ORGANIC LETTERS

2007
Vol. 9, No. 20
4065−4068

Organocatalytic Enantioselective Friedel–Crafts Reaction of Pyrrole Derivatives with Imines

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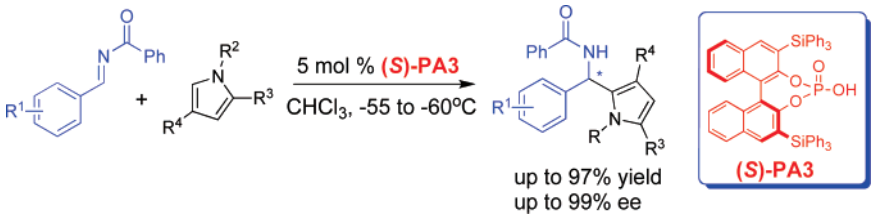
Received August 2, 2007

ABSTRACT



A highly enantioselective Friedel–Crafts reaction of pyrrole derivatives with *N*-acyl imines catalyzed by chiral phosphoric acids was developed. The reactions produced the pyrrole derivatives in high yields and enantioselectivity.

The Friedel−Crafts reaction is undoubtedly one of the most important carbon−carbon bond forming reactions in organic synthesis.[1] In recent years the asymmetric Friedel−Crafts reaction has attracted considerable interest among academics. An important aspect of enantioselective variants to this reaction is the resulting abillity to synthesize enantiopure arenes, which are desired synthetic intermediates and biologically active compounds.[2] Recently, there have been several reports of asymmetric Friedel−Crafts reactions of indole derivatives with both organocatalytic and metal-catalyzed systems.[3] However, pyrroles are also important heterocycles that are often found in natural products and drug candidates that could potentially be accessed by asymmetric Friedel−Crafts chemistry.[4] Methodologies for the asymmetric Friedel−Crafts reaction of pyrroles are very limited. The first example of a highly enantioselective Friedel−Crafts reaction of pyrrole was reported by MacMillan in 2001 using a chiral imidizolidinone catalyst.[5] Chiral Lewis acid complexes have also been demonstrated to be excellent catalysts for the enantioselective Friedel−Crafts reaction of pyrrole derivatives with α,β-unsturated systems.[6]

Organocatalytic enantioselective synthesis has witnessed rapid development in the past years owing to its potential

(1) (a) Olah, G. A. *Friedel-Crafts Chemistry*; Wiley & Sons: New York, 1973. (b) Olah, G. A.; Kishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 293.

(2) For reviews, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999. (b) Jørgensen, K. A. *Synthesis* **2003**, 1117. (c) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

(3) For asymmetric Friedel−Crafts reactions with organocatalysts, see: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (c) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (d) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (e) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (f) Jia, Y.; Zhong, J.; Zhu, S.; Zhang, C.; Zhou, Q. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565. For select examples with chiral Lewis acids see: (g) Johannsen, M. *Chem. Commun.* **1999**, 2233. (h) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (i) Jia, Y.; Xie, J.; Duan, H; Zhou, Q. *Org. Lett.* **2006**, *8*, 1621.

(4) (a) Della Bella, D. *Boll. Chim. Farm.* **1972**, *111*, 5. (b) Guzman, A.; Yuste, F.; Toscano, R. A.; Young, J. M.; Vanhorn, A. R.; Muchowski, J. M. *J. Med. Chem.* **1986**, *29*, 589. (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Thieme: New York, 2001. (d) Katritzky, A. R.; Jain, R.; Xu, Y.; Steel, P. J. *J. Org. Chem.* **2002**, *67*, 8220.

(5) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371.

(6) (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (c) Evans, D. A.; Fandrick, K, R. *Org. Lett.* **2006**, *8*, 2249.

10.1021/ol701881j CCC: $37.00
Published on Web 08/30/2007

environmentally friendly features.[7] Chiral phosphoric acids, which were first utilized as efficient asymmetric catalysts by Terada and Akiyama in 2004,[8] have now been shown to be excellent organocatalysts for a wide variety of asymmetric reactions.[9,10] Recently, we have reported the enantioselective aza-Friedel−Crafts reaction of indole derivatives with *N*-benzoyl imines.[11] Herein, we would like to report the application of this methodology to the catalytic, enantioselective aza-Friedel−Crafts reaction of *N*-benzoyl imines with pyrrole derivatives. This is, to our knowledge, the first example of a chiral phosphoric acid-catalzyed aza-Friedel−Crafts reaction utilizing pyrroles.

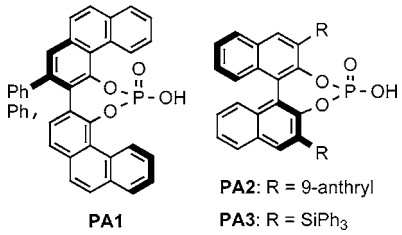
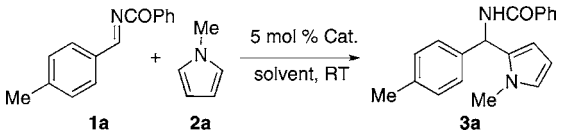


Figure 1. Chiral phosphoric acids.

Our initial focus was to optimize the reaction conditions (Table 1). With use of dichloromethane as the solvent and *N*-methylpyrrole as the substrate, three chiral phosporic acid catalysts were screened for activity (entries 1−3). The results indicated that catalyst **PA3** was slightly superior in terms of the observed selectivity of the reaction. Solvent also had a major effect on the enantioselectivity of the reaction. The use of nonpolar and weakly polar solvents gave promising results in terms of the product yield and enantioselectivity (entries 5−8). The more polar solvent acetonitrile resulted in decreased enantioselectivity of the reaction while affording the product in comparable yield to the less polar solvents

Table 1. Optimization of Reaction Conditions



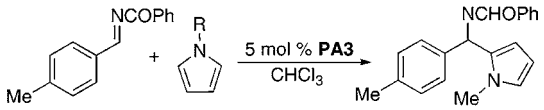
entry	catalyst	solvent	time, h	yield,[a] %	ee,[b] %
1	**PA1**	CH_2Cl_2	15	56	25
2	**PA2**	CH_2Cl_2	15	82	48
3	**PA3**	CH_2Cl_2	15	72	51
4	**PA3**	CH_3CN	22	75	26
5	**PA3**	$(CH_2Cl)_2$	21	76	47
6	**PA3**	toluene	21	85	62
7	**PA3**	ether	22	82	60
8	**PA3**	$CHCl_3$	21	87	64

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

(entry 4). From the solvent study, it was determined that chloroform was the solvent of choice (entry 8).

Further optimization indicated that a benzyl protecting group on the pyrrole nitrogen had a detrimental effect on both the yield and the enantioselectivity of the reaction (Table 2, entry 1). This is a possible indication of a severe sensitivity

Table 2. The Effect of Temperature and *N*-Substitution



entry	R	temp, °C	time, h	yield, %	ee, %
1[a]	Bn	rt	21	72	36
2	Me	−40	26	82	85
3	Me	−60	25	95	89
4	Me	−60	26	86	89
5[b]	Me	−60	26	88	89
6	*i*-Pr	−60	26	trace	nd[c]
7	H	−60	26	69	14

[a] Dichloromethane was used as the solvent. [b] 2.5 mol % catalyst was used. [c] nd = not determined.

to sterics for the reaction. It is also worth noting that double addition (two imines to one pyrrole) was observed when the reaction was performed at ambient temperature. Decreasing the reaction temperature to −40 °C resulted in increased yield and enantioselectivity of the desired single-addition product. Further lowering of the temperature to −60 °C proved to be the optimal in terms of both enantioselectivity and yield of the resulting product (entry 3). The use of *N*-isopropylpyrrole resulted in the production of only a trace amount of product (entry 6). This is also presumably due to the steric bulk of the isopropyl substituent. The use of unprotected pyrrole allowed for the desired product in respectable yield, but the

(7) 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.

(8) (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.

(9) 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.

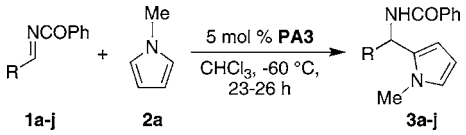
(10) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chenamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (c) Hoffmann, S.; Saeyad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (d) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (e) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (f) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (g) Rueping, M.; Antonchick, A. P.; Thiessmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (h) Rueping, M.; Antonchick, A. P.; Thiessmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (i) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (j) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (k) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (l) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830.

(11) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609.

enantioselectivity was much lower than that obsereved for *N*-methylpyrrole (entry 7).

With the optimized reaction conditions in hand, we turned our attention to the effect of substituion on the imine substrate (Table 3). A variety of *N*-acyl imines were investigated for

Table 3. Variation of Imine Substrate



1a-j **2a** **3a-j**

entry	R	product	yield, %	ee, %
1	*p*-$CH_3C_6H_4$	**3a**	95	89
2	PH	**3b**	86	90
3	*p*-$CH_3OC_6H_4$	**3c**	91	96
4	*m*-$CH_3OC_6H_4$	**3d**	97	>99
5	*o*-$CH_3OC_6H_4$	**3e**	91	88
6	*p*-FC_6H_4	**3f**	96	85
7	*p*-ClC_6H_4	**3g**	90	81
8	*p*-BrC_6H_4	**3h**	92	79
9	*p*-$CF_3C_6H_4$	**3i**	89	58
10	1-naph	**3j**	88	82

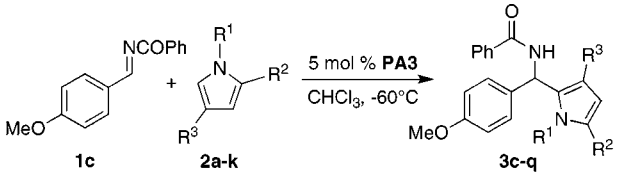
the generality of this reaction with use of the optimal reaction conditions. As shown in Table 3, the imines containing election-donating groups on the phenyl ring usually were excellent substrates, providing for products with very high enantiomeric excess. For example, imine **1c** provided product **3c** in 96% enantiomeric excess (entry 3) and imine **1d** gave almost optically pure product with 99% enantiomeric excess (entry 4).

A slight decrease in enantioselectivity was observed with imines bearing election-withdrawing groups on the aromatic ring (entries 6−8). The presence of a strong electron-withdrawing group gave a much lower ee value (entry 9). Along with electronic effects, the steric effects were also visible in this reaction. For instance, imines **1d** and **1e** with a methoxy group at meta and ortho sites, respectively, afforded much different enantioselectivities (entries 4 and 5).

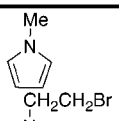
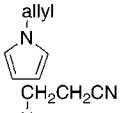
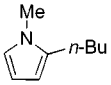
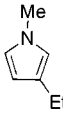
We next chose to screen the reaction for the scope of the pyrrole substrate (Table 4). We have already shown that the presence of sterically hindered isopropyl substituent on the pyrrole was almost inactive for this reaction (Table 2, entry 6). On the basis of this result we thought that it would be interesting to further vary this group. A decrease in enantiomeric excess was observed as the length of the *N*-alkyl substituent of the pyrrole was increased (Table 4, entries 1−4). This is probably due to an increase in sterics. Pyrroles **2e**, **2h**, and **2i**, which are similar in steric effect, gave nearly the same enantioselectivity (entries 2, 5, and 6). In addition, other substituted *N*-methyl pyrroles were evaluated. 2-Butyl-*N*-methylpyrrole (**2j**) afforded a low ee value (entry 7), and 3-ethyl-*N*-methylpyrrole (**2k**) provided moderate enantioselectivity as a substrate (entry 8).

Pyrrolo[1,2-*a*]pyrazine derivatives are medicinally important compounds reported to possess antiarrhythmic, anti-

Table 4. The Reaction Scope with Substituted Pyrroles

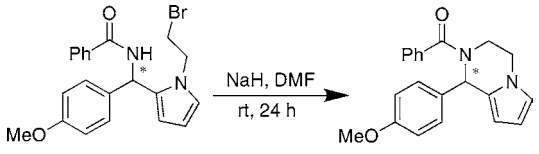


1c **2a-k** **3c-q**

Entry	Pyrrole	Time,h	Product	Yield %	ee %
1	**2a** 	20	**3c**	95	96
2	**2e** 	46	**3k**	87	92
3	**2f** 	40	**3l**	81	76
4	**2g** 	41	**3m**	68	69
5	**2h** 	23	**3n**	66	91
6	**2i** 	24	**3o**	72	90
7	**2j** 	24	**3p**	97	42
8	**2k** 	23	**3q**	89	76

amnesic, antihypoxic, psychotropic, antihypersensitive, and aldose reductase inhibitor activities.[12] As a demonstration of the synthetic potential of the reactions we started with enantiomerically enriched **3k** (92% ee). The chiral pyrrolo-[1,2-*a*]pyrazine derivative **4** could be easily synthesized in just one step from the precursor in the presence of NaH without racemization and in good chemical yield (Scheme 1).

Scheme 1. Synthesis of Pyrrolo[1,2-*a*]pyrazine



3k (92% ee) **4** 92% ee, 81% yield

In conclusion, we have developed an efficient method for the highly enantioselective Friedel−Crafts reaction between pyrrole derivatives and *N*-acyl imines catalyzed by chiral phosphoric acids. When the observed steric and electronic effects of the substrates were controlled, excellent enantiomeric excess and yields could be achieved. We have applied

the developed methodology to the synthesis of a pyrrolo-[1,2-*a*]pyrazine without racemization. Further studies with regard to the generality and scope of this reaction and related Friedel−Crafts reactions catalyzed by organocatalysts are ongoing in our lab and will be reported in due course.

(12) (a) Ohtani, M.; Fuji, M.; Okada, T. PCT Int. WO9951605 A1, 1999, 128 pp. (b) Katritzky, A. R.; Jain, R.; Xu, Y.-J.; Steel, P. J. *J. Org. Chem.* **2002**, *67*, 8220. (c) Likhosherstov, A. M.; Filippova, O. V.; Peresada, V. P.; Kryzhanovskii, S. A.; Vititnova, M. B.; Kaverina, N. V.; Reznikov, K. M. *Pharm. Chem. J.* **2003**, *37*, 6.

Acknowledgment. We thank the University of South Florida for generous start-up funds and a New Researcher Award, J.C.A. We also thank the Petroleum Research Fund for additional funding (PRF 45899-G1).

Supporting Information Available: Full experimental procedures, characterization data, and spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701881J