

Chiral Brønsted Acid Catalyzed Enantioselective Friedel–Crafts Reaction of Indoles and α -Aryl Enamides: Construction of Quaternary Carbon Atoms**

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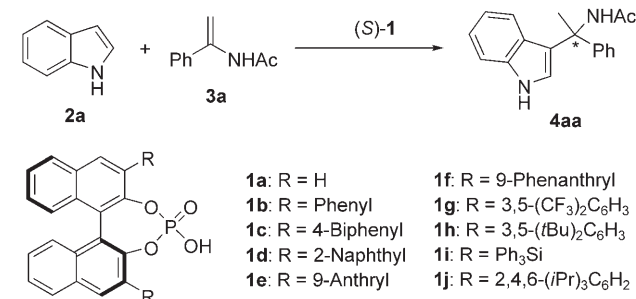
The asymmetric construction of a stereogenic carbon center with four non-hydrogen substituents, that is, a quaternary carbon atom, represents one of the most challenging and demanding topics in the synthesis of natural products and chiral drugs.^[1] The construction of quaternary carbon centers bearing a nitrogen atom, which is a fairly ubiquitous structure in natural alkaloids,^[2] has drawn increasing attention and several catalytic asymmetric procedures have been successfully developed.^[3] The catalytic asymmetric Friedel–Crafts reaction has attracted much attention over the past decades as a versatile C–C bond-forming process, and great progress has been reported.^[4] However, to the best of our knowledge, no efficient method has been reported for the creation of a nitrogen-containing quaternary carbon center by using the asymmetric Friedel–Crafts reaction.^[5] Herein, we describe an enantioselective Friedel–Crafts reaction of indoles (**2**) with α -aryl enamides **3** catalyzed by chiral Brønsted acids **1**^[6] to provide chiral tertiary amines **4** with a quaternary carbon center in excellent yields and high enantioselectivities (Scheme 1).^[7] It is noteworthy that while the enamides have

generally been used as nucleophiles in acid-catalyzed reactions,^[8] the α -aryl enamides **3** have played the role of the electrophile in the reaction with indoles.^[9]

The initial reaction of indole (**2a**) and α -phenyl enamide (**3a**) was performed at room temperature in dichloromethane in the presence of 10 mol % of the chiral binol-based phosphoric acid **1a** as the catalyst (binol = 2,2'-dihydroxy-1,1'-binaphthyl). The Friedel–Crafts product, *N*-(1-(3-indolyl)-1-phenylethyl)acetamide (**4aa**) was obtained in 74 % yield but with almost no enantioselectivity (Table 1,

Table 1: Chiral Brønsted acid catalyzed asymmetric Friedel–Crafts reaction of **2a** and **3a**.^[a]

Entry	Catalyst	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1a	CH ₂ Cl ₂	3	74	4
2	1b	CH ₂ Cl ₂	3	79	32
3	1c	CH ₂ Cl ₂	3	84	35
4	1d	CH ₂ Cl ₂	3	87	10
5	1e	CH ₂ Cl ₂	6	52	66
6	1f	CH ₂ Cl ₂	6	54	22
7	1g	CH ₂ Cl ₂	6	72	38
8	1h	CH ₂ Cl ₂	6	78	72
9	1i	CH ₂ Cl ₂	6	58	25
10	1j	CH ₂ Cl ₂	6	64	91
11 ^[d]	1j	CH ₂ Cl ₂	6	90	91
12 ^[d]	1j	DCE	6	90	91
13 ^[d]	1j	benzene	6	97	92
14 ^[d]	1j	toluene	6	99	92
15 ^[d]	1j	xylene	6	99	91
16 ^[d,e]	1j	toluene	14	99	91
17 ^[d,f]	1j	toluene	40	98	94
18 ^[d]	1j	<i>t</i> BuOMe	14	n.r. ^[g]	–
19 ^[d]	1j	THF	14	n.r.	–
20 ^[d]	1j	dioxane	14	n.r.	–



Scheme 1. Asymmetric Friedel–Crafts reaction of indole (**2a**) and *N*-(1-phenylvinyl)acetamide (**3a**) catalyzed by a chiral Brønsted acid.

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[a] Unless otherwise noted, all reactions were performed with 0.14 mmol of **2a**, 0.10 mmol of **3a**, 0.01 mmol of **1** in 1.5 mL solvents at RT. [b] Yield of isolated product. [c] Determined by chiral HPLC on a Chiralpak AD-H column. [d] 90 mg of 4-Å molecular sieves were added. [e] 5 mol % catalyst was used. [f] The reaction was performed at 0 °C. [g] No reaction.

entry 1). We then concentrated on the modification of the structure of the chiral phosphoric acid catalyst. A series of chiral phosphoric acids **1** with different substituents at the 3,3'-positions of the binaphthyl ring were prepared and tested in the reaction of indole (**2a**) and α -phenyl enamide (**3a**). The sterically congested phosphoric acid catalysts were found to be crucial for achieving high enantioselectivity, with the catalyst **1j** bearing bulky 2,4,6-trisopropylphenyl groups at

the 3,3'-positions being the most enantioselective (91% *ee*, entry 10). The yield of the Friedel–Crafts product was only moderate (64%) because of hydrolysis of the enamide substrate. This hydrolysis was prevented when 4-Å molecular sieves were added, and the yield was remarkably improved from 64% to 90% without diminishing the enantioselectivity (entry 11). The reaction could also be performed in CH₂ClCH₂Cl (DCE), benzene, toluene, and xylene to give the desired product in high yields and high enantioselectivities (entries 12–15). However, the reaction was fully prohibited in coordinating solvents such as *t*BuOCH₃, THF, and dioxane (entries 18–20). Decreasing the reaction temperature to 0°C slightly enhanced the enantioselectivity to 94% *ee*, but a longer reaction time was needed (entry 17).

A wide array of indole derivatives **2** and α -aryl enamides **3** were investigated in the asymmetric Friedel–Crafts reaction in the presence of catalyst **1j** under the optimal reaction conditions (Table 2). All the substituted α -aryl enamides and

tioselectivity of the reaction. For example, the reaction of 2-methoxy-substituted α -aryl enamide **3j** needed 3 days at 25°C to generate the Friedel–Crafts product in only 73% *ee* value (Table 2, entry 10). The reaction of the enamide **3k** with a 2-chloro substituent under the same conditions gave only a trace amount of the Friedel–Crafts product (Table 2, entry 11). Besides the substituted α -phenyl enamides, the naphthyl enamide **3l** also gave the asymmetric Friedel–Crafts product in high yield and enantioselectivity (Table 2, entry 12). Treatment of indole with *N*-(1-phenyl-propenyl)acetamide or *N*-(1-*tert*-butyl-vinyl)acetamide gave no reaction, even at 80°C. Various substituted indoles have also been investigated in the Friedel–Crafts reaction with α -phenyl enamide. The corresponding tertiary amine products were obtained in excellent yields with high enantiomeric excess (Table 2, entries 13–15).

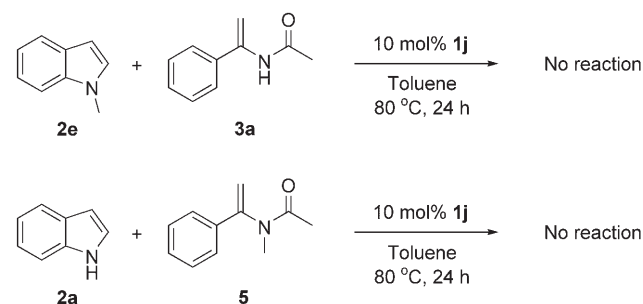
When *N*-methylindole (**2e**) and *N*-methyl enamide **5** were prepared and treated with enamide **3a** and indole, respectively, no reaction was observed (Scheme 2), thereby demon-

Table 2: Chiral Brønsted acid catalyzed asymmetric Friedel–Crafts reaction of indoles **2** and enamides **3**.^[a]

Entry	R ¹	Ar	Product (%)	<i>ee</i> [%] ^[b]
1	H (2a)	C ₆ H ₅ (3a)	4aa (98)	94
2	H (2a)	4-MeC ₆ H ₄ (3b)	4ab (99)	92
3	H (2a)	4-MeOC ₆ H ₄ (3c)	4ac (94)	90
4	H (2a)	4-BrC ₆ H ₄ (3d)	4ad (98)	92 (S) ^[c]
5	H (2a)	4-CF ₃ C ₆ H ₄ (3e)	4ae (98)	93
6	H (2a)	3-MeC ₆ H ₄ (3f)	4af (97)	90
7	H (2a)	3-MeOC ₆ H ₄ (3g)	4ag (99)	97
8	H (2a)	3-ClC ₆ H ₄ (3h)	4ah (99)	92
9	H (2a)	3,4-Me ₂ C ₆ H ₄ (3i)	4ai (99)	95
10 ^[d]	H (2a)	2-MeOC ₆ H ₄ (3j)	4aj (95)	73
11 ^[d]	H (2a)	2-ClC ₆ H ₄ (3k)	4ak (trace)	31
12	H (2a)	2-naphthyl (3l)	4al (95)	92
13	4-OH (2b)	C ₆ H ₅ (3a)	4ba (95)	86
14	5-Br (2c)	C ₆ H ₅ (3a)	4ca (98)	90
15	5-MeO (2d)	C ₆ H ₅ (3a)	4da (99)	92

[a] The reaction conditions were the same as those in Table 1, entry 17, at 0–25°C, 6–48 h. [b] For analysis of the *ee* values of the products, see the Supporting Information. [c] Absolute configuration determined by single-crystal X-ray diffraction analysis. [d] At 25°C for 3 days.

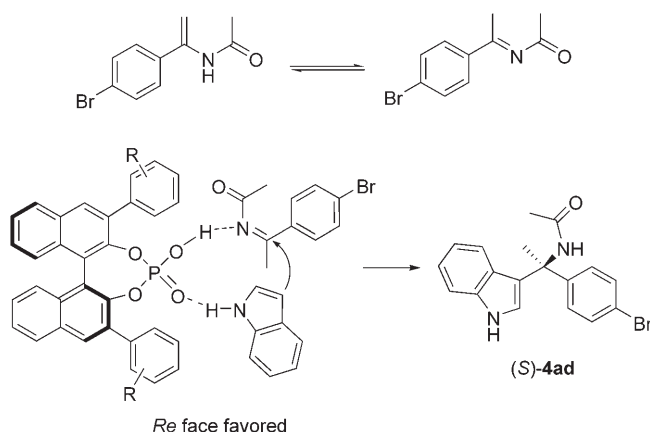
indole derivatives underwent the Friedel–Crafts reaction smoothly to give the corresponding products in excellent yields. The α -aryl enamides with either an electron-donating or -withdrawing substituent at the *meta* or *para* position gave high enantioselectivities, thus showing that the electronic nature of the substituents in the enamide substrates has very little effect on the enantioselectivity (Table 2, entries 1–9). However, by contrast, *ortho* substituents in the α -aryl enamides strongly diminished both the reactivity and enan-



Scheme 2. Chiral phosphoric acid catalyzed Friedel–Crafts reactions of *N*-methylindole (**2e**) and *N*-methylated enamide (**5**).

strating that the hydrogen atoms on the N atoms of both the indole and enamide moieties are crucial for the activation of the reactants by phosphoric acid catalysts **1** in this Friedel–Crafts reaction. A proposed reaction model calls for the chiral phosphoric acid catalyst to activate the indole and enamide moieties through two hydrogen bonds. The enamide forms an equilibrium with the corresponding ketimine, which is protonated and activated by the chiral phosphoric acid to accept the nucleophilic attack of the indole. The failure of the reaction of the *N*-methylated enamide **5** with indole is consistent with this mechanism, as the enamide **5** can not be converted into its imine version.^[10] The fact that *N*-methylindole (**2e**) gives no reaction supports the necessary existence of the hydrogen bond between the N–H atom of the indole and the phosphoric acid. The indole attacks the ketimine from the *Re* face, thereby affording the Friedel–Crafts product with an *S* configuration (Scheme 3), which was confirmed by X-ray measurement of a single crystal of product **4ad** (Figure 1).^[11]

In summary, we have developed an asymmetric Friedel–Crafts reaction of indoles with α -aryl enamides catalyzed by chiral phosphoric acids that provides simple and direct access to chiral amines with a quaternary carbon atom in high



Scheme 3. Proposed reaction model.

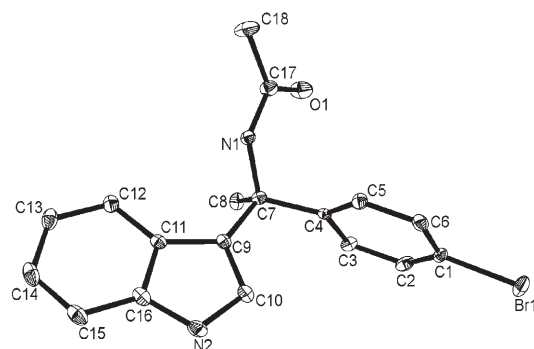


Figure 1. X-ray structure of (S)-4ad.

enantioselectivities. Further applications of the present enantioselective protocol to other reactions are in progress.

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- [1] For reviews, see a) K. Fuji, *Chem. Rev.* **1993**, 93, 2037; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, 110, 402; *Angew. Chem. Int. Ed.* **1998**, 37, 388; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, 113, 4725; *Angew. Chem. Int. Ed.* **2001**, 40, 4591.
- [2] a) Y. Ohfuné, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127; b) G. A. Cordell in *The Alkaloids: Chemistry and Biology*, Vol. 60, Elsevier, San Diego, **2003**; c) D. J. Ramon, M. Yus, *Curr. Org. Chem.* **2004**, 8, 149; d) J. Kobayashi, H. Morita, *Alkaloids* **2003**, 60, 165; e) I. Moldvai, E. Temesvári-Major, M. Incze, G. Döörnyei, É. Szentirmay, C. Szántay, *Helv. Chim. Acta* **2005**, 88, 1344.
- [3] a) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, 120, 11532; b) M. Chavarot, J. J. Byrne, P. Y. Chavant, Y. Vallee, *Tetrahedron: Asymmetry* **2001**, 12, 1147; c) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, 124, 10012; d) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 5634; e) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, 125, 13368; f) X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, 7, 167; g) D. Ikeda, M. Kawatsura, J. Uenishi, *Tetrahedron Lett.* **2005**, 46, 6663; h) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, 128, 7687; i) H. Miyabe, Y. Yamaoka, Y. Takemoto, *J. Org. Chem.* **2006**, 71, 2099.
- [4] For representative organo-catalyzed asymmetric Friedel–Crafts reactions, see a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, 123, 4370; b) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 11804; c) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, 117, 6734; *Angew. Chem. Int. Ed.* **2005**, 44, 6576; d) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, 128, 8156; e) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, 129, 1484; for representative metal-catalyzed asymmetric Friedel–Crafts reactions, see f) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, 116, 560; *Angew. Chem. Int. Ed.* **2004**, 43, 550, and references therein; g) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia, A. Linden, *J. Am. Chem. Soc.* **2005**, 127, 4154; h) D. A. Evans, K. A. Fandric, H.-J. Song, *J. Am. Chem. Soc.* **2005**, 127, 8942; i) Y.-X. Jia, Y. Yang, S.-F. Zhu, Q.-L. Zhou, *J. Org. Chem.* **2006**, 71, 75; j) Y.-X. Jia, J.-H. Xie, H.-F. Duan, L.-X. Wang, Q.-L. Zhou, *Org. Lett.* **2006**, 8, 1621.
- [5] For the construction of oxygen-containing quaternary carbon centers by using the asymmetric Friedel–Crafts reaction, see a) W. Zhuang, N. Gathergood, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2001**, 66, 1009; b) M. P. A. Lyle, N. D. Draper, P. D. Wilson, *Org. Lett.* **2005**, 7, 901; c) B. Török, M. Abid, G. London, J. Esquivel, M. Torok, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem.* **2005**, 117, 3146; *Angew. Chem. Int. Ed.* **2005**, 44, 3086; d) H. Li, Y.-Q. Wang, L. Deng, *Org. Lett.* **2006**, 8, 4063.
- [6] For applications of chiral Brønsted acids in other asymmetric transformations, see a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, 116, 1592; *Angew. Chem. Int. Ed.* **2004**, 43, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 5356; c) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, 117, 7590; *Angew. Chem. Int. Ed.* **2005**, 44, 7424; d) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, 128, 84; e) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, 128, 1086; f) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, 118, 2679; *Angew. Chem. Int. Ed.* **2006**, 45, 2617; g) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, 118, 4914; *Angew. Chem. Int. Ed.* **2006**, 45, 4796; h) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, 128, 9626; i) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, 128, 13070; j) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, 128, 14802.
- [7] During the preparation of this manuscript, an asymmetric Friedel–Crafts reaction of indoles with *N*-vinyl carbamates to form chiral secondary amines in high enantioselectivities was reported, see M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, 129, 292.
- [8] a) R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem.* **2004**, 116, 1711; *Angew. Chem. Int. Ed.* **2004**, 43, 1679; b) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, 118, 2312; *Angew. Chem. Int. Ed.* **2006**, 45, 2254.
- [9] For other examples where enamides functioned as electrophiles, see S. Kobayashi, T. Gustafsson, Y. Shimizu, H. Kiyohara, R. Matsubara, *Org. Lett.* **2006**, 8, 4923 and Ref. [7].
- [10] The models involving imine intermediates were reported by Kobayashi et al. in Lewis acid catalyzed Mannich-type reactions of 1,3-dicarbonyl compounds with enecarbamates (Ref. [9]) and Terada and Sorimachi in asymmetric Friedel–Crafts reactions of indoles with *N*-vinyl carbamates (Ref. [7]).
- [11] CCDC-284174 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.