

Hydrogen-Bond-Mediated Supramolecular Iminium Ion Catalysis**

Yao Wang, Tian-Yang Yu, Hong-Bo Zhang, Yong-Chun Luo, and Peng-Fei Xu*

The manufacture of enantiomerically pure pharmaceutical and agrochemical products is an ongoing requirement for the chemical industry. As a result, the challenge of significantly improving the efficiency of expensive chiral catalysts and exploring their new reactivities has captured the attention of synthetic chemists. Over the past decade, iminium ion activation has been demonstrated to be a powerful strategy for asymmetric catalysis and many reactions catalyzed by iminium ions have been successfully applied in the synthesis of medicinal agents and natural products.^[1] To date, this so-called iminium catalysis generally involves an amine catalyst and an acid cocatalyst, and iminium ions form as ion pairs.^[1] We envisioned that an appropriate cocatalyst (denoted as **Y**) could disperse the negative charge and consequently separate the ion pair by interaction with the counteranion (Figure 1).

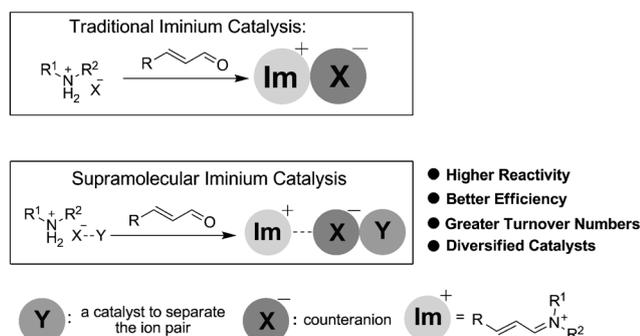


Figure 1. The concept of supramolecular iminium catalysis.

Such strategies based on supramolecular iminium catalysis (SIC) could significantly improve the catalytic activity of iminium catalysts and provide new opportunities for asymmetric catalysis. In view of the limitations on the use of organocatalysis in industry, the design and discovery of catalysts with higher reactivity, better efficiency, and greater turnover numbers is a major goal. This concept is very important because, in principle, it will aid in accelerating the reaction rate, reducing the loading of the expensive chiral catalysts, and improving the efficiency of some of the more

inefficient reactions. Another advantage of this strategy is that the stereocontrol of the modularly designed supramolecular iminium catalysts can be easily fine-tuned by simple modification or replacement of any of the components. As a consequence, a library of diverse catalysts could be used to make a wide range of enantioselective supramolecular iminium catalysts.

We envisaged that cocatalyst **Y** might interact with the iminium ion pair by a weak interaction such as anion binding or Coulomb interactions or by a combination of these types of forces. A related approach, thiourea anion-binding catalysis, has emerged as a new method for asymmetric catalysis.^[2] By judicious choice of catalysts, we reasoned that the merging of these fields in a SIC approach could result in desirable levels of stereocontrol and efficiency for a wide range of catalytic asymmetric transformations associated with new reactivity. Notably, despite important advances in the development and application of supramolecular catalysis,^[3] the use of discrete and rationally designed chiral supramolecular catalysts for asymmetric transformations still remains a significant challenge.^[4] Herein, we report our findings on this new strategy.

The generation of iminium ions is crucial to iminium catalysis. Thus, to determine the influence of the hydrogen-bond-mediated supramolecular ammonium catalysts on the generation of iminium ions, several control ¹H NMR experiments were carried out in C₆D₆. To test the feasibility of our hypothesis, diphenylprolinol trimethylsilyl ether and imidazolinone were selected as amine catalysts since they are the most widely used and reliable iminium catalysts and have been successfully applied in numerous transformations.^[1] To clearly identify and interpret the ¹H NMR signals of crucial protons, it was necessary to employ easily identifiable acids as cocatalysts and a symmetrical thiourea as an anion-binding catalyst.

In initial studies when diphenylprolinol trimethylsilyl ether served as the amine catalyst and traditional organic salts **B** (**B**¹–**B**⁴) were condensed with cinnamyl aldehyde (**1**) (1:1 ratio), to our surprise neither iminium ions nor any other new species were detected by ¹H NMR spectroscopy (Figure 2). The signal ratios of both cinnamyl aldehyde and carboxylic acid remained unchanged. As shown in Figure 2, only a single set of signals appeared which correspond to organic salts **B**. In sharp contrast, the supramolecular ammonium complex **A** reacted with cinnamyl aldehyde (1:1 ratio) to afford a considerable amount of the supramolecular iminium complex **A-Im** (**A-Im**/**A** > 1:1 equilibrium ratio). As shown in Figure 2, two sets of signals for the pyrrolidine ring and the cinnamyl group appeared. Meanwhile, when the reaction mixture of **A**¹ and cinnamyl aldehyde was analyzed by ESI-MS (see the Supporting Information), strong signals at *m/z* 440.2407 and *m/z* 613.0067 were observed which correspond to the iminium cation (*m/z*(calcd) 440.2404) and

[*] Dr. Y. Wang, T.-Y. Yu, H.-B. Zhang, Dr. Y.-C. Luo, Prof. Dr. P.-F. Xu
 State Key Laboratory of Applied Organic Chemistry
 College of Chemistry and Chemical Engineering
 Lanzhou University, Lanzhou 730000 (P.R. China)
 E-mail: xupf@lzu.edu.cn

[**] We thank the NSFC (21032005, 20972058, 21172097), the National Basic Research Program of China (no. 2010CB833203), and the “111” program from MOE of P.R. China.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201206881>.

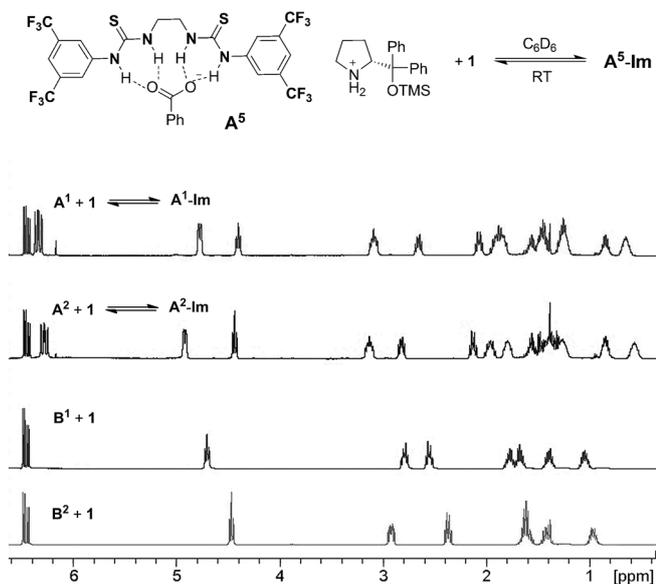
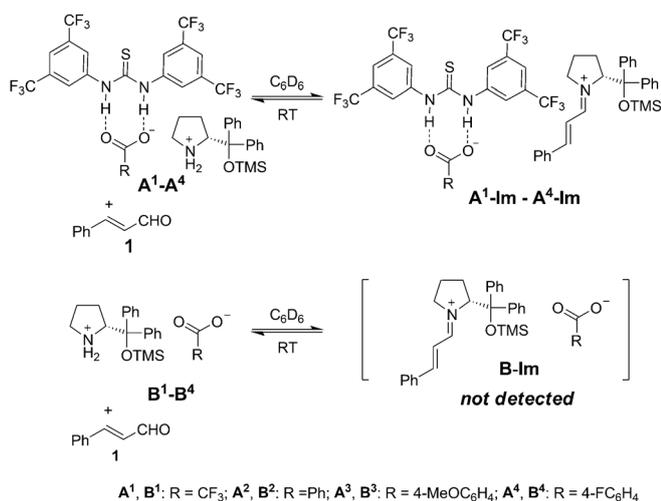


Figure 2. Top: The generation of iminium ions through supramolecular ammonium complexes and traditional organic salts with the diphenylprolinol trimethylsilyl ether catalyst. Bottom: ¹H NMR spectra (C₆D₆, 400 MHz).

thiourea anion-binding unit (*m/z*(calcd) 613.0072), respectively, of the supramolecular iminium complex **A¹-Im**.

With this useful information in hand, we tested different acids as components in the supramolecular ammonium complex. We found that iminium generation improved with increased acidity (Table 1, entries 1–4). Note that the acidity of *N,N'*-bis[3,5-bis(trifluoromethyl)]phenyl thiourea is quite high in the polar solvent DMSO.^[5] However, its relative acidity in the nonpolar solvent C₆D₆ is not known. The use of the strong Brønsted acid CF₃COOH also resulted in a high concentration of the iminium ion. This finding indicates that the generation of the supramolecular iminium ion complex is not necessarily a result of the higher p*K*_a of thiourea. Furthermore, also when a less acidic thiourea (corresponding to **A⁵**) was used, a high concentration of the iminium ion complex was generated (Table 1, entry 5). Strong signals at *m/z* 613.0077 and 613.0066, which correspond to the thiourea-

Table 1: Generation of iminium ions by supramolecular ammonium ion pairs and traditional organic salts; compounds shown in Figures 2 and 3.

Entry	R	A	A-Im	A-Im/A ^[a]	B	B-Im	B-Im/B
1	CF ₃	A¹	A¹-Im	1.66:1	B¹	–	–
2	Ph	A²	A²-Im	1.31:1	B²	–	–
3	4-MeO-C ₆ H ₄	A³	A³-Im	1.14:1	B³	–	–
4	4-F-C ₆ H ₄	A⁴	A⁴-Im	1.52:1	B⁴	–	–
5	Ph	A⁵	A⁵-Im	2.63:1	B²	–	–
6	CF ₃	A⁶	A⁶-Im	0.34:1	B⁶	B⁶-Im	0.04:1
7	Ph	A⁷	trace	n.d. ^[b]	B⁷	–	–

[a] Determined by ¹H NMR analysis. [b] n.d. = not determined.

anion complex, were found by analysis of **A¹** and **A⁶** using ESI-MS.^[6] Given the fact that H-bond interactions to stabilize the charged intermediate or transition state will be favored and can significantly promote the proton-transfer equilibrium process, we suggest H-bond-stabilized ammonium salts **A¹-A⁷** to be favorable equilibrium products. In sharp contrast, traditional organic salts do not form high concentrations of iminium ions, regardless of the acids employed (Table 1, entries 1–4). Similar results were observed when imidazolinone was employed as an iminium catalyst. A trace amount of the iminium ion was generated by condensation of **B⁶** with cinnamyl aldehyde. However, in sharp contrast, newly designed catalyst **A⁶** can successfully generate a significant amount of iminium **A⁶-Im** (Table 1, entry 6).

Imidazolinone has been proven to be an efficient organo-catalyst, generally with a strong Brønsted acid as a cocatalyst. Indeed, we find here in the presence of benzoic acid that only a trace amount of iminium formed in the presence of supramolecular iminium catalyst **A⁷** in C₆D₆ and no iminium generation was detected with the organic salt **B⁷** (Figure 3; Table 1, entry 7). Furthermore, when these reactions in the presence of supramolecular ammonium catalysts were monitored in toluene by in situ infrared spectroscopy, we found the generation of iminium ions achieved equilibrium almost immediately (generally within several seconds). These novel results are very important because they not only provide a powerful and general strategy for the expeditious formation of high concentrations of iminium ions, but shed new light on the selection of an acid cocatalyst.

Interestingly, when the benzoic acid module of both **A²** and **B²** was replaced by 4-nitrobenzoic acid, both of the ion pairs formed white suspensions in Et₂O. However, in sharp contrast, when cinnamyl aldehyde was added to 10 mol% supramolecular ammonium catalyst in Et₂O, a clear yellow solution formed immediately; in the presence of 10 mol% traditional organic salt the white suspension remained even after several hours (see the Supporting Information). The above observation can be explained by the fact that the supramolecular ammonium catalyst could immediately generate the iminium ion.

With this useful information in hand, we next questioned whether a supramolecular iminium catalyst could significantly enhance the catalytic activity in an iminium-catalyzed reaction. In order to clearly illustrate the new concept, it is necessary to choose model reactions that are not only widely

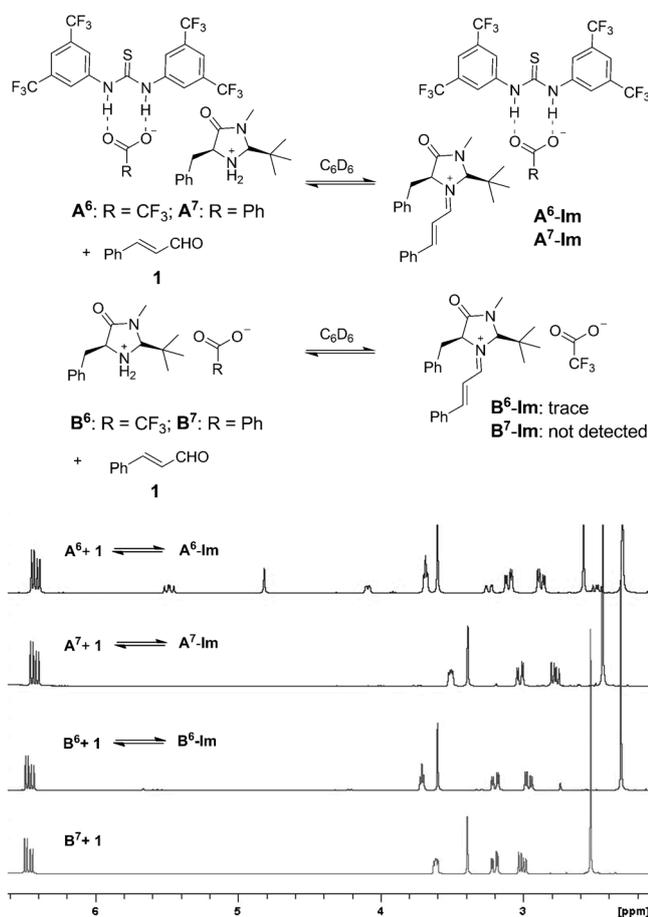


Figure 3. Top: The generation of iminium ions through supramolecular ammonium complexes and traditional organic salts with the imidazolone catalyst. Bottom: ¹H NMR spectra (C₆D₆, 400 MHz).

used in organic synthesis but also do not include interferential proton-transfer processes. Therefore, we selected the Diels–Alder reaction and the Friedel–Crafts reaction as model reactions for investigation.

To identify and explain crucial information clearly and exclude thiourea itself from interfering in the Diels–Alder reaction, an intramolecular Diels–Alder reaction^[7] can be an ideal model. As shown in Figure 4, for the intramolecular reaction of triene aldehyde **2** in a range of solvents such as toluene, CH₂Cl₂, and CH₃CN, the reactivities of the supramolecular ammonium catalyst **A⁸** and the traditional organic salt **B⁶** strongly diverged. The reaction proceeded efficiently to afford product **3** with 75% and 67% conversion catalyzed by **A⁶** and **A⁸** after 1 h in toluene, respectively. In contrast, only 28% conversion was obtained in the presence of **B⁶** after 1 h. When the loading of **A⁶** was reduced to 5 mol%, the reaction proceeded smoothly to give more than 90% conversion after 5 h with the same excellent selectivity. The enhanced reactivity was also observed with the bulky, sterically hindered chiral thioureas in **A⁹** and **A¹⁰** and these two catalysts maintain the high stereoselectivity. All these reactions catalyzed by supramolecular iminium catalysts can achieve more than 90% conversion after 4 h. With respect to

lent selectivity, regardless of thiourea, it is evident that the expeditious formation of higher concentrations of iminium ion and the generation of a more reactive charge-separated iminium ion account for the increased reaction rate.

The new concept was next applied to the asymmetric organocatalytic Friedel–Crafts alkylation reaction of *N*-methylindole with an α,β -unsaturated aldehyde.^[8] The control experiments of the reaction between *N*-methylindole and cinnamyl aldehyde were carried out in various solvents, such as CH₂Cl₂, toluene, and CHCl₃ at –50 °C in the presence of catalysts **A¹¹** and **B⁶**, respectively. In all of these solvents the catalytic activities of the supramolecular ammonium catalysts **A¹¹** and traditional organic salt **B⁶** contrasted sharply. As shown in Figure 5, the reaction catalyzed by 5 mol% **A¹¹** in CH₂Cl₂ at –50 °C proceeded efficiently to afford product **5** in 81% yield at 92% conversion after 45 h. Similarly, enhanced reactivity was also displayed by catalyst **A¹²** at a loading of 5 mol%. In sharp contrast, only 27% conversion was obtained in the presence of **B⁶** after 45 h. As expected, conversions of 81% and 63% were obtained in the presence of **A¹¹** in toluene and CHCl₃, respectively. In contrast, conversions of 43% and 24% were observed under the catalysis of **B⁶**. However, thioureas **6** or **7** alone could not catalyze this reaction. These results clearly indicate that

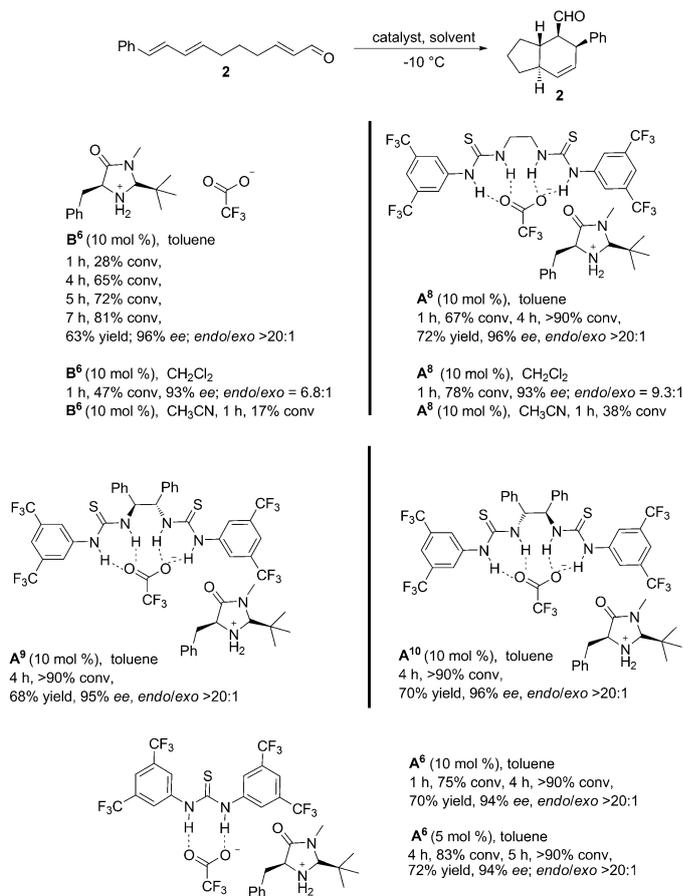


Figure 4. An intramolecular Diels–Alder reaction used to test the new strategy and traditional iminium catalysis.

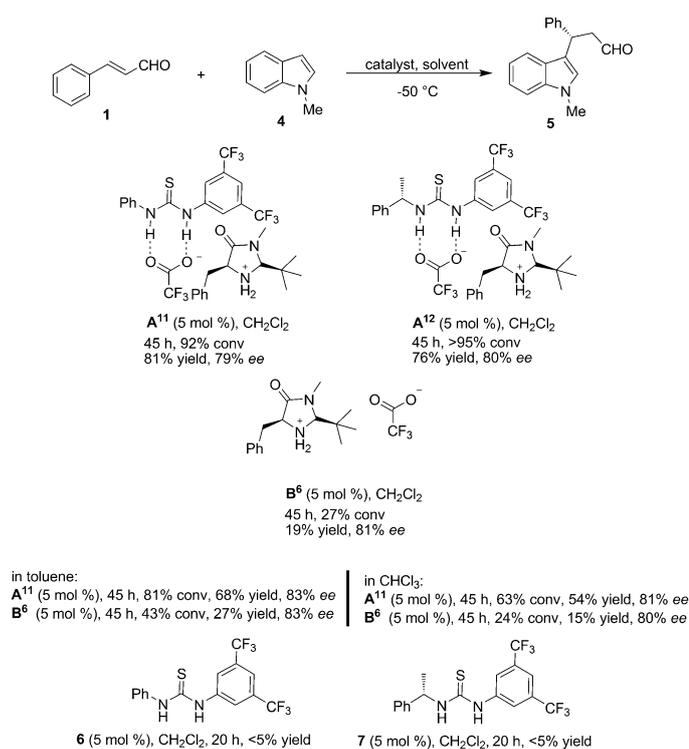


Figure 5. A Friedel–Crafts alkylation reaction to test the new strategy and traditional iminium catalysis.

supramolecular ammonium catalysts could significantly improve the reactivities of traditional organic salts.

In conclusion, we have developed a new strategy for asymmetric catalysis. The supramolecular ammonium catalysts described here have higher reactivity, better efficiency, and greater turnover numbers. This concept should be applicable to a vast number of iminium- as well as hydrogen-bond-catalyzed processes and provide new insights into asymmetric catalysis beyond the scope developed in our group. We are currently focusing our research on the wide application of this strategy.

Received: August 24, 2012

Published online: November 4, 2012

Keywords: asymmetric catalysis · iminium catalysis · organocatalysis · supramolecular chemistry

[1] For selected reviews, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; b) B. List, *Chem. Commun.* **2006**, 819–824; c) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; d) A. Erkkilä, I. Majander, P. M.

- Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; e) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; f) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; g) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; h) E. Marqués-López, R. P. Herrerabc, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138–1167; i) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; j) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649.
- [2] For selected reviews on anion-binding chemistry, see: a) C. Caltagirone, P. A. Gale, *Chem. Soc. Rev.* **2009**, *38*, 520–563; b) S. Kubik, *Chem. Soc. Rev.* **2009**, *38*, 585–605; c) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; For leading references on thiourea anion-binding catalysis, please see: d) M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434–439; e) M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779–790; f) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405; g) C. K. De, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 17060–17061; h) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968–970; i) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986–990; j) R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558–9560; k) E. G. Klauber, C. K. De, T. K. Shah, D. Seidel, *J. Am. Chem. Soc.* **2010**, *132*, 13624–13626; l) N. Z. Burns, M. G. Witten, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 14578–14581.
- [3] For selected reviews on supramolecular catalysis, see: a) P. W. N. M. van Leeuwen, *Supramolecular Catalysis*, Wiley-VCH, Weinheim, **2008**; b) J. Meeuwissen, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 615–621, and references therein. For selected examples of the application of hydrogen-bonding-assisted supramolecular catalysts in asymmetric catalysis: c) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188–4189; d) M. L. Clarke, J. A. Fuentes, *Angew. Chem.* **2007**, *119*, 948–951; *Angew. Chem. Int. Ed.* **2007**, *46*, 930–933; e) J. Park, K. Lang, K. A. Abboud, S. Hong, *J. Am. Chem. Soc.* **2008**, *130*, 16484–16485; f) P.-A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem.* **2009**, *121*, 2196–2199; *Angew. Chem. Int. Ed.* **2009**, *48*, 2162–2165.
- [4] D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120–123.
- [5] For a report on the acidity of thiourea, please see: a) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724–1727. For selected examples on the use of *N,N'*-bis[3,5-bis(trifluoromethyl)]phenyl thiourea, please see: b) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217–220; c) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407–414; d) T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513–1516.
- [6] For an elaborate study of H-bond interactions involving thiourea through a combination of ESI-MS and NMR spectroscopy, please see: Z. Zhang, K. M. Lippert, H. Hausmann, M. Kotke, P. R. Schreiner, *J. Org. Chem.* **2011**, *76*, 9764–9776.
- [7] a) S. A. Selkälä, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2005**, 1620–1624; b) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616–11617.
- [8] J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.