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Merging Nucleophilic and Hydrogen Bonding Catalysis: An Anion Binding Approach to the Kinetic Resolution of Amines

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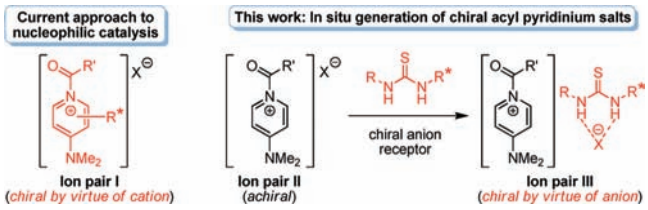
Nucleophilic catalysis is a powerful concept for instilling asymmetry into a variety of different reactions.[1,2] Chiral derivatives of 4-(dimethylamino)pyridine (DMAP) feature prominently among the catalysts used for kinetic resolution and desymmetrization processes.[1] The intermediate chiral ion pairs (e.g., **I**) are more reactive than the acylating reagents used to generate them, thus enabling enantioselective acyl transfer pathways. Here we present a new concept for asymmetric nucleophilic catalysis and its application to the kinetic resolution of primary amines.

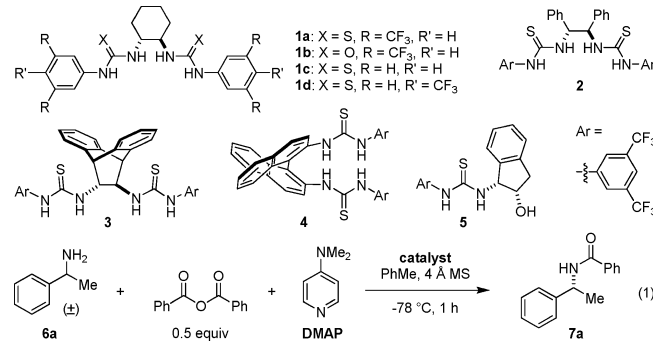


We envisioned a simple achiral acyl pyridinium salt to be rendered chiral upon binding of the corresponding anion to a chiral anion receptor (e.g., a thiourea compound), resulting in the formation of chiral ion pair **III**. This strategy provides an alternative to the use of chiral DMAP analogues and might offer potential advantages. First, **III** could be a better acylating agent than **II**, as binding of a chiral receptor to the anion should serve to lower interactions of the latter with the acyl pyridinium species, making it more electrophilic. In addition, the proper choice of X^- and the reaction medium could cause **II** to be significantly less soluble than **III**, further favoring reaction of the substrate to occur with **III** over **II**. Furthermore, the achiral nucleophilic promoter or the acyl pyridinium salt itself (e.g., **II**) could be used in stoichiometric amounts. Inspiration for this concept was drawn from the field of anion binding receptors[3] as well as the recent elegant contributions by Jacobsen,[4] Schreiner,[5] and others.[6,7]

The kinetic resolution of amines was considered a worthy challenge, suited ideally to demonstrate the potential of this new concept. The inherent nucleophilicity of primary amines, being comparable to the reactivity of many potential nucleophilic promoters, has hampered the development of small molecule catalysts that can efficiently resolve this important class of substrates. We are aware of only one example, an insightful contribution by Fu and co-workers, in which simple amines such as **6a** were resolved successfully using a combination of a chiral PPY catalyst and an azlactone based acylating reagent.[8,9]

In the realm of small molecule catalysis,[10] there are no examples that employ catalytic amounts of a chiral promoter in combination with a simple acylating reagent.[11] Table 1 summarizes our efforts in identifying a viable hydrogen bonding (HB) catalyst[12,13] for the process outlined in eq 1. Toluene solutions of benzoic anhydride and DMAP were prepared at room temperature in the presence of molecular sieves, followed by cooling to −78 °C and addition of catalyst and amine. Enantioenriched products were obtained at various substrate concentrations, with a 0.01 M concentration providing the best *s*-factor (entry 4).[14] We next studied the efficiency of this process with regards to

Table 1. Evaluation of Reaction Parameters[a]



entry	catalyst (mol %)	DMAP (mol %)	concn [M]	conversion (%)	*s*-factor
1	**1a** (20)	50	0.06	47	5.5
2	**1a** (20)	50	0.03	47	7.0
3	**1a** (20)	50	0.02	47	8.6
4	**1a** (20)	50	0.01	45	9.5
5	**1a** (20)	50	0.005	44	9.4
6	**1a** (20)	40	0.01	47	9.4
7	**1a** (20)	30	0.01	47	10
8	**1a** (20)	20	0.01	45	10
9	**1a** (20)	10	0.01	43	8.5
10	**1a** (20)	5	0.01	44	7.7
11	**1a** (15)	15	0.01	46	9.0
12	**1a** (10)	10	0.01	46	9.0
13	**1a** (5)	5	0.01	44	8.5
14	none	none	0.01	<1	N/A
15	none	20	0.01	<2	N/A
16	**1a** (20)	none	0.01	40	1.4
17	**1b** (20)	20	0.01	40	8.6
18	**1c** (20)	20	0.01	43	4.5
19	**1d** (20)	20	0.01	21	4.1
20	**2** (20)	20	0.01	44	7.2
21	**3** (20)	20	0.01	42	3.7
22	**4** (20)	20	0.01	30	1.2
23	**5** (20)	20	0.01	38	1.5

[a] Reactions were performed on a 0.2 mmol scale. The *s*-factors were determined by HPLC analysis; see the Supporting Information for details.

the amount of DMAP used. Remarkably, the use of only 20 mol % of DMAP gave rise to an improved *s*-factor of 10 (entry 8). Lower amounts of DMAP resulted in reduced *s*-factors. While loadings for both catalysts could be lowered further (entries 11−13), the *s*-factors were slightly reduced in these instances. Interestingly, virtually no conversion occurred in the absence of both DMAP and catalyst **1a** (entry 14). Addition of DMAP (20 mol %) as the only catalyst had no discernible effect on the reaction rate (entry 15). Use of the thiourea catalyst **1a** (20 mol %) in the absence of DMAP gave rise to significant amounts of enantioenriched product (entry 16). However, the efficiency of this process is considerably lower in comparison to the optimized process in which the DMAP cocatalyst is present. Other HB catalysts were also evaluated but gave inferior results (entries 17−23).[15] We

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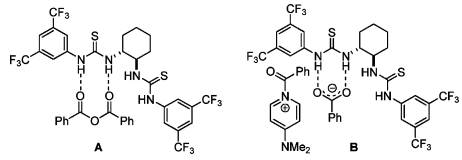
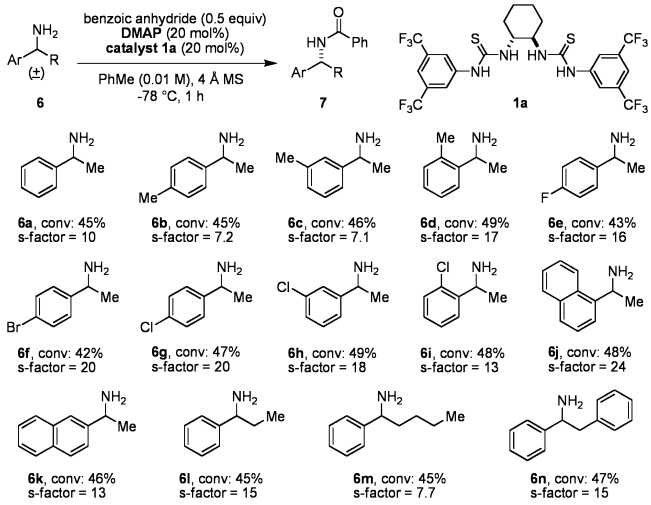
propose that catalysis in the absence of DMAP involves HB activation of the anhydride via an intermediate such as **A**.[16] In the presence of DMAP, intermediates related to **B** appear to dominate the outcome of this reaction, as the direct interaction of an acyl pyridinium species with a thiourea is unlikely.[4a] Binding of benzoate to thiourea **1a** may have an effect on the equilibrium concentrations of DMAP and its corresponding acyl pyridinium salt, a factor that is likely playing an important role in the overall process.[17−19]



The scope of the reaction was explored under the previously optimized conditions (Chart 1). A number of benzylic amines were resolved with good selectivities. Notably, electron-poor substrates gave higher *s*-factors, regardless of the position of the electron-withdrawing group. Catalysis via the competing and s-factor lowering pathway **A** is likely reduced in these cases. Remarkably, the seemingly more challenging substrates **6l** and **6n** were resolved with better selectivities as compared to the parent substrate **6a**. Using only 5 mol % of each DMAP and **1a**, amine **6g** could be resolved with an only slightly reduced *s*-factor of 19 (47% conversion, 2 h). This trend appears to be general, and other substrates performed well at this lower catalyst loading.[20]

Chart 1. Scope of the Reaction[a]



[a] Reactions were performed on a 0.25 mmol scale. The s-factors were determined by HPLC analysis; see the Supporting Information for details

In summary, we have introduced a new concept for asymmetric nucleophilic catalysis that involves the use of chiral anion receptors to generate chiral ion pairs in situ from simple acyl pyridinium salts. This strategy was successfully applied to the kinetic resolution of amines. Current efforts are aimed at developing a more complete mechanistic understanding of this reaction and at exploring related processes.

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

References

(1) (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (c) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (d) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (e) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436. (f) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (g) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.

(2) Nucleophilic catalysis is also classified as a type of Lewis base catalysis: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(3) For selected reviews, see: (a) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882. (b) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, UK, 2006; p 413. (c) Caltagirone, C.; Gale, P. A. *Chem. Soc. Rev.* **2009**, *38*, 520.

(4) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (d) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (e) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328.

(5) (a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434. (b) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779.

(6) For examples of asymmetric catalysis involving chiral anions, see: (a) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803. (b) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165. (c) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373. (d) Carter, C.; Fletcher, S.; Nelson, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1995. (e) Llewellyn, D. B.; Arndtsen, B. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1789. (f) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (g) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (h) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (i) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (j) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (k) Goncalves-Farbos, M.-H.; Vial, L.; Lacour, J. *Chem. Commun.* **2008**, 829. (l) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119. (m) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984.

(7) Asymmetric Brønsted acid catalysis frequently involves chiral ion pairs. For a review, see: Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

(8) (a) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234. For the kinetic resolution of indolines, see: (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264.

(9) For the kinetic resolution of oxazolidinones, see: Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536.

(10) Remarkable advances have been made in enzymatic amine resolutions. For examples, see: (a) Alexeeva, M.; Carr, R.; Turner, N. J. *Org. Biomol. Chem.* **2003**, *1*, 4133. (b) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620. (c) Turner, N. J. *Nat. Chem. Biol.* **2009**, *5*, 567. (d) Höhne, M.; Bornscheuer, U. T. *ChemCatChem* **2009**, *1*, 42.

(11) Kinetic resolutions of amines with stoichiometric amounts of chiral acylating reagents have been reported. For examples, see: (a) Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119. (b) Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314.

(12) For selected reviews on HB catalysis, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (f) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (g) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

(13) For selected uses of the catalysts employed in this study, see: (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (b) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (c) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037. (d) Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008**, *130*, 2456. (e) Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785. (f) Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron* **2008**, *64*, 9423.

(14) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(15) Cocatalysts such as pyridine, NMI, PPY, DBU, and DABCO are less efficient than DMAP. The use of Et_3N in place of DMAP gave results almost identical to those using **1a** as the only catalyst (Table 1, entry 16).

(16) HB activation of anhydrides by (thio)urea catalysts is a well precedented concept. For examples, see: (a) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 2454. (b) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872. (c) Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2009**, *351*, 547.

(17) The acyl pyridinium salt derived from DMAP and benzoic anhydride is not formed quantitatively but is likely present in equilibrium concentrations only. For an excellent study on such equilibria, see: (a) Lutz, V.; Glatthaar, J.; Würtele, C.; Serafin, M.; Hausmann, H.; Schreiner, P. R. *Chem.—Eur. J.* **2009**, *15*, 8548. See also: (b) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751.

(18) The nature of the anion is crucial with benzoate giving the best results. Acylating reagents such as PhCOF, PhCOCl, PhCOBr, Ac_2O, and trifluoroacetic anhydride were inferior to benzoic anhydride.

(19) The role of the second thiourea subunit is not clear at present.

(20) Additional results using **1a** (5 mol%) and DMAP (5 mol%): **6d** ($s = 15$, 46% conv.), **6f** ($s = 19$, 44% conv.), **6l** ($s = 12$, 41% conv.).

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