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Highly Enantioselective Friedel−Crafts Reaction of Indoles with Imines by a Chiral Phosphoric Acid

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The use of small organic molecules as catalysts, so-called organocatalysts, to promote asymmetric reactions has emerged as a new frontier in synthetic organic chemistry.[1] Among numerous chiral organocatalysts reported, chiral phosphoric acids **1**, pioneered by Akiyama et al. and Terada et al.,[2] have recently received considerable attention and have been applied in a wide range of asymmetric organic transformations (Figure 1).[3,4] Further extension of reaction types catalyzed by chiral phosphoric acid remains the focus in this field. The asymmetric Friedel−Crafts reaction of indoles with imines is an important reaction to which chiral phosphoric acid organocatalysts can be applied. The products of this reaction provide easy access to the synthesis of enantiopure 3-indolyl methanamine derivatives.[5] The latter exist in numerous natural and unnatural products with significant biological activities.[6] An efficient, organocatalytic approach to 3-indolyl methanamine is extremely desirable. Recently, Deng and co-workers applied bifunctional organocatalysts to the asymmetric Friedel−Crafts reaction of indoles with imines, affording the 3-indolyl methanamine derivatives with up to 97% ee.[7] In our recent studies on applications of chiral phosphoric acids to asymmetric catalysis, we found that chiral phosphoric acids are efficient organocatalysts for the Friedel−Crafts reactions of indoles with imines. The reactions proceed to completion within hours for most of the substrates, affording the 3-indolyl methanamine derivatives with up to >99% ee. In this communication, we report our preliminary results.[8]

We first examined the reaction between indole **2a** and imine **3a** catalyzed by phosphoric acid **1d**. In the presence of 10 mol % of **1d** in toluene at room temperature, reaction of **3a** with equimolar **2a** gave the desired product **4a** in 59% yield with 67% ee (for details, see Supporting Information), along with a bisindole addition byproduct (5% yield). When we increased the amount of indole, the reaction proceeded faster and led to the product with a slightly higher enantioselectivity. When 5 equiv of indole was used, an optimal result was obtained in terms of both the yield and enantioselectivity of **4a** (80% yield, 83% ee, entry 4, Table 1). Under these reaction conditions, several phosphoric acids with varying substituents at the 3- and 3′-positions of the binaphthyl scaffold were tested, and the results are listed in Table 1. The simplest catalyst **1a** could catalyze the reaction smoothly (85% yield) but afforded a racemic product (entry 1, Table 1). The product was obtained with 73% ee when phosphoric acid **1b** was used (entry 2, Table 1). Surprisingly, phosphoric acid **1c**, with a very bulky triphenylsilyl substituent, only afforded the product with moderate enantioselectivity, 73% ee (entry 3, Table 1). We are very delighted to find that high enantioselectivities of 92 and 93% ee could be obtained using phosphoric acids **1e** and **1f**, respectively, as the catalysts. It should be noted that the reaction was complete in 10 min in the presence of 10 mol % of **1e** or **1f**.

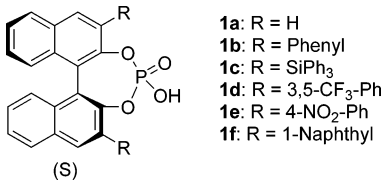
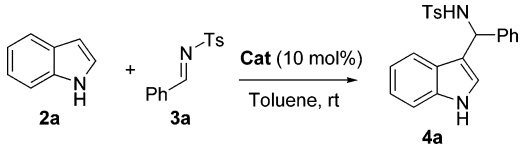


Figure 1. Chiral phosphoric acids.

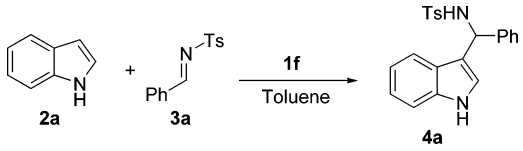
Table 1. Screening of the Phosphoric Acid Catalysts



entry[a]	cat	time	yield (%)[b]	ee (%)[c]
1	**1a**	4 h	85	0
2	**1b**	14 h	60	73
3	**1c**	4 h	69	73
4	**1d**	30 min	80	83
5	**1e**	10 min	66	92
6	**1f**	10 min	78	93

[a] Reaction conditions: 10 mol % of catalyst, 5 equiv of **2a**, 0.25 mol/L of **3a** in toluene at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD−H).

Table 2. Investigation of the Reaction Temperature and Catalyst Loadings



entry[a]	**1f** (mol %)	temp	time	yield (%)[b]	ee (%)[c]
1	10	rt	10 min	78	93
2	10	0 °C	10 min	80	95
3	10	−40 °C	10 min	75	97
4	10	−60 °C	30 min	83	98
5	10	−78 °C	2 h	81	98
6	5	−60 °C	1.5 h	83	96
7	2	−60 °C	10 h	72	75

[a] Reaction conditions: 5 equiv of **2a**, 0.25 mol/L of **3a** in toluene. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD−H).

We next investigated the effect of the reaction temperature and catalyst loading using catalyst **1f**. The results are summarized in Table 2.

In general, lowering the temperature resulted in a decrease of the reaction rate but an increase of the enantioselectivity. In the presence of 10 mol % of **1f**, 95 and 97% ee of **4a** was obtained at 0 and −40 °C, respectively (entries 2 and 3, Table 2). Up to 98% ee was attained when the reaction was run at −60 °C (entry 4,

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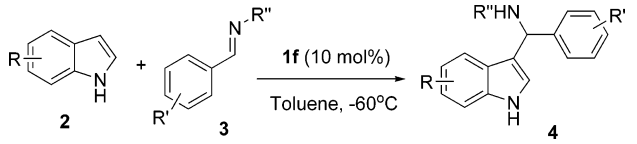
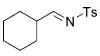
Table 3. Enantioselective Friedel−Crafts Reaction of Indoles with *N*-Sulfonyl Aldimines



entry[a]	2, R	3	time	yield (%)[b]	ee (%)[c]
1	**2a**, H	**3a**: R′ = H, R″ = Ts	30 min	83	98
2		**3b**: R′ = H, R″ = Bs	15 min	88	99
3	**2b**, 5-OMe	**3a**	20 min	87	97
4		**3b**	15 min	84	99
5	**2c**, 5-Me	**3a**	15 min	89	>99
6		**3b**	15 min	83	99
7	**2d**, 5-Br	**3a**	40 min	82	98
8		**3b**	40 min	89	>99
9	**2e**, 6-Cl	**3a**	2 h	68	98
10		**3b**	1.5 h	87	>99
11	**2a**, H	**3c**: R′ = 4-Me, R″ = Ts	10 min	93	>99
12	**2a**, H	**3d**: R′ = 3-NO_2, R″ = Ts	15 min	85	89
13[d]	**2a**, H	**3e**: R′ = 4-Cl, R″ = Ts	24 h	91	94
14[d,e]	**2a**, H	**3f**: R′ = 4-Br, R″ = Ts	24 h	71	82(*R*)
15[d,e]	**2a**, H	**3g**: R′ = 4-CF_3, R″ = Ts	14 h	83	85(*R*)
16	**2a**, H	**3h**: R′ = 3-OMe, R″ = Ts	1 h	90	96
17	**2a**, H	**3i**: R′ = 3-OMe, R″ = Bs	1 h	90	97
18	**2a**, H	**3j**: 	5 h	56	58
19[f]	**2a**, H	**3b**	40 min	94	>99

[a] Reaction conditions: 5 equiv of indole, 10 mol % of **1f**, −60 °C, 0.25 mol/L of **3** in toluene. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] **1d** (10 mol %) was used instead of **1f**. [e] Absolute configuration was determined by comparison of the optical rotation with the known compounds in the literature.[5a,7] [f] Two equivalents of **2a** and 5 mol % of **1f** were used in a 10 mmol scale of **3b**.

Table 2). Further decreasing the temperature to −78 °C also gave the product in 98% ee but with a longer reaction time (entry 5, Table 2). With 5 mol % of **1f**, the product could be obtained with 96% ee in 1.5 h at −60 °C. However, only 75% ee resulted in the presence of 2 mol % of **1f**, and the reaction was much slower (entries 6 and 7, Table 2).

Several solvents have been tested for the reaction with 10 mol % of **1f** at −60 °C. A significant drop of both reaction rate and enantiomeric excess of the product was observed for many tested solvents, such as DCM, Et_2O, THF, and CH_3CN.

A wide range of substituted indoles and imines have been tested under the optimized reaction conditions (5 equiv of indole and 10 mol % of **1f** in toluene at −60 °C), and the results are summarized in Table 3.

When the protecting group in **3** was changed from *N*-Ts to *N*-Bs, high enantioselectivities could also be realized (99% ee, entry 2, Table 3). The phosphoric acid catalyzed Friedel−Crafts reaction of indoles with *N*-sulfonyl aldimines was found to be general with indoles bearing different substituents. Several substituted indoles **2b**−**e**, containing either electron-donating groups or electron-withdrawing groups, have been tested in the reaction with imines **3a** and **3b**, respectively. In all cases, high yields and excellent enantioselectivities could be achieved (97−99% ee, entries 3−10, Table 3), which contrast the results of a chiral Cu complex that shows a strong electronic effect for substituted indoles.[5a] We then examined the different substituents R′ on the imines **3**. For the substrates with electron-donating group such as **3c**, **3h**, and **3i**, the reactions went smoothly, affording the products with high yields and excellent enantioselectivities (entries 11, 16, and 17, Table 3). By introducing an electron-withdrawing group into the imine, we observed a drop in the enantioselectivity. In the case of **3d** having a 3-nitro group, 89% ee was given (entry 12, Table 3). Similarly, good to excellent enantioselectivities were obtained with substrates **3e**−**g** (which contain electron-withdrawing groups), where phosphoric acid **1d** proved to be superior to **1f** (entries 13−15, Table 3). Unfortunately, when an aliphatic aldehyde derived imine, such as **3j**, was tested, only moderate yield and enantioselectivity were obtained (56% yield, 58% ee, entry 18, Table 3). To test the practicality of the current catalytic system, reaction of **3b** with 2 equiv of indole in the presence of 5 mol % of **1f** was carried out in a 10 mmol scale of **3b**. The desired product was afforded in 94% yield with >99% ee (entry 19 versus entry 2, Table 3).

In summary, we have identified chiral phosphoric acids as efficient organocatalysts for the Friedel−Crafts reactions of indoles with imines, especially for the imines derived from aromatic aldehydes. The reaction features a metal-free approach, high efficiency of the catalyst, mild reaction conditions, high yields, and excellent enantioselectivities, providing a practical method to synthesize highly enantiopure 3-indolyl methanamine derivatives. Further investigation of the reaction mechanism and extension of the reaction scope are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

(2) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804−11805.

(3) Reviews on chiral Brønsted acid catalysis: (a) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909−3912. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (d) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758−1763. (e) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. (f) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296.

(4) Recent examples: (a) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802−14803. (b) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023−6026. (c) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832−7835. (d) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368−13369. (e) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074−13075. (f) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070−13071. (g) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751−6755. (h) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796−4798. (i) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686. (j) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617−2619. (k) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254−2257. (l) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (m) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84−86. (n) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141−143.

(5) For reactions catalyzed by a chiral Cu complex, see: (a) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621−1624. (b) Johannsen, M. *Chem. Commun.* **1999**, 2233−2234.

(6) (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278−311. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48. (c) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587−596.

(7) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156−8157.

(8) After submission of this paper, Terada and Sorimachi reported a phosphoric acid catalyzed Friedel−Crafts reaction of indoles with electron-rich alkenes. For details, see: Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292−293.

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