

Enantioselective β -Protonation by a Cooperative Catalysis Strategy

Michael H. Wang, Daniel T. Cohen, C. Benjamin Schwamb, Rama K. Mishra, and Karl A. Scheidt*

Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Northwestern University, Silverman Hall, Evanston, Illinois 60208, United States

S Supporting Information

ABSTRACT: An enantioselective *N*-heterocyclic carbene (NHC)-catalyzed β -protonation through the orchestration of three distinct organocatalysts has been developed. This cooperative catalyst system enhances both yield and selectivity, compared to only the NHC-catalyzed process. This new method allows for the efficient conversion of a large scope of aryl-oxobutenates to highly enantioenriched succinate derivatives and demonstrates the benefits of combining different activation modes in organocatalysis.

Advances in sustainable and selective reaction development for applications in bioactive molecule construction, chemical synthesis, and material science rely on translating innovative concepts into new catalytic asymmetric approaches.¹ The orchestration of independent catalysts to promote unique transformations is a powerful strategy for reaction discovery.² Within the field of *N*-heterocyclic carbene (NHC) catalysis,³ cooperative catalysis has been demonstrated as a viable strategy for improving yield, selectivity, and expanding substrate scope.^{2d,4} Of particular interest is the ability of NHCs to generate homoenolates, or carbonyl β -anions.⁵ These unique nucleophiles have been utilized in various C=X π systems to form C–C/C–N bonds, allowing access to a wide array of heterocycles and bioactive compounds.^{4b,6} Yet, C–H bond formation through the β -protonation of homoenolates has only been achieved with low enantioselectivity.⁷ The proton is effectively the simplest functional group in chemistry, and its manipulation is the basis of many modern catalytic processes.^{1a,8} The development of catalytic asymmetric α -protonations of enolates through malonates, silyl enol ethers, ketenes, and α,β -unsaturated carbonyls has led to novel strategies for the synthesis of compounds of interest possessing tertiary carbon stereocenters (Figure 1).^{1a,2b,9} By contrast, to the best of our knowledge a highly enantioselective β -protonation has not been achieved. In addition to general considerations of enantioselective α -protonation—racemization under protonation conditions and selectively generating pure *E*- or *Z*-enolates— β -protonation encounters the additional challenges of generating the necessary homoenolate under catalytic conditions and imparting enantioinduction through interactions with remote functional groups of the chiral catalyst.^{9b–d} Hence, a selective β -protonation would be an enabling and distinctive addition to the broad class of asymmetric protonation transformations.

We decided to pursue cooperative NHC/H-bond donor (HBD)^{3e,10} activation for an enantioselective β -protonation of α,β -unsaturated aldehydes. If successful, this process would offer

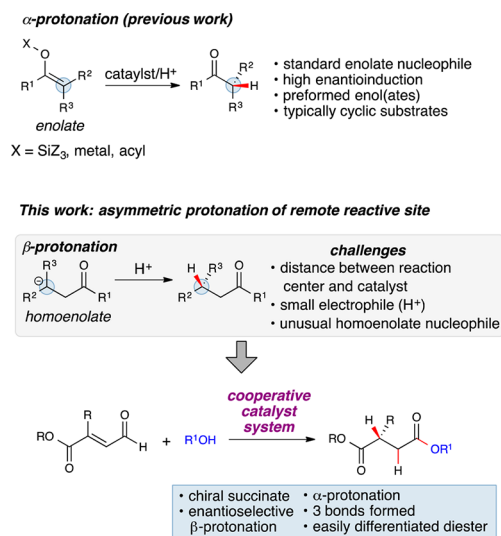


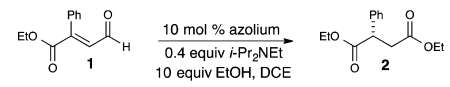
Figure 1. Asymmetric protonation.

an organocatalytic alternative to chiral auxiliary and metal-mediated transformations,¹¹ as well as direct access to easily differentiated succinate products. An unexplored route to chiral succinic esters is asymmetric β -protonation of 2-substituted-oxobutenates. Compared to standard alkyl/aryl substituted homoenolates, the ester/aryl substitution of oxobutenates carries two important functions: to provide an opportunity for cooperative carbonyl activation and to promote rapid NHC-homoenolate equivalent formation.^{4b} We proposed that HBD cocatalyst coordination would impart greater steric bulk near the β -position and therefore enhance enantioselectivity. This new approach would provide a conceptually distinct and complementary *Umpolung* strategy¹² to known reductions of β,β -disubstituted carbonyl substrates^{11a,13} and access chiral succinic esters in the process.

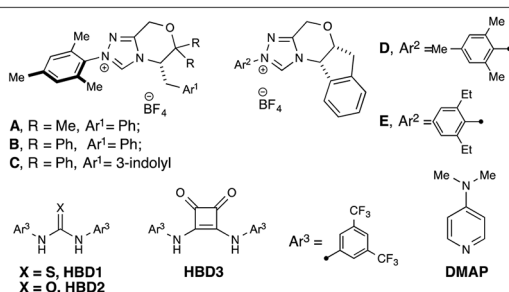
Our investigation commenced by examining the enantioselective β -protonation of β -ethyl ester cinnamaldehyde derivative **1**. Combining **1** with ethanol in the presence of Hünig's base and triazolium salt **A** produced saturated *bis*-ester **2** in 80% isolated yield and 66:34 er (Table 1, entry 1). We then directed our efforts toward optimizing the reaction through cooperative catalysis. Addition of thiourea **HBD1**, which has demonstrated high reactivity among achiral H-bond donors,^{10a,14} produced a significant increase in enantioselectivity but also resulted in diminished yield (entry 2). Conducting the reaction at a lower

Received: March 19, 2015

Table 1. Optimization of Reaction Conditions



Entry	Azolium	Temp. (°C)	Additive (mol %)	yield (%) ^a	er ^b	time (h)
1	A	23	none	80	66:34	12
2	A	23	HBD1 (30)	44	88:12	12
3	A	0	HBD1 (30)	41	93:7	12
4	A	0	HBD1 (30), DMAP (10)	71	92:8	10
5	B	0	HBD1 (30), DMAP (10)	40	84:16	-
6	C	0	HBD1 (30), DMAP (10)	17	66:34	-
7	D	0	HBD1 (30), DMAP (10)	42	73:27	-
8	E	0	HBD1 (30), DMAP (10)	40	74:26	-
9	A	0	HBD2 (30), DMAP (10)	84	92:8	20
10	A	0	HBD3 (30), DMAP (10)	94	91:9	24
11	A	0	HBD3 (30)	81	96:4	36
12	A	0	HBD3 (30), DMAP (5)	85	94:6	24

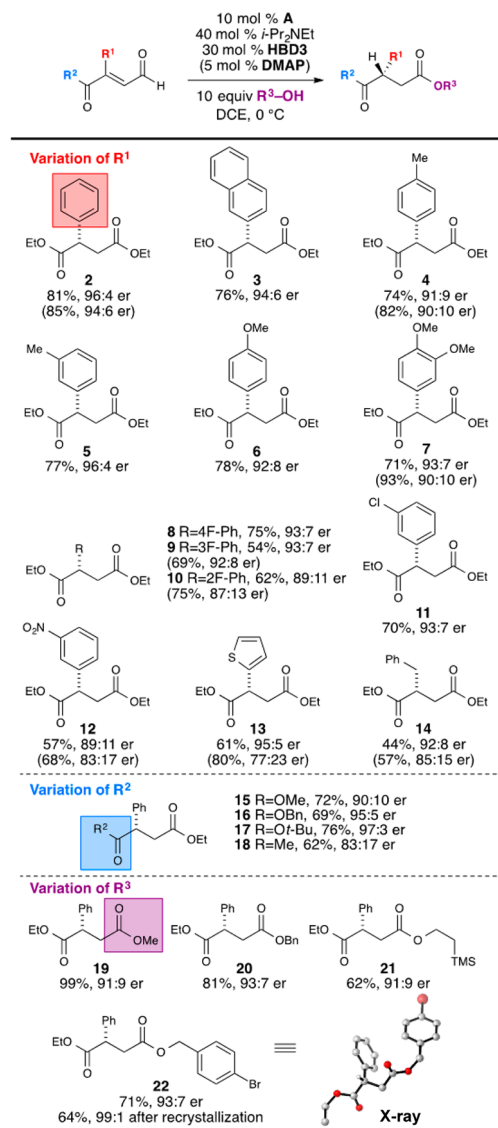


^aIsolated yields. ^bDetermined by HPLC (chiral stationary phase).

temperature provided an increase in enantioselectivity, though the yield was further suppressed (entry 3). We hypothesized that side reactions were occurring following the β -protonation event (but prior to catalyst regeneration) thereby furnishing unproductive byproducts. To test this hypothesis we introduced an acyl transfer agent to increase the rate of catalyst regeneration.¹⁵ Gratifyingly, addition of a **DMAP** cocatalyst incorporated higher enantioselectivity and good yield (entry 4) compared to the initial single catalyst system. After a survey of triazolium precatalysts showed no improvement in either yield or selectivity (entries 5–8), the HBD was evaluated. The urea analog (**HBD2**) provided a significant increase in yield, with minimal impact on enantioselectivity (entry 9). Further inquiries into the core structure of the carbonyl-activation cocatalyst led to the investigation of squaramides, which Rawal has demonstrated to be excellent H-bond donor catalysts.¹⁶ Incorporation of **HBD3** provided high yields with a slight erosion of enantioselectivity (entry 10). While the omission of **DMAP** provided the highest levels of enantioselectivity (entry 11), addition of only 5 mol % of **DMAP** provided moderately improved yields and, more importantly, a significant decrease in reaction time (entry 12, 24 h vs 36 h for 100% conversion).

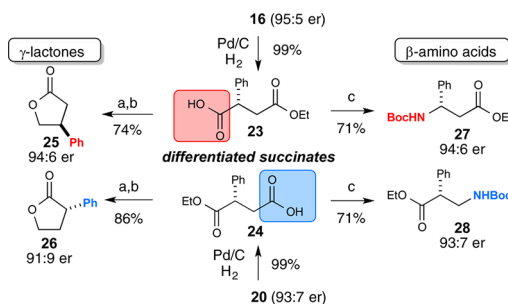
With an optimized system that balances selectivity and reactivity, the scope for the asymmetric β -protonation was explored (Table 2).¹⁷ Both electron-rich and -poor substituents about the aryl ring were well tolerated (**6**–**12**). *Ortho*-substitution on the aryl group led to lower enantioselectivity (**10**). Changing the steric size of the ester functionality had a positive impact on enantioselectivity (**15**–**17**), with *tert*-butyl ester (**17**) giving the highest level of enantioselectivity. Finally, the catalytic system was tolerant of different nucleophiles necessary for catalyst turnover (**19**–**22**).^{18,19}

A practical advantage of this catalytic strategy is the ease of chemoselectively elaborating these succinic esters. Succinic acids are valuable chiral building blocks for the synthesis of bioactive natural products, peptidomimics, and β -amino acids,²⁰ and

Table 2. Substrate Scope^a

^aYields are of isolated product after column chromatography; er was determined by chiral HPLC analysis. Yield and er values given in parentheses represent substrates run with 5 mol % **DMAP** cocatalyst.

succinate derivatives have various therapeutic applications.²¹ The ability to independently synthesize the ester groups allows for complete regioselectivity in the synthesis of butanoic acids, γ -butyrolactones, and β -amino esters (Scheme 1). Starting with

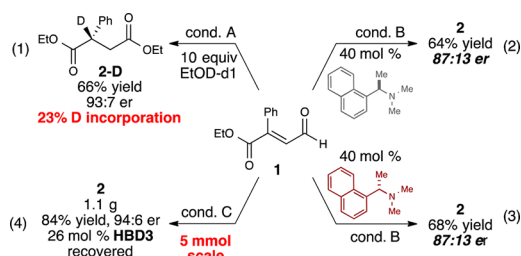
Scheme 1. Succinate Differentiation^a

^aReagents: (a) BH₃·THF; (b) BF₃·OEt₂; (c) DPPA, *t*-BuOH.

benzyl ester **16** or **20**, hydrogenolysis furnishes the α - or β -aryl-butanoic acid (**23** and **24**, respectively) quantitatively. Selective borane reduction of the acid followed by Lewis acid catalyzed lactonization gave 2- and 3-aryl- γ -butyrolactone derivatives (**25** and **26**). Alternatively, a Curtius rearrangement in *tert*-butanol affords Boc-protected β^2 - and β^3 -amino esters (**27** and **28**). From simple starting materials, our NHC/HBD cooperative catalysis system allows easy synthetic differentiation to access privileged regioisomers rapidly, efficiently, and selectively.

In key control experiments to probe the complementary roles of the base and proton source, we observed low deuterium incorporation at the β -position (Scheme 2, eq 1). This suggests a

Scheme 2. Control Experiments^a



^aReagents: (cond A) 10 mol % A, 30 mol % HBD3, 40 mol % *i*-Pr₂NEt, 72 h; (cond B) 10 mol % A, 30 mol % HBD3, 10 equiv EtOH; (cond C) 10 mol % A, 30 mol % HBD3, 40 mol % *i*-Pr₂NEt, 5 mol % DMAP.

strong kinetic isotope effect as a result of proton exchange between the azolium salt, base, and Breslow intermediate.²² Additionally, while the base presumably acts as a proton shuttle to facilitate the overall transformation, the chirality of the base does not affect the stereoselectivity of the protonation step (eqs 2 and 3). Finally, this catalytic system is amenable to larger scale reactions (5 mmol), with a negligible difference in yield or enantioselectivity. Furthermore, on a larger scale, the HBD cocatalyst can be efficiently recovered by precipitation from the unpurified reaction mixture by dilution with CH₂Cl₂ (eq 4).

To gain insight into the roles of each catalyst, we combined our DFT calculations and experimental evidence to propose a model for facial selectivity of the NHC homoenolate (Figure 2). This observed stereochemical assignment was corroborated by DFT modeling of ground state structures, which proposed homoenolate intermediate NHC_HE2 as more energetically favorable. The benzyl group of the NHC framework blocks the *re*-face

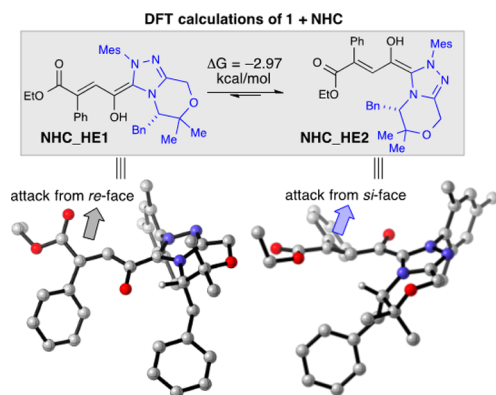


Figure 2. DFT calculations of homoenolate, computed with Schrödinger interface using Jaguar DFT with B3LYP/6-31G**.

thereby allowing for an *si*-face protonation. NMR spectroscopy provided evidence that the HBD is involved in the protonation event: the intermolecular interaction of substrate and HBD was observed through 1D NOESY where the methylene protons of **1** exhibited an NOE with the *ortho*-aryl-hydrogens of HBD1 (Figure 3).²³ Combining the DFT calculations, observed NOE,

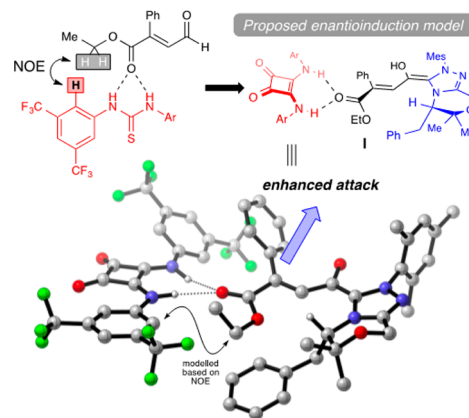
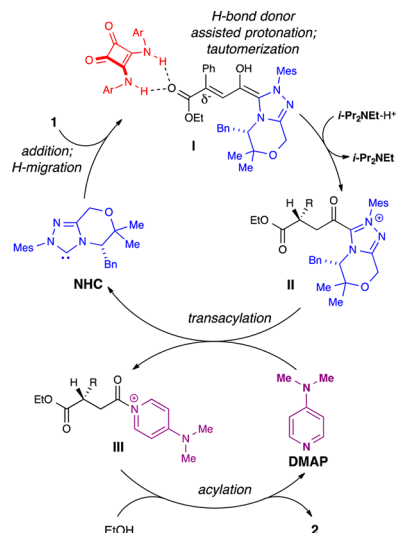


Figure 3. Stereoinduction model.

knowledge of NHC catalysis, and the known activation modes of HBDs, intermediate **I** (Figure 3) emerges as the working stereochemical model for activation and enantioinduction. The coordination of the HBD presumably increases the steric interaction proximal to the β -position of the homoenolate and allows for more selective protonation. This hypothesis is further supported by our substrate scope, which demonstrated increased enantioselectivity as the β -ester increased in steric size (Table 2, 15–17) and decreased enantioselectivity when there were competing sites for hydrogen bonding (**12**).²⁴

Given the data above, we propose the following reaction pathway (Scheme 3): initial deprotonation of **A** gives the active catalyst species, the free carbene (NHC). Following addition of the NHC to **1**, a formal [1,2] proton shift gives extended Breslow intermediate **I**. HBD3 coordinates to the ester, providing additional steric interactions near the β -position, and enhances facial selectivity. β -protonation and subsequent tautomerization

Scheme 3. Proposed Reaction Pathway



affords acyl azolium **II**. Catalyst turnover can be enhanced by acyl transfer catalyst **DMAP**, which forms pyridinium **III** and regenerates the NHC catalyst. Finally, acylation of the alcohol regenerates **DMAP** and furnishes chiral succinate **2**.

This novel cooperative process is a new, metal-free route to succinic esters and the strategy of deploying multiple catalysts in unison expands the concepts and utility of organocatalysis. Ultimately, this catalytic system delivers the first highly enantioselective, high yielding β -protonation of β,β -disubstituted enals, due in part to unique contributions of *all three* catalysts: the NHC, HBD, and acyl transfer species. This system leverages distinct reactivity modes modeled from different organocatalysis strategies (nucleophilic catalysis + hydrogen bond donor activation) in a synergistic manner to efficiently promote a challenging bond-forming reaction. The efficient and operational simplicity of utilizing distinct, *compatible* catalysts versus complex, elaborated single structures with multiple activation sites could lend itself to many catalytic systems in the future.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, spectral data, and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02887.

■ AUTHOR INFORMATION

Corresponding Author

*scheidt@northwestern.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the NIH NIGMS (GM073072).

■ REFERENCES

- (1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) Shang, G.; Li, W.; Zhang, X.; Ojima, I. *Catalytic Asymmetric Synthesis*; John Wiley & Sons: New York, 2010.
- (2) (a) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, 33, 302. (b) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Blackwell Science Publishers: Oxford, 2005. (c) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, 3, 633. (d) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, 3, 53.
- (3) (a) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, 42, 55. (b) Campbell, C. D.; Ling, K. B.; Smith, A. D. *N-Heterocyclic Carbenes in Organocatalysis*; Springer: Dordrecht, 2011; Vol. 32. (c) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, 51, 314. (d) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, 51, 11686. (e) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, 510, 485.
- (4) (a) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, 2, 766. (b) Zhao, X.; DiRocco, D. A.; Rovis, T. J. *Am. Chem. Soc.* **2011**, 133, 12466. (c) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, 51, 4963. (d) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, 134, 8810.
- (5) For a recent review, see: Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, 40, 5336.
- (6) For selected examples, see: (a) Nair, V.; Varghese, V.; Babu, B. P.; Sinu, C. R.; Suresh, E. *Org. Biomol. Chem.* **2010**, 8, 761. (b) White, N. A.; DiRocco, D. A.; Rovis, T. J. *Am. Chem. Soc.* **2013**, 135, 8504. (c) McCusker, E. O. B.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2013**,

52, 13616. (d) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2014**, 136, 17402.

(7) (a) Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, 1306. (b) Maki, B. E.; Patterson, E. V.; Cramer, C. J.; Scheidt, K. A. *Org. Lett.* **2009**, 11, 3942.

(8) *C–H Activation*; Yu, J.-Q., Shi, Z., Eds.; Springer Berlin Heidelberg: Berlin, 2010; Vol. 292.

(9) (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, 118, 12854. (b) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, 1, 359 and references cited therein. (c) Poisson, T.; Kobayashi, S. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2013. (d) Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, 2014, 6103.

(10) For selected reviews, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, 107, 5713. (b) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2014, 2633. For examples of combining NHCs with HBDs, see: (c) Brand, J. P.; Siles, J. I. O.; Waser, J. *Synlett* **2010**, 2010, 881. (d) Jin, Z.; Xu, J.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, 52, 12354. (e) Nawaz, F.; Zaghouani, M.; Bonne, D.; Chuzel, O.; Rodriguez, J.; Coquerel, Y. *Eur. J. Org. Chem.* **2013**, 2013, 8253. (f) Youn, S. W.; Song, H. S.; Park, J. H. *Org. Lett.* **2014**, 16, 1028.

(11) For selected examples of asymmetric hydrogenation, see: (a) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, 42, 728. (b) Bernasconi, M.; Müller, M.-A.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2014**, 53, 5385. For a selected example of a chiral auxiliary, see: (c) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, 64, 6411.

(12) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, 107, 5606. (b) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, 465, 1027. (c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, 41, 3511.

(13) (a) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, 44, 108. (b) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, 40, 1327.

(14) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, 4, 217. (b) Connon, S. J. *Synlett* **2009**, 2009, 354. (c) Schreiner, P. R.; Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S. *Eur. J. Org. Chem.* **2012**, 2012, 5919.

(15) (a) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem. – Eur. J.* **2005**, 11, 4751. (b) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, 50, 6012. (c) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, 132, 13624. (d) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, 133, 13872.

(16) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, 130, 14416.

(17) All substrates were evaluated with the NHC-HBD cooperative catalyst conditions. If the isolated yields were deemed lower than a practical level of ~60%, then 5 mol % DMAP was employed (yield and *er* given in parentheses).

(18) The absolute configuration of **22** was established by X-ray diffraction. The remainder products were assigned by analogy.

(19) The use of the Z-alkene isomer of **1** undergoes an intramolecular cyclization to provide a substituted furanone (not shown; see Supporting Information for details).

(20) *Enantioselective Synthesis of β -Amino Acids*, 2nd ed.; Blackwell Science Publishers: Oxford, 2005.

(21) Arason, K. M.; Bergmeier, S. C. *Org. Prep. Proced. Int.* **2002**, 34, 337.

(22) A full analysis of this result is currently underway.

(23) The propensity of ureas and squaramides to form insoluble aggregates (vs more soluble thiourea variants) prevented the observation of the analogous interactions under similar, relevant conditions. Despite those limitations, all of the HBDs most likely share similar function in our catalyst system, as evidenced by their advantageous contribution to enantioselectivity (vide supra, Table 1).

(24) (a) Amendola, V.; Fabbri, L.; Mosca, L. *Chem. Soc. Rev.* **2010**, 39, 3889. (b) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, 357, 253.