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Enantioselective Friedel−Crafts Reaction of Electron-Rich Alkenes Catalyzed by Chiral Brønsted Acid

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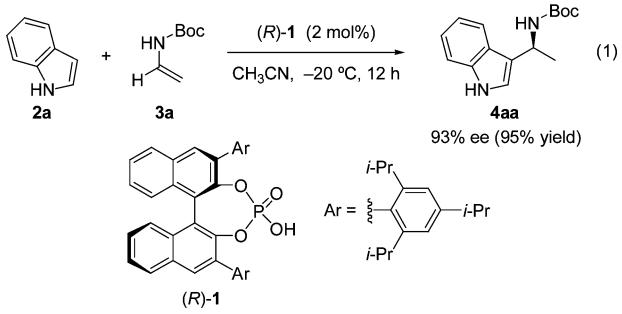
The Friedel−Crafts (F−C) reaction is one of the most powerful methods for the formation of a new carbon−carbon bond and has been widely utilized from benchtop experiments to industrial processes.[1] Enantioselective variants of this fundamental transformation have also been investigated using metal-based chiral complex catalysts[2] or chiral organocatalysts.[3] These enantioselective catalyses have been accomplished via activation of electron deficient multiple bonds, such as C═O, C═NR, and C═C−X (X: electron-withdrawing group), etc. Acid-catalyzed F−C reactions of arenes with electron-rich alkenes are practical and atom-economical methods for providing alkylated arenes and have been applied to numerous industrial processes. However, to the best of our knowledge, there have been no previous reports on enantioselective catalysis of the F−C reaction initiated by an activation of electron-rich multiple bonds. Herein we describe the first highly enantioselective F−C reaction of electron-rich alkenes activated by a chiral Brønsted acid catalyst.[4−6] Thus, a BINOL-derived monophosphoric acid (**1**)[5,6] exhibited excellent performance for this activation mode, in which the catalytic reaction of indoles (**2**) with enecarbamates (**3**) as the electron-rich alkenes yielded the desired F−C products (**4**) in high enantioselectivities as exemplified in eq 1.[7] The method provides easy and practical access to enantioenriched 1-indolyl-1-alkylamine derivatives of pharmaceutical and biological importance.



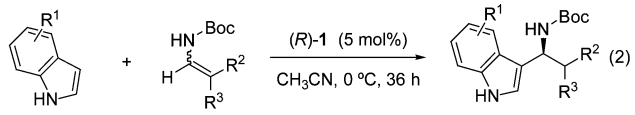
The proposed enantioselective F−C reaction was first examined using indole (**2a**), *N*-Boc protected enamine (**3a**), and 2 mol % of (*R*)-**1** at room temperature in various organic solvents. As shown in Table 1, it is noteworthy that not only the catalytic activity but also the asymmetric induction were highly dependent on the solvents employed. The less polar aromatic solvent, toluene, was useful for a chiral monophosphoric acid-catalyzed F−C reaction via the activation of electron deficient double bond, C═NR,[5b] but in this activation mode **1** suffered from a marked retardation in the catalytic activity (entry 1). Whereas, in the more polar aromatic solvent $PhCF_3$, **1** exhibited high catalytic efficiency affording the F−C product (**4aa**) in high chemical yield without notable loss of enantiomeric excess (entry 2). Halogenated solvents possessing a similar polarity[8] to $PhCF_3$ were also tolerated by the reaction (entries 3, 4). However, either the chemical yields or the enantioselectivities were seriously diminished in highly polar and protophilic solvents[9] such as DMF and DMSO (entries 5, 6). Among the solvents tested, the highly polar but protophobic acetonitrile[9] was found to be the best with respect to the catalytic activity and the asymmetric induction (entry 8). As expected, enantiomeric excess increased with a decrease in reaction temperature, reaching 93% ee at −20 °C (entries 9, 10).

Table 1. Solvent Effect on the Enantioselective Friedel−Crafts Reaction of **2a** with **3a** Catalyzed by **1** (eq 1)[a]

entry	solvent	time	yield (%)	ee (%)[b]
1	toluene	3 h	26	80
2	$PhCF_3$	3 h	91	79
3	CH_2Cl_2	3 h	84	84
4	$(CH_2Cl)_2$	3 h	83	83
5	DMF	24 h	17	54
6	DMSO	24 h	22	10
7	CH_3NO_2	3 h	93	87
8	CH_3CN	3 h	84	88
9[c]	CH_3CN	6 h	85	91
10[d]	CH_3CN	12 h	95	93

[a] Unless otherwise noted, all reactions were carried out with 0.002 mmol of (*R*)-**1** (2 mol %), 0.11 mmol of **2a**, and 0.10 mmol of **3a** in 0.5 mL of the indicated solvent at room temperature. [b] Enantiomeric excess was determined by chiral HPLC analysis. See Supporting Information for details. [c] Reaction run at 0 °C. [d] Reaction run at −20 °C.

In order to demonstrate the scope and potential of the present enantioselective F−C reaction, we next examined a series of indole derivatives (**2**) and substituted enecarbamates (**3**) (eq 2).



2b: R^1 = 5-MeO
c: R^1 = 5-Me
d: R^1 = 5-Br
e: R^1 = 6-Br
f: R^1 = 5-CO_2Me

3b: R^2 = H, R^3 = Me (>99% *E*)
c: R^2 = H, R^3 = *n*-Bu (1:1 *E*/*Z* mixture)
d: R^2 = H, R^3 = Bn (1:1 *E*/*Z* mixture)
e: R^2 = H, R^3 = *i*-Pr (1:1 *E*/*Z* mixture)
f: R^2 = H, R^3 = Ph (>99% *E*)
g: R^2, R^3 = Me

Representative results are summarized in Table 2. The acid catalyst **1** displayed excellent performance for the reaction of various indole derivatives (**2**) with a broad range of substituted enecarbamates (**3**). Uniformly high enantioselectivities and chemical yields were obtained in the reaction of indole (**2a**) with **3** bearing a linear or a branched alkyl group as well as an aromatic substituent (entries 1−5). In addition, the sterically hindered disubstituted enecarbamate (**3g**) was also applicable for the present enantioselective F−C reaction (entry 6). Moreover, the enantioselectivities were maintained at an equally high level for a wide variety of indole derivatives (**2**), irrespective of their electronic properties (entries 7−11). It is noteworthy that the present catalytic system allows for the reaction of indoles (**2d**−**f**) substituted by electron-withdrawing groups affording the F−C product in high yield (entries 9−11).

As shown in eq 3, the geometric isomers (*E*)-**3b** and (*Z*)-**3b** gave the product (**4ab**) with the same level of enantioselectivitiy.

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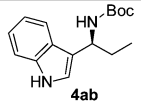
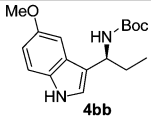
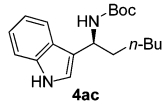
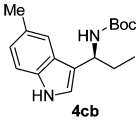
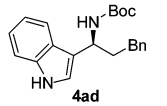
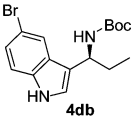
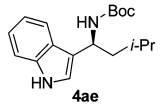
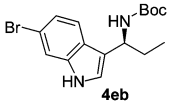
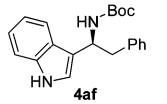
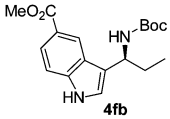
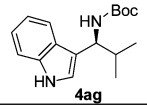
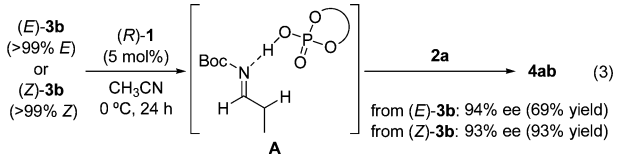
Table 2. Enantioselective Freidel−Crafts Reaction of Indole Derivatives (**2**) with Substituted Enecarbamates (**3**) Catalyzed by (*R*)-**1**[a]

entry	4	yield[b] ee[c]	entry	4	yield[b] ee[c]
1	 **4ab**	87% 94% ee	7	 **4bb**	90% 90% ee
2	 **4ac**	98% 94% ee	8	 **4cb**	84% 93% ee
3[d]	 **4ad**	82% 93% ee	9	 **4db**	91% 93% ee
4	 **4ae**	80% 91% ee	10	 **4eb**	78% 96% ee
5[e,f]	 **4af**	63% 90% ee	11[i]	 **4fb**	86% 93% ee
6[e,g]	 **4ag**	69% 94% ee[h]			

[a] Unless otherwise noted, all reactions were carried out with 0.005 mmol of (*R*)-**1** (5 mol %), 0.11 mmol of **2**, and 0.10 mmol of **3** in 0.5 mL of CH_3CN at 0 °C for 36 h. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Reaction run at room temperature for 48 h. [e] The reactions were conducted using 0.005 mmol of (*R*)-**1** (5 mol %), 0.10 mmol of **2a**, and 0.15 mmol of **3**. [f] Reaction run at 50 °C for 48 h. [g] Reaction run at 50 °C for 20 h. [h] Absolute configuration was determined to be *S* for **4ag**. See Supporting Information for details. [i] Reaction run at room temperature for 6 h.



(3)

These results suggest that both reactions proceeded through the common intermediate (**A**), composed of **1** and an imine, as it was generated by the protonation of enecarbamates **3b**. Hence the present activation mode is regarded as an efficient alternative to generating aliphatic imines,[10] which are generally labile and difficult to isolate.[11] Furthermore, the reaction rate was dependent on the geometry of the enecarbamate employed; (*Z*)-**3b** showed higher reactivity than (*E*)-**3b**. It can be considered that the protonation of **3** by **1** via ionic transition states would be the rate-determining step. This mechanistic assumption is strongly supported by the solvent effect, in which a high catalytic efficiency was observed in a highly polar but protophobic solvent.

In conclusion, we have demonstrated the first enantioselective Friedel−Crafts reaction catalyzed by a chiral monophosphoric acid via activation of electron-rich alkenes. Further application of the present method, a practical protocol for in situ generation of aliphatic imines, is in progress with the aim of developing efficient asymmetric organic transformations.

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Supporting Information Available: Representative experimental procedure, spectroscopic data for enecarbamates (**3**) and Friedel−Crafts products (**4**), and determination of absolute stereochemistry of **4ag**. This material is available free of charge via the Internet at http://pubs.acs.org.

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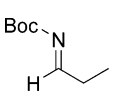
(10) During the preparation of this manuscript, Kobayashi, et al. reported the metal salt-catalyzed Mannich reaction of 1,3-dicarbonyl compounds with enecarbamates as an aliphatic imine surrogate, see: Kobayashi, S.; Gustafsson, T.; Shimizu, Y.; Kiyohara, H.; Matsubara, R. *Org. Lett.* **2006**, *8*, 4923−4925.

(11) Imine (**5**) was completely isomerized to enecarbamate (**3b**) during distillation, and hence it can be considered that enecarbamates (**3**) serve as stable and useful precursors of aliphatic imines in the present activation mode.



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