DOI: 10.1002/ejoc.201100683

The Asymmetric Friedel–Crafts Reaction of Indoles with Fluoroalkylated Nitroalkenes Catalyzed by Chiral Phosphoric Acid

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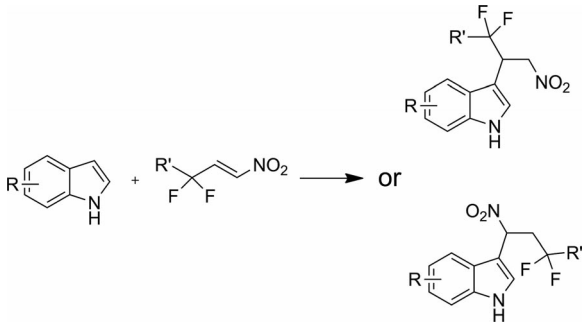
Keywords: Asymmetric catalysis / Organocatalysis / Friedel–Crafts reactions / Fluoroalkylation / Enantioselectivity

The enantioselective Friedel–Crafts fluoroalkylation of indoles with fluoroalkylated nitroalkenes, catalyzed by chiral phosphoric acid is described. The regioselectivity of fluoroalkylated nitroalkenes is a problem worth discussing, and it was found that the carbon atom adjacent to the fluoroalkyl group is more reactive than that adjacent to NO_2 group.

Introduction

The enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes has attracted considerable attention because it is recognized as one of the most efficient methods for the preparation of biologically active compounds such as indole alkaloids. Over the past several years, the reaction has witnessed significant progress, and much effort has been focused on the development of new catalyst systems for the asymmetric alkylation.[1–4] But the design of novel nitroalkenes, which might lead to novel products with strong bioactivities, is largely ignored. Within the realm of medicinal chemistry, the introduction of CF_3– or –CF_2– groups is a powerful and widely employed tactic to improve the biological properties of drugs.[5] Therefore, it would be interesting to incorporate fluoroalkylated nitroalkenes into the Friedel–Crafts reaction of indoles. Furthermore, the regioselectivity of fluoroalkylated nitroalkenes might become a problem worth discussing because of the strong electronegativity and large steric hindrance of the fluoroalkylated substituents[6] (Scheme 1), relative to the non-fluoroalkylated analogues.

Recently, chiral BINOL-derived phosphoric acid has been found to be a versatile organocatalyst in a variety of reactions.[7] The asymmetric nitroalkylation of indoles catalyzed by phosphoric acid was realized by Akiyama et al. in 2008.[1e] To improve the yield and enantioselectivity of the reaction, activated and powdered molecular sieves (MS) must be added. Besides, low temperatures were necessary for good enantioselectivity. However, the reaction becomes retarded at low temperature. Especially for the aliphatic nitroalkenes, the reaction time had to be prolonged to 10 d with 20 mol-% catalyst in order to achieve moderate yields. Recently, You et al. also found that the reaction of 4,7-dihydroindoles[8] or pyrroles[9] with nitroalkenes could be catalyzed by chiral phosphoric acid. However, the reaction did not work very well with aliphatic nitroalkenes either. It seemed that the aliphatic nitroalkenes could not efficiently be activated by chiral phosphoric acid. Fluoroalkylated nitroalkenes should possess a different reactivity to the usual aliphatic ones because of the presence of fluorine. To explore the reactivity of the fluoroalkylated nitroalkenes and to develop a practical synthetic method for the fluorinated indole derivatives, we investigated the chiral phosphoric acid catalyzed asymmetric reaction of indoles with fluoroalkylated nitroalkenes.



Scheme 1.

Results and Discussion

Under the catalysis of phosphoric acid **3a** (10 mol-%), the reaction of indole (**1a**) (1 equiv.) with 3,3,3-trifluoro-1-nitroprop-1-ene (**2a**) (2 equiv.) in dichloromethane proceeded smoothly to give **4a** in 85% yield (Table 1, Entry 1). The CF_3 group exhibits a comparable electronegativity with that of the NO_2 group and a higher steric hindrance. However, the reaction occurs exclusively at the carbon atom adjacent to the CF_3 group. Unfortunately, almost no enantio-

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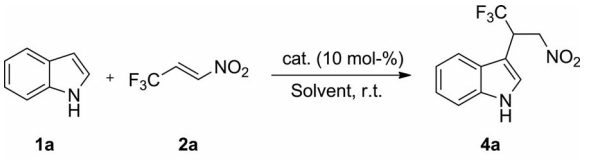
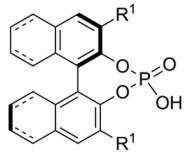
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100683.

selectivity was observed under the catalysis of **3a**. After the introduction of substituents at the 3,3′-positions of the binaphthyl scaffold, the enantioselectivity was still very poor (Entries 2–5). To our delight, the enantioselectivity could be significantly improved with further increase in the size of the substituent at the 3,3′-positions. The reaction catalyzed by **3f** with two triphenylsilyl substituents gave an *ee* value of 67% of **4a**(Entry 6). However, the phosphoric acids with other bulky substituents were not so efficient for the reaction (Entry 7 and 8). Catalyst **3i**, derived from octahydro-(*R*)-BINOL, could not induce good enantioselectivity either (Entry 9). These results showed that **3f** is a suitable catalyst for this asymmetric fluoroalkylation.

Table 1. Screening of reaction conditions.[a]





3a: R^1 = H
3b: R^1 = 3,5-$(CF_3)_2$-C_6H_3
3c: R^1 = 2-Naphthyl
3d: R^1 = 4-$NO_2C_6H_4$
3e: R^1 = 4-(2-Naphthyl)C_6H_4
3f: R^1 = $SiPh_3$
3g: R^1 = 2,4,6-(*i*Pr)$_3$-C_6H_2
3h: R^1 = 9-Anthryl
3i: R^1 = 4-ClC_6H_4 [H_8]

Entry	Catalyst	Solvent	Time [d]	Yield [%][b]	*ee* [%][c]
1	**3a**	CH_2Cl_2	3	85	1
2	**3b**	CH_2Cl_2	2.5	93	1
3	**3c**	CH_2Cl_2	1	83	21
4	**3d**	CH_2Cl_2	3	89	25
5	**3e**	CH_2Cl_2	2	89	13
6	**3f**	CH_2Cl_2	3.5	93	67
7	**3g**	CH_2Cl_2	3	81	27
8	**3h**	CH_2Cl_2	4.5	78	7
9	**3i**	CH_2Cl_2	2.5	94	9
10	**3f**	$CHCl_3$	2.5	78	46
11	**3f**	$ClCH_2CH_2Cl$	2.5	85	71
12	**3f**	$ClCH_2CH_2Cl/C_6H_6$[d]	1.5	93	73
13	**3f**	PhMe	2	93	73
14	**3f**	THF	2	trace	–
15	**3f**	$ClCH_2CH_2Cl/C_6H_6$[d,e]	1	94	50
16	**3f**	PhMe[e]	1	93	51
17	**3f**	CH_2Cl_2[f]	1	93	39
18	**3f**	$ClCH_2CH_2Cl/C_6H_6$[d,g]	6	93	83
19	**3f**	$ClCH_2CH_2Cl/C_6H_6$[d,g,h]	5	93	85

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol) and catalyst **3** in solvent (1 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] $ClCH_2CH_2Cl/C_6H_6$ (0.6 mL/0.6 mL) were used. [e] 3-Å MS (10 mg) was used. [f] 4-Å MS (10 mg) was used. [g] The starting materials were mixed at –35 °C, and the reaction proceeded at –5 °C. [h] 20 mol-% catalyst was used.

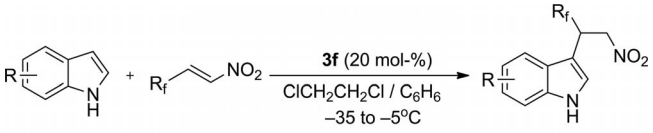
Suitable solvents were then also screened in the presence of **3f** (Table 1, Entries 10–14). The *ee* value was slightly improved when the reaction was conducted in a mixture of $ClCH_2CH_2Cl/C_6H_6$ or toluene. However, in $ClCH_2CH_2Cl/C_6H_6$, a shorter reaction time was needed than that in toluene. Therefore, a mixture of $ClCH_2CH_2Cl/C_6H_6$ was chosen as the optimal solvent.

Both Akiyama[1e] and You[8,9] found that the addition of molecular sieves is of great importance in chiral phosphoric acid catalyzed Friedel–Crafts reactions. Therefore, we examined the effect of molecular sieves on this fluoroalkylation (Table 1, Entries 15–17). In contrast to their results, we found that the presence of molecular sieves decreases the *ee* substantially, even though the reaction time was shortened.

It was found that the reaction of **1a** with **2a** proceeded smoothly at room temperature without any catalyst or solvent. It might be probable to obtain a higher *ee* by lowering the reaction temperature. The starting materials were mixed at –35 °C. The reaction mixture was then warmed to –5 °C and stirred at this temperature until completion of the reaction (Entries 18 and 19). As expected, the *ee* increased (Entry 18), but the reaction time became longer; therefore further lowering of the temperature is not necessary. In an attempt to shorten the reaction time, 20 mol-% catalyst was used (Entry 19). As can be seen, the reaction time was shortened and a higher *ee* was obtained. Therefore, 20 mol-% of **3f** as catalyst, $ClCH_2CH_2Cl/C_6H_6$ as the solvent, and –5 °C were considered to be the most suitable reaction conditions.

A series of indoles and fluoroalkyl nitroalkenes were then subjected to these optimal reaction conditions. As summarized in Table 2, the reactions of indole with fluoroalkylated 1-nitroprop-1-ene proceeded smoothly to give the desired products with good yields and enantioselectivities (Entries 1–4). The introduction of bulky groups such as $PhCF_2$ or 4-MeO$PhCF_2$ into nitroalkene had no effect on the regioselectivities, but resulted in lower yields and *ee* values (En-

Table 2. Asymmetric Friedel–Crafts reactions of indoles with fluoroalkylated nitroalkenes, catalyzed by chiral phosphoric acid.[a]



Entry	R	R_f	Time [d]	**4**, yield [%][b]	*ee* [%][c]
1	H	CF_3	5	**4a**, 93	85
2	H	CF_2Cl	3.5	**4b**, 92	77
3	H	CF_2Br	4.5	**4c**, 89	84
4	H	CF_2H	6	**4d**, 98	82
5	H	$PhCF_2$	9	**4e**, 78	79
6	H	4-$MeOC_6H_4CF_2$	10	**4f**, 70	75
7	4-Cl	CF_3	5	**4g**, trace	–
8	5-MeO	CF_3	4	**4h**, 97	86
9	6-Me	CF_3	3	**4i**, 90	89
10	4-MeO	CF_2Br	6	**4j**, 88	76
11	5-MeO	CF_2Br	2.5	**4k**, 98	87
12	6-Me	CF_2Br	2.5	**4l**, 90	89

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol) and catalyst **3f** (20 mol-%) in $ClCH_2CH_2Cl/C_6H_6$ (1.2 mL/1.2 mL) at –5 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

tries 5 and 6). This indicates that the steric hindrance of nitroalkene influences the yield and selectivity. In the case of 4-chlorinated indole, only trace amounts of product were detected by TLC (Entry 7). The presence of chlorine leads to an electron deficiency of indole, which results in low reactivity of indole toward nitroalkenes. When this procedure was applied to other indoles with electron-donating groups, good yields and enantioselectivities were obtained again (Entries 8–12).

As shown in Figure 1, a transition state is proposed. Chiral phosphoric acid acts as a bifunctional catalyst, which activates both the nucleophile and electrophile by hydrogen bonding. To support this hypothesis, further evidence has been collected (Scheme 2). It was found that the absence of a hydrogen atom on the nitrogen atom or the presence of a methyl group at the 2-postion of indole decreases the enantioselectivity greatly under the same reaction conditions. Hence, the N–H moiety is responsible for the formation of hydrogen bonds. The presence of the methyl group at the 2-position of indole might block the formation of hydrogen bonding as a result of steric hindrance.

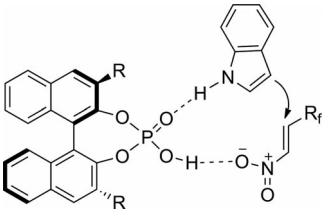
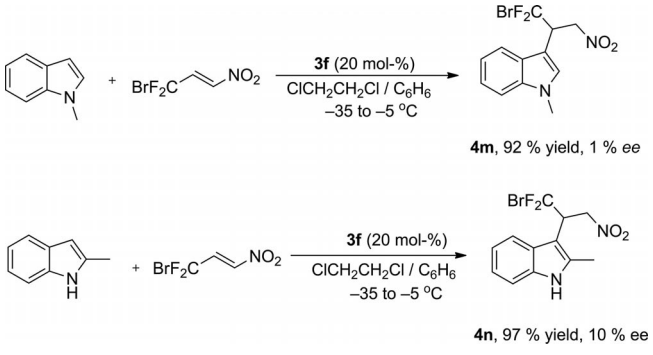


Figure 1. Proposed transition state.



Scheme 2.

Conclusions

An enantioselective Friedel–Crafts fluoroalkylation of indoles catalyzed by chiral phosphoric acid has been described. The CF_3– or –CF_2– containing stereogenicity could conveniently be constructed therewith. The carbon atom adjacent to the –CF_2– group of the nitroalkenes is more reactive than that adjacent to the NO_2 group. This procedure provides a versatile platform for the asymmetrical synthesis of fluoroalkyl compounds. Studies to apply the chiral phosphoric acid to other fluoroalkylations are currently underway.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker AM-300 (300 MHz) or Varian VXR (300 MHz) spectrometer. ^{19}F NMR spectra were recorded with a Bruker AM-300 (282 MHz) with $CFCl_3$ as an external standard (negative for upfield). ^{13}C NMR spectra were recorded with a Bruker AM-400 (100 MHz) spectrometer. MS was recorded with a Hewlett–Packard HP-5989A spectrometer. Elemental analyses were obtained with a Perkin–Elmer 2400 Series II Elemental Analyzer. Infrared spectra were measured with a Perkin–Elmer 983 spectrometer. Optical rotations were measured on a JASCO $P\bar{1}030$ Polarimeter at λ = 589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on a Waters 515 instrument (2487 dual λ absorbance detector and a 515 HPLC pump) by using a chiral column. Unless otherwise noted, reagents were commercially available and used as received.

Typical Procedure for the Asymmetric Friedel–Crafts Reactions: Under N_2 atmosphere, the solution of indole (23.4 mg, 0.2 mol) and chiral phosphoric acid **3f** (34.3 mg, 0.04 mmol) in $ClCH_2CH_2Cl/C_6H_6$ (0.6 mL/0.6 mL) was cooled to 35 °C. The solution of 3,3,3-trifluoro-1-nitroprop-1-ene (56 mg, 0.4 mmol) in $ClCH_2CH_2Cl/C_6H_6$ (0.6 mL/0.6 mL) was then added slowly over 15 min. The resulting solution was warmed to –5 °C and stirred at this temperature until the reaction was complete as monitored by TLC.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of the fluoroalkylated nitroalkenes and for the asymmetric Friedel–Crafts reactions are presented. The ^{1}H NMR, ^{19}F NMR, ^{13}C NMR and HPLC spectra of the compounds are also given.

Acknowledgments

We thank the Chinese Academy of Sciences and the National Natural Science Foundation (20972179, 21032006) for financial support.

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Received: May 15, 2011
Published Online: July 12, 2011

