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Internal Lewis Acid Assisted Hydrogen Bond Donor Catalysis

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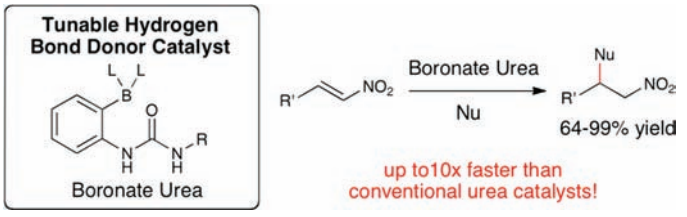
ABSTRACT



Boronate ureas are introduced as a new class of noncovalent catalysts for conjugate addition reactions with enhanced activity. Through intramolecular coordination of the urea functionality to a strategically placed Lewis acid, rate enhancements up to 10 times that of more conventional urea catalysts are observed. The tunable nature of boronate ureas is a particularly attractive feature and enables the rational design of catalysts for optimal performance, in terms of both activity and stereocontrol, in new bond-forming processes.

Chemical transformations catalyzed by small organic molecules operating through hydrogen bonding interactions are remarkable new tools for the preparation of important synthetic building blocks.[1] Urea and thiourea derived hydrogen bond donors (HBDs) have proven to be particularly useful noncovalent organic catalysts employed in a variety of reactions.[2] While the potential associated with urea and thiourea catalysis cannot be denied, current challenges in the area, including low catalyst turnover and limited reaction scopes, must be overcome before these catalysts can find more widespread applications in both academia and industry. One strategy to address the limitations includes the development of enhanced urea catalysts. Reactions catalyzed by more active ureas may benefit from lower catalyst loadings, improved enantioselectivity, and expanded substrate scopes and, ultimately, may lead to the development of novel reactivity patterns.[3] A 2007 report from Ellman and co-workers lending support to this notion demonstrates that an *N*-sulfinyl group on the urea significantly increases the urea acidity and results in a more active HBD catalyst.[4] More recently, Seidel and co-workers have introduced the idea of internal Brönsted acid activation of the urea functionality.[5] Building on these founding reports, a research program in our laboratory is focused on developing modular and tunable internal Lewis acid assisted urea catalysts that not only benefit from improved activity but also have the added advantage of being rationally designed for optimal performance.[6] Herein we report significant advances in the development of boronate ureas as tunable HBD catalysts with enhanced reactivity.

Inspiration for this study of more active HBD catalysts originated from both Etter's pioneering work proposing weak urea polarization due to internal hydrogen

(1) (a) Pihko, P. *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH: Weinheim, 2009. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (f) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.

(2) For examples, see: (a) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

(3) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748.

(4) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.

(5) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.

(6) For a review of combined acid catalysis, please see: Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

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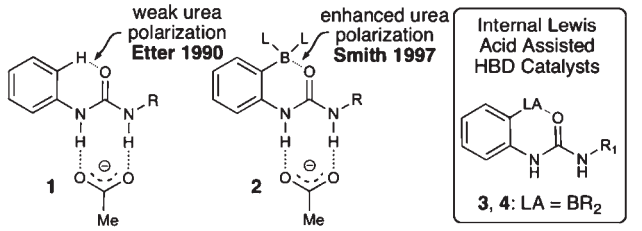


Figure 1. Internal Lewis acid assisted hydrogen bond donor catalysis.

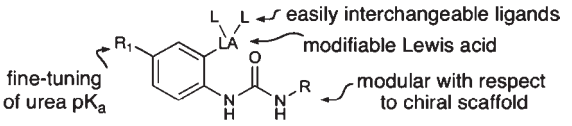
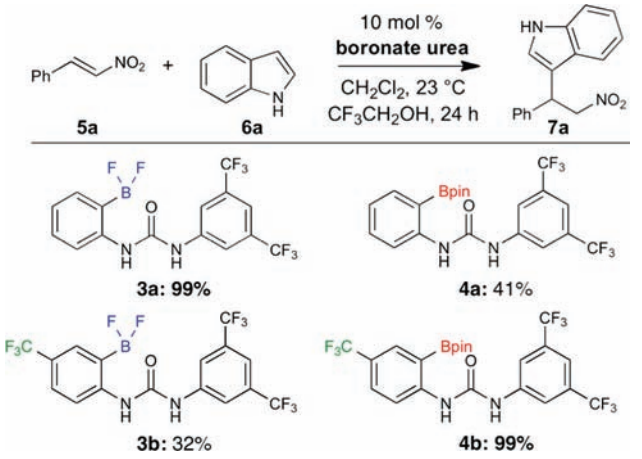


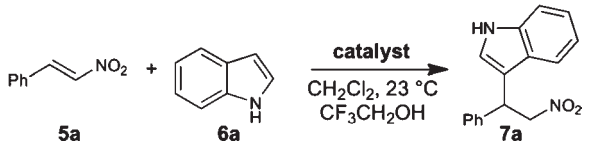
Figure 2. Key catalyst parameters.

Scheme 1. Boronate Ureas as Enhanced Hydrogen Bond Donor Catalysts



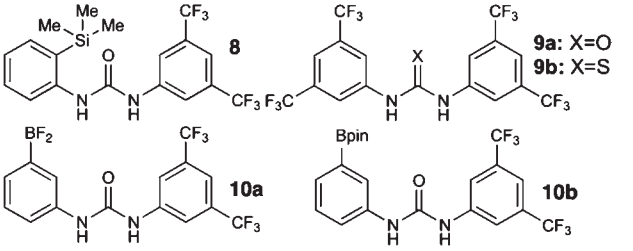
bonding[7] (**1**) and Smith's more recent discovery that an appropriately placed internal Lewis acid enhances urea polarization and significantly increases acetate anion recognition of ureas (**2**, Figure 1).[8] The possibility of applying the concept of internal Lewis acid assisted urea polarization toward organic catalysis intrigued us for two main reasons: (1) the potential to access an entirely new family of activated HBD catalysts and (2) the development of a class of HBDs containing several tunable parameters to facilitate the development of a highly active and stereoselective catalyst. Key

Table 1. Boronate Urea Catalyst Activity Study[a]



entry	catalyst	mol % cat.	time (h)	yield[b] (%)
1	**3a**	10	24	99
2	**3a**	1	**72**	**95**
3	**4b**	10	24	99
4	**4b**	1	**72**	**92**
5	**8**	20	24	50
6	**9a**	10	24	43
7	**9b**	10	24	80
8	**10a**	10	24	41
9	**10b**	10	24	28

[a] Reactions performed using 1.5 equiv of indole at a concentration of 1 M. See Supporting Information for detailed experimental procedures. [b] Isolated yield



features of internal Lewis acid assisted ureas include an alterable Lewis acid component, an easily modified chiral scaffold, and the ability to fine-tune the electronic nature and chiral environment via modification of the ligands on the Lewis acid and/or introduction of functional groups on the aryl amino borane (Figure 2). While it was reasoned that internal Lewis acid assisted HBD catalysis was a promising avenue to explore, the study began with a number of uncertainties. There were concerns regarding the synthesis and stability of the activated ureas, and the potential issue of low catalyst turnover as a result of overly strong hydrogen bonding was also considered. Despite these concerns, we were excited by the potential surrounding internal Lewis acid assisted ureas and set out to investigate boronate ureas (**3** and **4**) as new classes of enhanced HBD catalysts.

To rapidly evaluate the potential of internal Lewis acid assisted HBD catalysis, the nucleophilic addition of indole (**6a**) to β-nitrostyrene (**5a**) was selected as a test bed due to literature precedent demonstrating the success of urea and thiourea catalysts in this reaction (Scheme 1).[9,10] Almost

(7) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Ziaebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.

(8) (a) Hughes, M. P.; Shang, M. Y.; Smith, B. D. *J. Org. Chem.* **1996**, *61*, 4510. (b) Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492.

(9) For reports of urea/thiourea catalyzed indole additions, see: (a) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, *13*, 2374. (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.

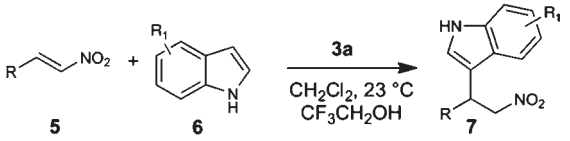
(10) For examples of phosphoric acid catalyzed indole additions, see: (a) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *120*, 4016.

immediately we were delighted to find 10 mol % of **3a** affords a quantitative yield of desired product **7a** after 24 h in dichloromethane in the presence of an alcohol additive. A more in-depth investigation into the internal Lewis acid assisted urea structure allowed the identification of a key element of the catalyst design: *the ligands on boron significantly influence the activity of the catalyst*. Difluoroboryl urea **3a** is considerably more active than the analogous pinacol ester **4a**, which is able to provide only 41% of **7a** under identical reaction conditions. Fine-tuning of the pinacol ester urea was achieved through the installation of an additional electron-withdrawing group on the amino phenyl borane side of the urea to afford the significantly more active catalyst **4b**. It was initially a surprise to find difluoroboryl urea **3b** operates as a less active catalyst with 10 mol % able to afford just 32% of **7a**. However, after consideration of the structure it was reasoned this may be due to overly acidic NH protons.[11]

With highly active boronate urea catalysts **3a** and **4b** in hand, attention was turned toward testing the limits of the reaction with respect to catalyst loadings (Table 1). We were pleased to find excellent yields of product can be obtained at catalyst loadings of just 1 mol % with **3a** or **4b** after 72 h (95% and 92%, entries 2 and 4). To examine the role of the Lewis acid on the catalyst activity, we tested the effect of a strategically placed silicon. The importance of the boron became apparent when 20 mol % of **8** afforded only a 50% yield of **7a** (entry 5). Key control experiments further probing the catalyst activity revealed **3a** and **4b** *provide enhanced yields* in otherwise identical reaction conditions when directly compared to more conventional catalysts **9a** and **9b** (Table 1, entries 1 and 3 vs 6 and 7). This significant finding demonstrates that internal Lewis acid activation of ureas is one strategy to overcome the low turnover rates that limit the synthetic utility of traditional urea catalysts. The reduced activity observed with control catalysts **10a** and **10b**, ureas unable to participate in internal Lewis acid coordination, provided further support for this improved method of urea activation (entries 8 and 9).

To test the generality of internal Lewis acid assisted hydrogen bond donor catalysis, a brief investigation evaluating the scope of the reaction was carried out, and the results are listed in Table 2. The process tolerates both electron-donating and electron-withdrawing substituents on the nitrostyrene; just 2.5 and 5 mol % of **3a** afford excellent yields of corresponding products after 24 h (87% and 88%, entries 2 and 3). Although alkyl nitroalkenes derived from hexanal and cyclohexanecarboxaldehyde

Table 2. Boronate Urea Catalysis Substrate Screen[a]



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entry	R	R_1	product	mol % **3a**	time (h)	yield[b] (%)
1	Ph	H	**7a**	5	48	91
2	4-Br-C_6H_4	H	**7b**	2.5	24	87
3	4-MeO-C_6H_4	H	**7c**	5	24	88
4	*n*-pentyl	H	**7d**	10	48	64
5	cyclohexyl	H	**7e**	10	48	69
6	Ph	5-MeO	**7f**	5	24	89
7	Ph	5-Br	**7g**	10	48	70

[a] See Supporting Information for more details. [b] Isolated yields.

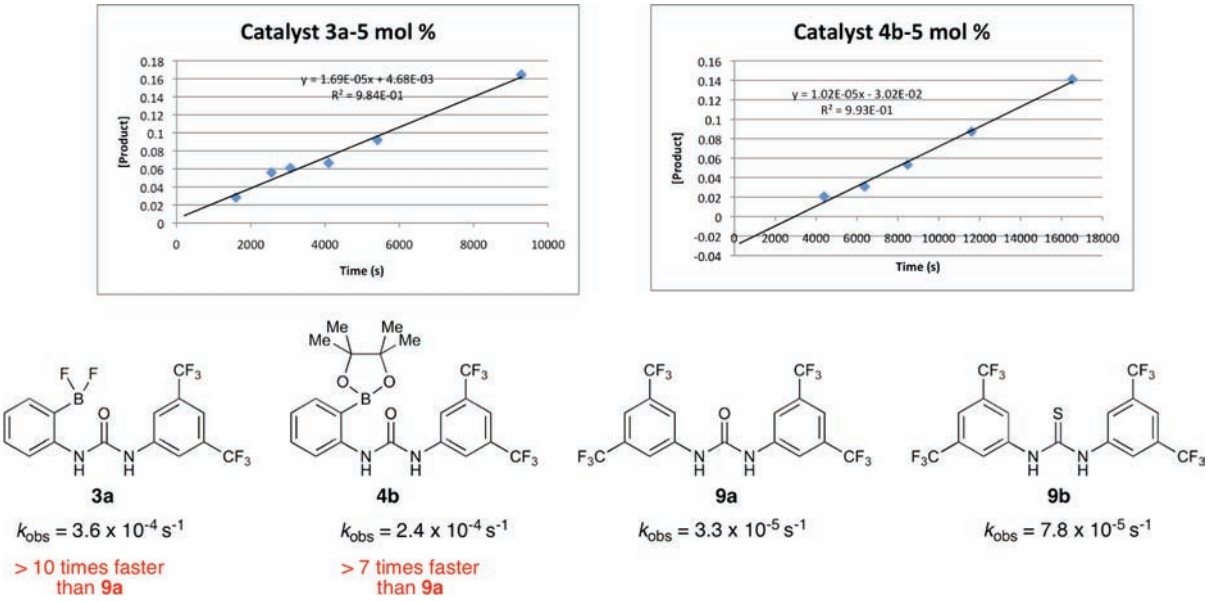
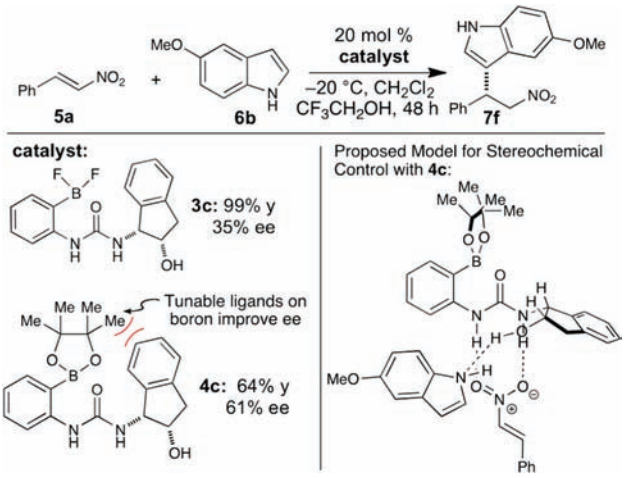


Figure 3. Comparison of the rate data of boronate ureas and more conventional urea and thiourea catalysts.

Scheme 2. Chiral Boronate Urea Catalysis



proved to be more challenging electrophiles, good yields of the desired products were obtained after 48 h with 10 mol % of **3a** (64% and 69%, entries 4 and 5). A short investigation of indoles revealed certain substituents can be well accommodated in the reaction. For example, more nucleophilic 5-methoxyindole afforded an 89% yield of the desired adduct with 5 mol % of **3a** after 24 h (entry 6). The slightly less nucleophilic 5-bromoindole proved to be somewhat more sluggish yet afforded a good yield of product after 48 h (70%, entry 7).

Preliminary kinetic studies probing the activity of catalysts **3a** and **4b** were conducted in direct comparison to catalysts **9a** and **9b**. Using the method of initial rates, the rate of the reaction was measured at several catalyst loadings. The results at 5 mol % are depicted in Figure 3 and show that there is strong evidence supporting boronate ureas as enhanced hydrogen bond donor catalysts. Most notably, the observed rate constant of difluoroboryl urea **3a** was found to be $3.6 \times 10^{-4}\ s^{-1}$, a rate more than *10 times faster* than that of the traditional urea catalyst **9a**. Pinacol ester **4b** has an observed rate constant of $2.4 \times 10^{-4}\ s^{-1}$, more than 7 times faster than that of **9a**. Both **3a** and **4b** were also found to be nearly 5 times and 3 times faster, respectively, than thiourea **9b**. The reaction was found to be first order with respect to catalyst, as shown by the linear relationship between the yield and concentration of the catalyst.

(11) Investigations to better understand this result, including the determination of the boronate urea pK_a's, are ongoing in our laboratory.

Initial investigations confirm that asymmetric catalysis with internal Lewis acid assisted HBDs is an area filled with opportunity (Scheme 2). Under relatively unoptimized reaction conditions *cis*-aminoindanol derived catalyst **3c** proved to be highly active, however; only moderate levels of enantioselectivity were obtained (35% ee) after 48 h at −20 °C. Chiral boronate urea **4c**, on the other hand, gave rise to 64% of **7f** with good enantioselectivity (61% ee). Notably, these ureas differing only by their ligands on boron have significantly different abilities to induce stereoselectivity into the transformation. These data demonstrate the importance of a catalyst scaffold that contains several tunable parameters to enable the development of the optimal catalyst, in regard to both activity and stereoselectivity, for a bond-forming reaction.

In summary, boronate ureas have been disclosed as a new class of HBD catalysts with enhanced reactivity due to the strategic placement of an internal Lewis acid. Importantly, the highly tunable nature of these ureas offers an ideal platform for the rational design of HBD catalysts to achieve optimal performance in terms of both activity and stereocontrol. Investigations into internal Lewis acid assisted HBD catalysis are ongoing in our laboratory, and we look forward to reporting our progress in this area.

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