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The Highly Enantioselective Addition of Indoles to *N*-Acyl Imines with Use of a Chiral Phosphoric Acid Catalyst

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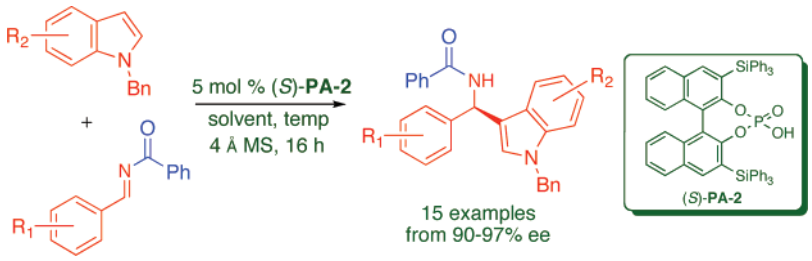
ABSTRACT



The highly enantioselective organocatalytic addition of *N*-benzyl indoles to *N*-acyl imines is reported. A total of 15 examples with product yield ranging from 89% to 99% and enantioselectivities from 90% to 97% are presented. A chiral phosphoric acid catalyst derived from a hindered binol derivative was employed most effectively in the reaction. Attractive features of the reaction include desirable catalyst loadings, good reactivity, generality of substrates, and easily removable groups from both nitrogen atoms.

Over the past two decades, the development of catalytic, enantioselective reactions has been near the forefront of synthetic organic research.[1] In recent years organocatalysis has been demonstrated to be one of the most promising areas for the development of environmentally friendly enantioselective processes.[2] An important benefit of organocatalysis is the lack of toxic metal byproducts that often accompany metal-catalyzed enantioselective reactions.[2a] A recently emerging direction for organocatalysis has been the development of phosphoric acid catalysts derived from chiral biaryl building blocks.[3] Chiral phosphoric acids have been shown to be remarkable catalysts for enantioselective Mannich reactions,[4] enantioselective reductions,[5] cycloaddition reactions,[6] and the addition of other nucleophiles to imines.[7]

In 2004, Terada reported the first chiral phosphoric acid-catalyzed enantioselective aza-Friedel−Crafts reaction of a single electron-rich furan with imines.[8] In a related reaction,

(1) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, Germany, 1999; Vols. I−III.

(2) For reviews of enantioselective organocatalysis see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *113*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(3) For reviews of chiral phosphoric acid catalysis see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal*. **2006**, 348, 999. (b) Connon, S. J. *Angew. Chem., Int. Ed*. **2006**, *45*, 3909.

(4) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(5) (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett*. **2005**, *7*, 3781. (b) Hoffmann, S.; Saeyad, A. M.; List, B. *Angew. Chem., Int. Ed*. **2005**, *44*, 7424. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2006**, *128*, 84. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 3683. (e) Mayer, S.; List, B. *Angew. Chem., Int. Ed*. **2006**, *45*, 4193. (f) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 6751.

(6) (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc*. **2006**, *128*, 13070. (b) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 7832.

(7) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc*. **2005**, *127*, 15696. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett*. **2005**, *7*, 2583. (c) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed*. **2006**, *118*, 7832.

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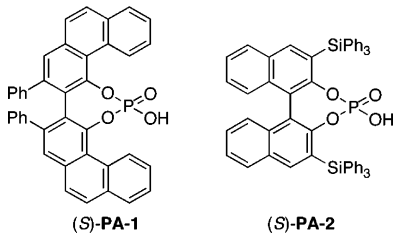
Terada also reported the enantioselective addition of indole nucleophiles to electron-rich alkenes.[9] Deng and co-workers reported the first enantioselective organocatalytic Friedel−Crafts addition of indoles to imines by using a modified quinine catalyst to provide chiral 3-indolyl methanamines with excellent selectivity.[10] However, the procedure required long reaction times and harsh conditions are needed for the removal of the tosyl group from the nitrogen products.[11] Most recently, You and co-workers reported a chiral phosphoric acid-catalyzed Friedel−Crafts reaction of indoles with similar *N*-tosyl imines.[12] The reaction gave chiral methanamines in good yield and with excellent enantioselectivity. However, 5 equiv of indole were required, and a drop in both yield and enantioselectivity was found with substrates that were substituted on the aromatic ring of the imine. We would like to report an aza-Friedel−Crafts reaction between substituted *N*-benzyl indoles and *N*-acyl imines catalyzed by chiral phosphoric acids to provide the addition products in excellent yield and with high enantioselectivities.

Inspired by our previous success[7a] with a chiral phosphoric acid derived from the VAPOL (Vaulted biPhenantrOL) ligand[13] shown in Figure 1, our initial investigation involved

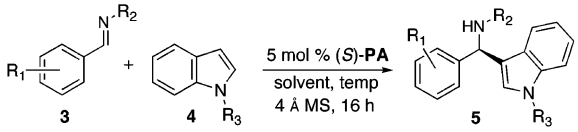


(*S*)-**PA-1** (*S*)-**PA-2**

Figure 1. Two hindered chiral phosphoric acid catalysts.

reaction of *N*-Boc protected imines with indoles catalyzed by **PA1** (Table 1, entry 1). This resulted in the formation of the product in excellent yield, but poor enantioselectivities were found. Our first notable improvement was the use of *N*-benzoyl imine substitution. This change resulted in a drastic increase in the stereoselectivity of the reaction (entry 2). After many attempts at optimization of the reaction using **PA1** we found that chiral phosphoric acid **PA2** provided for the formation of the product in excellent yield and enantioselectivity (entries 3−5). The lowering of the reaction temperature resulted in an increase in the enantioselectivity,

Table 1. Optimized Catalytic Asymmetric Conditions



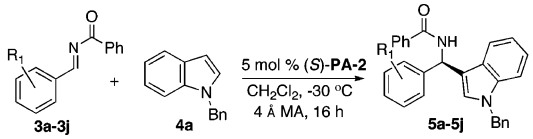
entry	R_1	R_2	R_3	solvent	temp, °C	(*S*)-**PA**	yield, %	ee, %[a]
1	4-OMe	BOC	Bn	C_6H_5Cl	RT	**PA-1**	96	60
2	H	C(O)Ph	Bn	CH_2Cl_2	-60	**PA-1**	89	86
3	H	C(O)Ph	Bn	CH_2Cl_2	RT	**PA-2**	99	80
4	H	C(O)Ph	Bn	CH_2Cl_2	-20	**PA-2**	98	92
5	H	C(O)Ph	Bn	CH_2Cl_2	-30	**PA-2**	99	94
6	H	C(O)Ph	Bn	CH_2Cl_2	-60	**PA-2**	92	97
7	H	C(O)Ph	H	C_6H_5Cl	-30	**PA-2**	70	30
8	H	C(O)Ph	Me	CH_2Cl_2	-30	**PA-2**	90	30

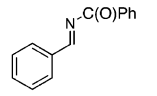
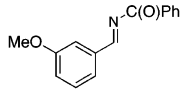
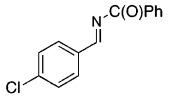
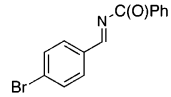
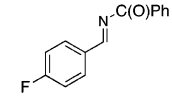
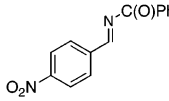
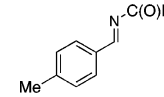
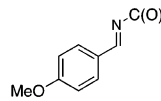
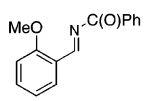
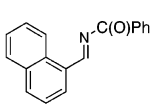
[a] Enantiomeric excess (ee) determined by chiral HPLC analysis.

with no adverse affect on the yield until the reaction was below −40 °C. However, an increase to 10 mol % catalyst loading at −60 °C was also necessary for the formation of the product with both high yield and selectivity (entry 6).

It was therefore determined that −30 °C was the optimal reaction temperature for both activity (5 mol % **PA2**) and selectivity (94% ee). Unprotected indole addition under these reaction conditions provided a moderate yield but with lower enantioselectivity (entry 7). Likewise, the use of *N*-methyl-

Table 2. Variation of the Imine Substrate



entry	imine	yield	ee
1		99	94
2		96	92
3		97	(*R*)-96[a]
4		92	96
5		97	95
6		99	94
7		96	97
8		93	94
9		97	95
10		99	95

[a] Absolute configuration of the product in entry 3 was determined to be (*R*) by X-ray crystallographic analysis, with the stereochemistry of the other products assumed by analogy (see the Supporting Information).

(8) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.
(9) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.
(10) Wang, Y. -Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.
(11) Schultz, A. G.; McClosky, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493.
(12) During the preparation of our manuscript, a publication by S. You appeared using similar reaction conditions but different substrates and catalyst. This work prompted our immediate submission. Please see: Kang, Q.; Zhao, Z. A.; You, S. -L. *J. Am. Chem. Soc.* **2007**, *129*, 1484.
(13) Bao, J.; Wulff, W. D.; Doming, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

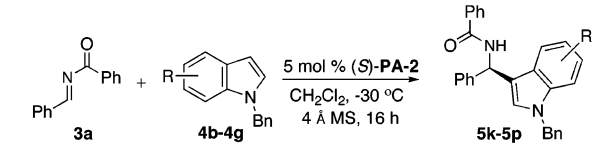
indole in the addition gave a lowered selectivity in comparison to the *N*-benzyl compound (entry 8).

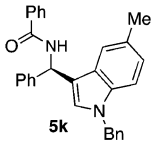
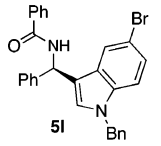
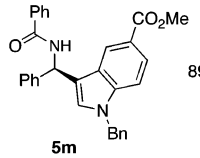
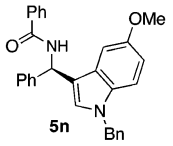
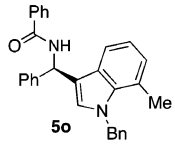
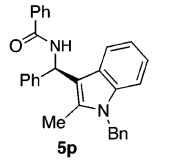
With an optimal set of reaction conditions in hand the reaction scope with regard to variation of the aryl substituent of the imine carbon was investigated (Table 2). A variety of substitutions proved to be very successful. For example, *m*-methoxy-substituted substrate **3b** allowed for excellent yield and enantioselectivity upon addition with **4a** (entry 2). Likewise, electron-withdrawing substituents in the *para* position of the imine (**3c**−**f**) were all excellent substrates for the reaction, giving from 94% to 96% ee (entries 3−6). Electron-donating substituents in the *para* position also provided suitable substrates and their reaction gave substituted products with 94% and 95% ee (entries 7 and 8). Sterically hindered *o*-methoxy substrate **3i** was not problematic, providing a high yield (97%) and high selectivity (95% ee). Likewise, a 1-naphthyl-substituted imine (entry 10) proved to be an excellent substrate for the reaction (99% yield, 95% ee of product **5j**).

Concentrating next on the variation of the indole substitution we tested six substrates (Table 3). We first examined a series of 5-substituted indoles and were pleased to find very good compatibility. For example, 5-methyl-, 5-bromo-, 5-carboxymethyl-, and 5-methoxyindole (entries 1−4) were all excellent substrates for reaction with **3a**, resulting in 90−95% ee. The use of 7-methylindole was an equally fine substrate that could provide for a product with a 98% yield and a 96% ee. The only substrate tested that gave lowered selectivity was the hindered 2-methylindole. In that case a moderate enantioselectivity was observed upon reaction with **3a** (64% ee). This lowering of the ee is presumably due to detrimental steric interactions.

In summary, we have developed a general method whereby indoles can be added in an enantioselective fashion to *N*-benzoyl-activated imines utilizing chiral phosphoric acids as efficient catalysts. The reaction proceeds with excellent enantioselectivity and is performed with indole as the limiting reagent. Further studies are being conducted with regard to scope and limitations of this reaction and related Friedel−Crafts-type additions catalyzed by chiral phosphoric acids.

Table 3. Variation of the Indole Substrate



entry	Product	yield	ee
1	 **5k**	97	95
2	 **5l**	94	92
3	 **5m**	89	90
4	 **5n**	98	95
5	 **5o**	98	96
6	 **5p**	91	64

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Supporting Information Available: Experimental procedures, characterization, chiral HPLC conditions, spectra, and X-ray crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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