Organocatalysis

DOI: 10.1002/anie.200800770

Chiral Phosphoric Acid Catalyzed Enantioselective Friedel–Crafts Alkylation of Indoles with Nitroalkenes: Cooperative Effect of 3 Å Molecular Sieves**

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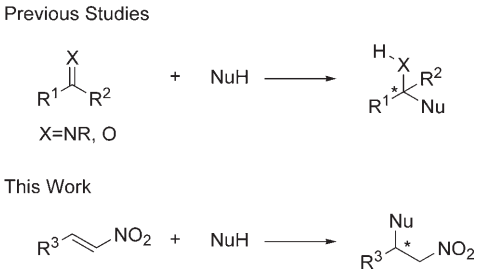
The enantioselective Friedel–Crafts alkylation[1] of indoles with nitroalkenes is one of the most important carbon–carbon bond-forming reactions for the preparation of biologically active compounds such as indole alkaloids.[2] Although several chiral catalysts, including salen/AlCl complexes,[3a] bis(sulfonamide) compounds,[3b] thiourea-contaning structures,[3c,f] and Zn^{II} or Cu^{II}–bisoxazoline complexes,[3d,e,g] have been reported for the reaction, the enantioselectivities are not always satisfactory. The development of more efficient catalysts is required.

Recently, novel Brønsted acid catalysts were developed and used in a number of asymmetric reactions,[4] and the chiral phosphoric acids derived from (*R*)-binol (binol = 2,2′-dihydroxy-1,1′-binaphthyl) have been extensively studied as versatile organocatalysts for enantioselective reactions.[5–7] Most of the phosphoric acid catalyzed reactions reported so far involve imine or iminium ion electrophiles, however, there are scattered examples that include carbonyl compounds[8a,b,9h,j] aziridines,[8c] or nitrones as electrophiles.[8d] The application of chiral phosphoric acid catalysis to other electrophiles is desirable, and the enantioselective addition of a nucleophile to a nitroalkene by using a chiral phosphoric acid has not previously been reported. We describe herein the first chiral phosphoric acid catalyzed Friedel–Crafts alkylation of indoles[9] with nitroalkenes to afford Friedel–Crafts adducts in excellent enantioselectivities (Scheme 1).

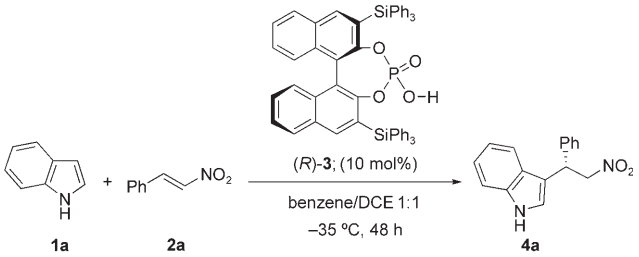
Chiral phosphoric acid (*R*)-**3** provided the best enantioselectivity in the Friedel–Crafts alkylation of indole **1a** with nitroalkene **2a** (2 equiv) in benzene/1,2-dichloroethane (1:1) at −35 °C. Although the system resulted in the formation of Friedel–Crafts adduct **4a** with good enantioselectivity, the yield was low (Table 1, entry 1).[10] To our delight, we found that the addition of activated, powdered molecular sieves (M.S.) significantly improved both the chemical yield and the enantioselectivity. Among the molecular sieves examined, the 3 Å molecular sieves gave the best result (Table 1, entry 2).[11] Since the addition of a small amount of water to the reaction mixture deteriorates the chemical yield (Table 1, entry 5),[12,13] we suppose that the molecular sieves absorb the small amount of water present in the reaction medium.



Scheme 1. Comparison of reactions from previous studies and this work.

We explored the scope and limitations of the reaction by using various indoles and nitroalkenes under the optimized reaction conditions, and the results are summarized in Table 2. A wide range of nitroalkenes bearing electron-donating (**2b–c**), electron-withdrawing (**2d–e**), and hetero-

Table 1: Effect of the 3 Å molecular sieves.[a]



1a 2a 4a

Entry	M.S.	Yield [%][b]	*ee* [%][c]
1		5	75
2	3 Å	76	91
3	4 Å	69	83
4	5 Å	59	88
5	3 Å[d]	1	60

[a] Reactions were carried out with **1a** (0.2 mmol) and **2a** (0.4 mmol; 2 equiv) in benzene (0.5 mL)/1,2-dichloroethane (0.5 mL). [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis. [d] Used 10 equiv of H_2O.

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[**] This work was partially supported by a Grant-in Aid for Scientific Research on Priority Areas "Advanced Molecular Transformation of Carbon Resources" from the Ministry of Education, Science, Sports, Culture, and Technology (Japan). J.I. thanks the JSPS Research Fellowships for Young Scientists.

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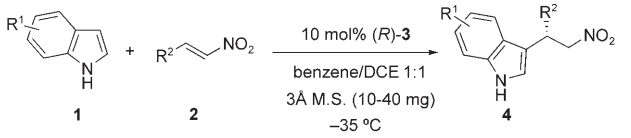
aromatic (**2f**) groups underwent the Friedel–Crafts alkylation reaction to afford Friedel–Crafts adducts **4** with excellent enantioselectivities (Table 2, entries 1–6). Aliphatic nitroalkenes (**2g–j**) gave the corresponding adducts with high enantioselectivities (Table 2, entries 7–10), but long reaction times were necessary to obtain good yields. The reaction tolerated a variety of different indoles (**1b–d**) and gave excellent results (Table 2, entries 11–13).

Table 2: Chiral Brønsted acid catalyzed Friedel–Crafts alkylation of indoles with nitroalkenes.[a]



1 **2** **4**

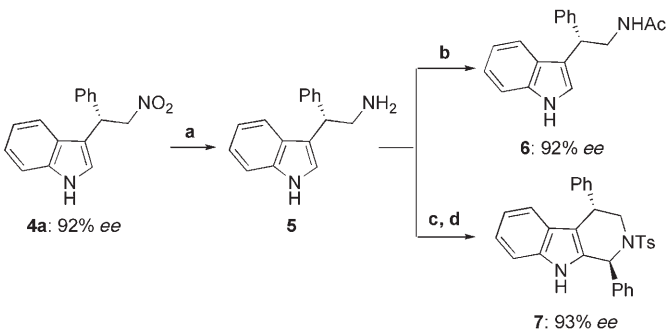
Entry	R^1	R^2	*t* [h]	Yield [%][b]	*ee* [%][c]
1	H (**1a**)	Ph (**2a**)	48	76 (**4a**)	91
2	H (**1a**)	4-MeC_6H_4 (**2b**)	116	64 (**4b**)	90
3[d,e]	H (**1a**)	4-$MeOC_6H_4$ (**2c**)	119	74 (**4c**)	91
4[e]	H (**1a**)	4-ClC_6H_4 (**2d**)	115	73 (**4d**)	91
5	H (**1a**)	4-$CF_3C_6H_4$ (**2e**)	72	84 (**4e**)	91
6[e]	H (**1a**)	2-thienyl (**2f**)	92	71 (**4f**)	90
7[e,f]	H (**1a**)	$Ph(CH_2)_2$ (**2g**)	95	57 (**4g**)	88
8[g]	H (**1a**)	$CH_3(CH_2)_2$ (**2h**)	234	70 (**4h**)	90
9[g]	H (**1a**)	$CH_3(CH_2)_4$ (**2i**)	234	77 (**4i**)	90
10[g]	H (**1a**)	$CH_3(CH_2)_8$ (**2j**)	235	62 (**4j**)	91
11[e]	5-Cl (**1b**)	Ph (**2a**)	119	63 (**4k**)	90
12[e]	5-Br (**1c**)	Ph (**2a**)	119	72 (**4l**)	90
13[e]	7-Me (**1d**)	Ph (**2a**)	83	70 (**4m**)	94
14[h]	H (**1a**)	Ph (**2a**)	95	>99 (**4a**)	91

[a] Reactions were carried out with **1** (0.2 mmol) and of **2** (0.4 mmol; 2 equiv) in benzene (0.5 mL)/1,2-dichloroethane (0.5 mL). [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis. [d] The reaction was performed at −20°C. [e] Employed 5 equiv of **2**. [f] Used 2 equiv of **1a** and 20 mol% of (*R*)-**3** at −20°C. [g] Used 20 mol% of (*R*)-**3**. [h] The reaction was performed on a one-gram scale (8.56 mmol) in the presence of 850 mg of 3 Å molecular sieves and 5 equiv of **2a**.

This reaction was carried out on a one-gram scale to demonstrate the synthetic utility of the present system. When 1.00 g of indole **1a** was treated with 5 equivalents of nitroalkene **2a**, 2.28 g of corresponding adduct **4a** was obtained in high chemical yield without any loss in the enantioselectivity (Table 2, entry 14).

Next, Friedel–Crafts adduct **4a** was transformed into triptamine **5**,[2a] melatonin analogue **6**,[2b] and 1,2,3,4-tetrahydro-β-carboline derivative **7**[2c] (Scheme 2). These products were obtained in good yields without racemization.

To gain insight into the reaction mechanism we examined *N*-Me indole as a substrate under the optimized conditions. As expected, both the chemical yield and the enantioselectivity deteriorated significantly (11% yield, 0% *ee*). The presence of the N–H moiety of indole ring is essential for attaining high yield and enantioselectivity, therefore we assume that the phosphoric acid activates the nitro moiety and at the same time the phosphoryl oxygen atom forms a hydrogen bond with the hydrogen atom of the indole N–H moiety (Figure 1). This arrangement is in agreement with the previously proposed nine-membered transition state,[6a,b,g] wherein the phosphoric acid worked as a bifunctional catalyst.



Scheme 2. Derivatization of the Friedel–Crafts adduct. Conditions: a) $NaBH_4$ (5 equiv), $NiCl_2{\cdot}6H_2O$ (1 equiv), MeOH, 30 min, 94%; b) AcCl (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 16 h, 91%; c) PhCHO (1.2 equiv), CF_3CO_2H (2 equiv), $MgSO_4$, CH_2Cl_2, 68 h, 80%, *anti*:*syn* = 91:9; d) TsCl (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 17 h, 97%. Ts = *p*-toluenesulfonyl.

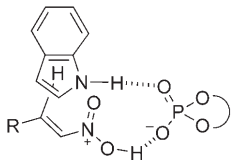


Figure 1. Plausible transition state. The vinylic hydrogen of the nitroalkene lies behind the indole ring.

In summary, we have developed a chiral phosphoric acid catalyzed Friedel–Crafts alkylation of indoles with nitroalkenes to generate Friedel–Crafts adducts with excellent enantioselectivities. We found that 3 Å molecular sieves lead to an efficient Friedel–Crafts alkylation in the presence of a chiral phosphoric acid. This reaction is the first example of nitroalkene activation catalyzed by a chiral phosphoric acid, and additional investigations to clarify the reaction mechanism and its application to other enantioselective reactions are underway.

Received: February 16, 2008
Published online: April 16, 2008

Keywords: asymmetric synthesis · Brønsted acids · enantioselectivity · Friedel–Crafts alkylation · indoles

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