee* [%][c]
1	no	5	1.0	96	80
2	yes	5	1.0	95	90
3	yes	5	2.0	96	91
4	yes	1	2.0	96	92
5	yes	0.5	2.0	96	92
6	yes	0.1	2.0	96	81

[a] Reaction conditions: 1.5 equiv of **2a**, x mol% **1**, rt, 0.25 mol L^{-1} of **3a** in CH_2Cl_2/benzene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (Chiralcel OD-H column).

was obtained by using only 0.5 mol% of the catalyst (entries 4 and 5, Table 2). Even with 0.1 mol% of the catalyst, the reaction was also able to proceed to completion within 2 h with 81% *ee* (entry 6, Table 2).

The chiral phosphoric acid catalyzed Friedel–Crafts reaction of 4,7-dihydroindoles with nitroolefins was found to be general for nitroolefins bearing different substituents (Table 3). Several substituted nitroolefins **3b–d**, containing electron-donating groups, have been tested in the reaction

Table 3. Enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with nitroolefins.



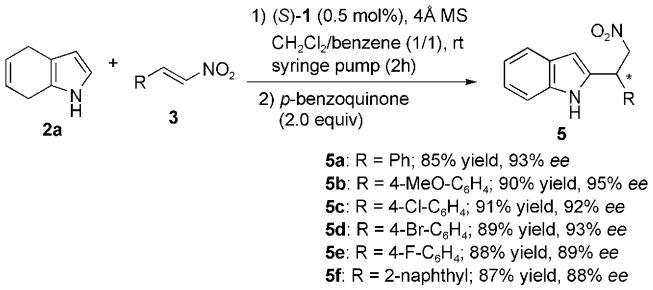
Entry[a]	**2**	**3**, R	**4**, Yield [%][b]	*ee* [%][c]
1	**2a**	**3a**, C_6H_5	**4aa**, 96	92
2	**2a**	**3b**, 4-MeO-C_6H_4	**4ab**, 97	96
3	**2a**	**3c**, 4-Me-C_6H_4	**4ac**, 97	92
4	**2a**	**3d**, 3-Me-C_6H_4	**4ad**, 97	88
5	**2a**	**3e**, 4-CF_3-C_6H_4	**4ae**, 94	92
6	**2a**	**3f**, 4-Cl-C_6H_4	**4af**, 97	91
7	**2a**	**3g**, 4-Br-C_6H_4	**4ag**, 98	91
8	**2a**	**3h**, 2-naphthyl	**4ah**, 96	92
9	**2a**	**3i**, 2-furyl	**4ai**, 97	95
10	**2a**	**3j**, 2-thienyl	**4aj**, 96	97
11	**2a**	**3k**, c-hexyl	**4ak**, 94	24
12[d]	**2b**	**3a**, C_6H_5	**4ba**, 94	92
13	**2c**	**3a**, C_6H_5	**4ca**, 93	89
14[e]	pyrrole	**3a**, C_6H_5	**4da**, 94	89

[a] Reaction conditions: 1.5 equiv of **2**, 0.5 mol% **1**, rt, 0.25 mol L^{-1} of **3** in CH_2Cl_2/benzene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 1 mol% of the catalyst was used. [e] 10 mol% of the catalyst was used.

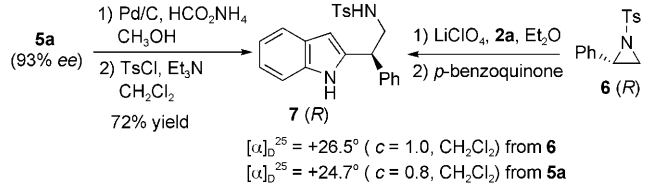
with 4,7-dihydroindole **2a**. In all cases, excellent yields and enantioselectivities were obtained for the desired alkylation products (97% yield, 88 to 96% *ee*, entries 2–4, Table 3). The reaction also worked well with substituted nitroolefins **3e–g**, which contained electron-withdrawing groups, and the desired alkylation products were obtained in 94 to 98% yield with 91 to 92% *ee* (entries 5–7, Table 3). When 2-naphthyl and heteroaryl-substituted nitroolefins **3h–j** were used, the reaction gave excellent results, 96 to 97% yield with 92 to 97% *ee* (entries 8–10, Table 3). Unfortunately, when aliphatic substituted nitroolefins such as **3k** were used, a low *ee* (24%) was obtained (entry 11, Table 3). 5-Methoxy-4,7-dihydroindole (**2b**) and 5-fluoro-4,7-dihydroindole (**2c**) were tested in the reaction with nitroolefin **3a**, the alkylation products were obtained in excellent yield and *ee* (entries 12 and 13, Table 3). When pyrrole was used, satisfying results were obtained with 10 mol% of the catalyst (94% yield, 89% *ee*, entry 14, Table 3).

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 derivatives was tested. After the reaction of the nitroolefin with 4,7-dihydroindole was complete, two equivalents of *p*-benzoquinone were added to the reaction mixture (Scheme 2). The desired 2-indolyl compounds **5** were obtained smoothly in 85 to 91% yield with 88 to 95% *ee*, indicating the perfect retention of the stereochemistry during the oxidation process.

The absolute configuration of the product **5a** was determined to be *R* as shown in Scheme 3. The nitro group in **5a** (93% *ee*) was reduced to amine followed by Ts protection, leading to compound **7** in an overall 72% yield. It has the same sign of optical rotation as that derived from enantio-

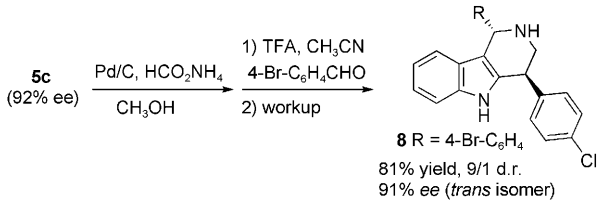


Scheme 2. Friedel–Crafts reaction of **2** with nitroolefin **3** and *p*-benzoquinone oxidation.



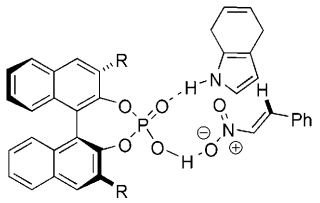
Scheme 3. Determination of the absolute configuration of **5a**.

pure aziridine (*R*)-**6**. As shown in Scheme 4, the Friedel–Crafts product **5c** was also transformed to tetrahydro-γ-carboline derivative **8** without racemization. The two isomers could be easily separated by silica gel column chromatography, providing a facile synthesis of enantiopure tetrahydro-γ-carboline derivatives. The latter exist extensively as biologically important compounds,[15] and their enantiopure forms are not readily accessible by known methods.



Scheme 4. Derivatization of the Friedel–Crafts product **5c**.

A working model for the stereochemistry was proposed as shown in Scheme 5. The chiral phosphoric acid acts as a bifunctional catalyst, in which the acidic proton and the P=O moiety of the catalyst form the hydrogen bond with the nitroolefin and the dihydroindole, respectively. This rigid conformation likely contributes to the high *ee* of this process.



Scheme 5. Proposed catalyst working model.

In summary, we have developed an enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with nitroolefins by utilizing chiral phosphoric acid **1** as an efficient catalyst. With slow addition of the nitroolefin substrate by syringe pump, the reaction allows the use of only 0.5 mol% of the catalyst and proceeds to completion in 2 h. This metal-free process together with the mild reaction conditions, high yields, and excellent enantioselectivities, provides a practical method to synthesize highly enantiopure 2-substituted-indole and tetrahydro-γ-carboline derivatives. Further application of the current methodology and study of the reaction mechanism are ongoing in our laboratory.

Experimental Section

General procedure for the catalytic asymmetric Friedel–Crafts reaction: 4,7-Dihydroindole (**2**, 0.45 mmol), chiral phosphoric acid (*S*)-**1** (1 mg, 0.0015 mmol), 4 Å molecular sieves (50 mg), and CH_2Cl_2/benzene (0.6 mL, 1:1) were placed in a dry Schlenk tube under argon. The reaction mixture was stirred at room temperature, and then a solution of nitroolefin **3** (0.3 mmol) in CH_2Cl_2/benzene (0.6 mL, 1:1) was added by syringe pump over two hours. The reaction was complete right after the addition for all cases. The reaction mixture was concentrated, and the residue was purified by flash chromatography (dichloromethane/petroleum ether = 1/10–1/1) to afford the product.

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

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