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Highly Efficient Hydrogen-Bonding Catalysis of the Diels−Alder Reaction of 3-Vinylindoles and Methyleneindolinones Provides Carbazolespirooxindole Skeletons

Bin Tan,[†] Gloria Hernández-Torres,[†,‡] and Carlos F. Barbas, III*[,†]

[†]The Skaggs Institute for Chemical Biology and Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

[‡]Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Supporting Information

ABSTRACT: Carbazolespirooxindole derivatives were synthesized in a high-yielding, atypically rapid, stereocontrolled Diels−Alder reaction catalyzed by a C_2-symmetric bisthiourea organocatalyst. Simple precursors and mild conditions were used to construct carbazolespirooxindole derivatives with high enantiopurity and structural diversity under H-bonding catalysis. The practical approach recycles the organocatalyst and solvent. This simple and efficient operational procedure will allow diversity-oriented syntheses of this intriguing class of compounds.

Despite rapid progress in organocatalyst development,[1] practical and efficient asymmetric approaches remain in high demand. An ideal asymmetric reaction would be atom-economical and rapid, performed under mild conditions to yield quantitative and enantiomerically pure products with catalyst and solvent recycling. Since the Diels−Alder (D−A) reaction[2] is arguably the most powerful organic transformation available for the synthesis of complex molecules, development of efficient organocatalytic approaches to this reaction is significant.[3] Organocatalytic asymmetric D−A reactions have been approached using iminium,[4] enamine,[5] and bifunctional acid−base catalysis[6] as well as hydrogen-bonding catalysis.[7] Here we describe an unusually efficient organocatalytic asymmetric D−A reaction of 3-vinylindoles and methyleneindolinones that uses the readily accessible bisthiourea catalyst **I** as a H-bonding catalyst.

Spirooxindole[8] and tetrahydrocarbazole[9] scaffolds are present in many natural and unnatural compounds that exhibit important biological activities (Figure 1). Recently, methyleneindolinones were used as highly reactive Michael acceptors[10] and as dipolarophiles[11] in domino reactions[12] and [2 + 3] cycloadditions.[11d] 3-Vinylindoles have been used as dienes in an organocatalytic D−A reaction;[6d] however, only moderate yields were obtained after long reaction times at low temperature (−55 °C). We envisioned that carbazolespirooxindole skeletons with multiple stereocenters could be constructed through simple D−A reactions between 3-vinylindoles (**1**) and methyleneindolinones (**2**) with suitable organocatalysts (Scheme 1).

Inspired by the pioneering work of Schreiner[7a,b] and Rawal[7c−e] on the use of H-bonding catalysts[13] in D−A reactions, we envisioned that bisthiourea catalyst **I**[14] (Scheme 2) should interact

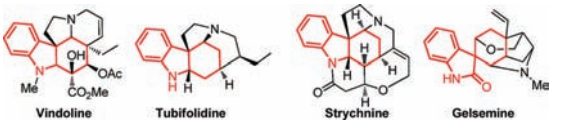
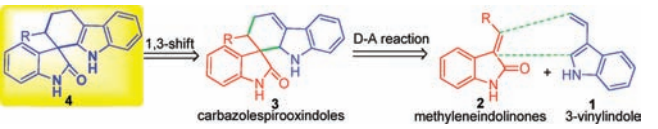
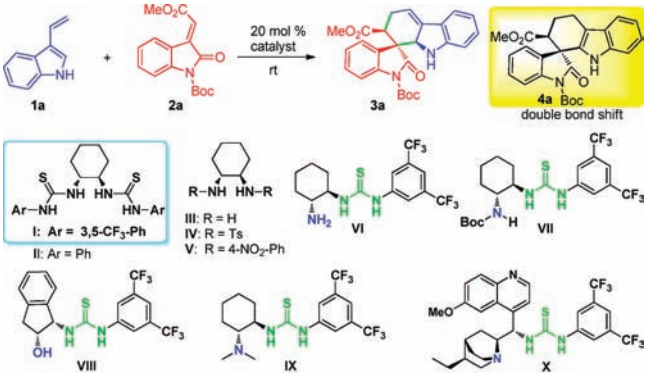


Figure 1. Natural products containing tetrahydrocarbazole or spirooxindole scaffolds.

Scheme 1. Carbazolespirooxindole Scaffold Synthesis



Scheme 2. Catalyst Structures



with methyleneindolinones through H-bonding. Therefore, the D−A reaction between **1a** and **2a** at room temperature in toluene with 20 mol % catalyst **I** was investigated. In the absence of any other additive, the reaction proceeded smoothly in quantitative yield with moderate stereoselectivity[15] [see Supporting Information (SI) Table 1, entry 1]. As expected, lower enantioselectivity was obtained using the phenyl-derivatized thiourea catalyst **II** (SI Table 1, entry 2), since this catalyst should not effectively H-bond with the substrate. Considering the poor asymmetric induction

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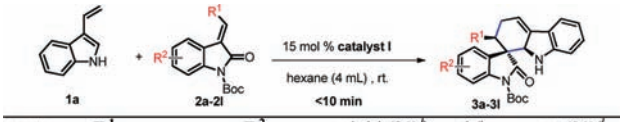
Table 1. Generality of the D−A Reactions[a]



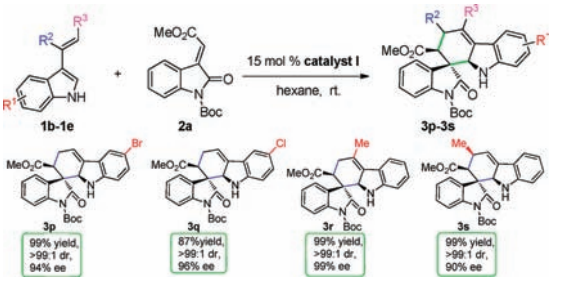
entry	R^1	R^2	yield (%)[b]	dr[c]	ee (%)[d]
1	CO_2Me	H	99 (**3a**)	>99:1	96
2	CO_2Me	5-Br	92 (**3b**)	>99:1	93
3	CO_2Me	5-F	96 (**3c**)	>99:1	93
4	CO_2Me	6-Cl	95 (**3d**)	>99:1	94
5	CO_2Me	5-Me	96 (**3e**)	>99:1	95
6	CO_2Me	5-OMe	95 (**3f**)	>99:1	93
7	CO_2Et	H	93 (**3g**)	>99:1	97
8	CO_2Bn	H	98 (**3h**)	>99:1	95
9	CO_2Bu-*t*	H	97 (**3i**)	>99:1	95
10	COPh	H	89 (**3j**)	>99:1	89
11	COC_6H_4Cl-*p*	H	94 (**3k**)	>99:1	88
12	COMe	H	96 (**3l**)	>99:1	94
13	CN	H	99 (**3m**)	>99:1	92
14[e]	Ts	H	94 (**3n**)	>99:1	90
15[f]	Ph	H	75 (**3o**)	>99:1	88

[a] Unless otherwise specified, all reactions were carried out using 3-vinylindole **1a** (0.15 mmol, 1.5 equiv) and methyleneindolinone **2a** (0.1 mmol, 1.0 equiv) in hexane (4 mL) with 15 mol % catalyst at room temperature (22 °C). [b] Isolated yields. Almost quantitative yields were obtained except for entry 15, as shown by ^{1}H NMR analysis of the crude product. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral-phase HPLC analysis of the [1,3]-H shift product. [e] The reaction was carried out at −20 °C. [f] Using 20 mol % catalyst **I** gave only 80% conversion after 12 h.

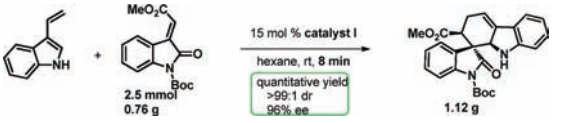
observed when the bisthiourea moiety was replaced by other common H-bond donor groups (SI Table 1, entries 3−8), we assumed that catalyst **I** acted to simultaneously activate both the diene and the dienophile and that the bisthiourea functionality was essential. To our surprise, catalyst **VIII**,[16] which efficiently catalyzes Michael reactions and Friedel−Crafts alkylations, provided only moderate stereoselectivity (SI Table 1, entry 8). It is noteworthy that bifunctional tertiary amine−thiourea catalysts[17] that might activate both the diene and the dienophile through H-bonding interactions gave rise to the desired product with moderate diastereoselectivity and low enantioselectivity (<10% ee; SI Table 1, entries 9 and 10).

Reactions catalyzed by **I** were further optimized (for more details, see the SI). The asymmetric induction was sensitive to solvent (SI Table 1, entries 11−14). Of those tested, hexane provided the best exo/endo selectivity (>99:1 dr) and enantioselectivity (93% ee) (SI Table 1, entry 14). In contrast to previously reported data for D−A reactions with vinylindoles, the exo cycloadduct **3a** was obtained as the only diastereoisomer under our reaction conditions. Moreover, the D−A adduct precipitated as a white solid when hexane was used as the solvent. The stereoinduction was not improved when the temperature was decreased to −20 °C (SI Table 1, entry 16). Optimal results were obtained in the reaction performed in hexane with 15 mol % catalyst at room temperature (SI Table 1, entry 15).

Scheme 3. Effect of Substituents on the 3-Vinylindole



Scheme 4. Preparative-Scale Experiment



To determine the substrate generality and limitations of this strategy, a number of donors and acceptors were evaluated (Table 1). Only one diastereomer was detected for each product, as determined from ^{1}H NMR spectra of the crude reaction mixtures, although 3−4 stereogenic centers were generated in these D−A reactions. Modifying the acceptor structure with substituents that altered its electronic nature had little effect on the yields and stereoselectivities (entries 1−6). Ester and ketone groups did not substantially impact the yield or stereoselectivity (entries 7−12). Furthermore, activating cyano and tosyl groups were good substrates for the reaction (entries 13 and 14). The wide scope of methyleneindolinone derivatives supports the generality of the reaction and makes possible subsequent transformations of the final products. The current system does have limitations: for example, a phenyl-substituted methyleneindolinone provided the corresponding product with lower chemical and optical yield (entry 15). Pharmacological agents often have chlorine or bromine atoms on the indole moiety. As shown in Table 1 and Scheme 3, halogenated carbazolespirooxindoles were obtained in excellent yields and diastereo- and enantioselectivities. In addition, substituted dienes served as substrates. In the case of **3s**, a new stereocenter was selectively created from the *E* vinylindole. The absolute configuration of **3p** was unambiguously assigned by X-ray analysis, and this result together with NMR analysis was used to establish the relative and absolute configurations of our compounds (see the SI).

To investigate recycling of the organocatalyst, the reaction of **1a** (0.15 mmol, 1.5 equiv) and **2a** (0.1 mmol, 1 equiv) in hexane was used as a model (see the SI). Reaction completion was accompanied by a color change of the reaction mixture from yellow to colorless. Because of the difference in the solubilities of the reagents and the D−A adduct, the final product was isolated by simple centrifugation. The catalyst and the excess **1a** remained in the filtrate, whereas the product was recovered as a white solid after filtration. **1a** (0.13 mmol) and **2a** (0.10 mmol) were then added to the solution for the next cycle of the D−A reaction. This procedure was repeated several times with only a marginal loss of performance in each cycle. Almost quantitative yield and excellent enantioselectivity were obtained after five cycles (see SI Table 2). When the reaction was carried out on a gram scale, there was no change in reactivity or stereoselectivity (Scheme 4). As the

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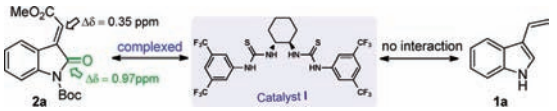
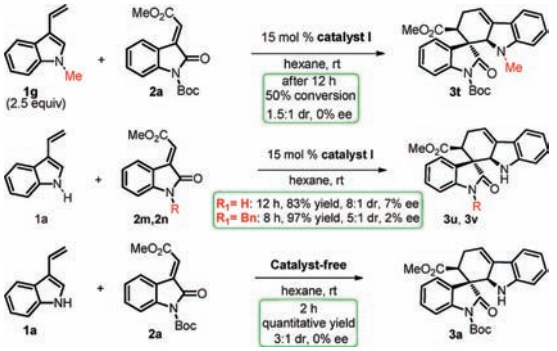


Figure 2. Chemical shift changes ($\Delta\delta$) observed for the ^{13}C NMR signals of methyleneindolininone **2a** complexed with catalyst **I**. No changes were observed in the spectra of 3-vinylindole **1a** after addition of catalyst **I**.

Scheme 5. Control Experiment for Mechanism Studies

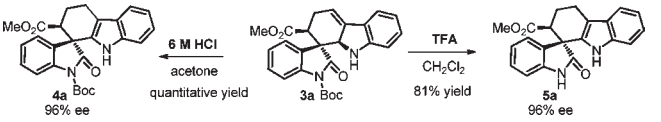


catalyst was readily recycled and the reaction was scalable, this method should be suitable for large-scale chemical production. This procedure is not limited to the synthesis of **3a**, since all products with the exception of **3c** precipitated from the reaction mixture.

Although the mechanism of this reaction has not been completely elucidated, we believe that the thiourea groups direct the stereoselectivity.[18] We initially hypothesized that the catalyst forms H-bonds with both the 3-vinylindole and the methyleneindolinone. However, in ^1H and ^{13}C NMR experiments, no evidence of catalyst interactions with 3-vinylindole alone was found, while strong interactions with the methyleneindolinone were observed in the ^{13}C NMR spectra, where H-bonding induced a downfield shift of up to 0.98 ppm (Figure 2). It remains possible that the 3-vinylindole is activated in a later tertiary complex. For more details, see the SI. The poor stereocontrol obtained in the reaction with 1-methyl-3-vinylindole (Scheme 5) indicated that the N−H group of the vinylindole is essential. This and the unusual exo selectivity obtained in the D−A product suggested that additional interactions between the oxindole and vinylindole reagents must be involved in the stereoselectivity. Furthermore, the effects of the *N*-methyleneoxindole protecting group on the ee were striking. A bulky electron-acceptor group at the 3-position was necessary, since only Boc-protected 3-methyleneoxindole derivatives provided a stereocontrolled product; the unprotected derivative and the Bn-protected derivative showed no stereoinduction. In the absence of catalyst, the reaction was significantly slower and required several hours to reach completion. On the basis of these data, we hypothesize that the vinylindole might be directed or oriented by interactions between the N−H group of the diene and the Boc group of the dienophile via $\pi-\pi$ and weak H-bonding interactions prior to C−C bond formation. This would provide a well-organized environment for asymmetric induction as well as a pocket to enable this reaction to proceed smoothly. However, more studies are needed to support such a model. While most organocatalytic D−A reactions require several hours to several days to reach completion, the H-bonding-accelerated reactions disclosed here are completed within minutes.

Finally, the Boc-protected carbazolespirooxindoles were successfully deprotected by treatment with trifluoroacetic acid. The [1,3]-H shift can be performed directly under acidic conditions without affecting the ester functionalities or changing the enantioselectivity (Scheme 6).

Scheme 6. Transformation of the Product



In summary, we have developed a highly rapid and efficient organocatalytic Diels−Alder reaction for the direct construction of carbazolespirooxindole derivatives containing three or four stereocenters, including one spiro quaternary chiral center. A simple bisthiourea was used as the organocatalyst, and this straightforward process provided the products in almost quantitative yield with excellent stereoselectivity (>99:1 dr, up to 99% ee) from simple starting materials. Very mild reaction conditions were used, and the reaction was scalable. Furthermore, the catalyst and solvent were recyclable. The bisthiourea activates methyleneindolinones though H-bonding interactions, and the mechanism we have proposed will serve as a useful model for development of other reactions catalyzed by H-bonding. Further synthetic application of this transformation and mechanistic studies are underway in our laboratory.

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
carlos@scripps.edu

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■ REFERENCES

(1) (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Gaunt, M. J.; Johnsson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (f) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (g) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (h) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (i) Organocatalysis Special Feature: Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20618 and subsequent articles.

(2) (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) Williams, R. M.; Stocking, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078.

(3) Recent reviews of enantioselective D−A reactions: (a) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen,

E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, p 1177. (b) Maruoka, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 467. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (d) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (e) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1.

(4) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (d) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (e) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616. (f) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6634. (g) Ishihara, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2008**, *10*, 2893. (h) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (i) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, 1956.

(5) (a) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, S.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 3817. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 6743. (c) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Synlett* **2003**, 1910. (d) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (e) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (f) Ramachary, D. B.; Barbas, C. F., III. *Chem. Eur. J.* **2004**, *10*, 5323. (g) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas, C. F., III. *J. Org. Chem.* **2004**, *69*, 5838. (h) Samanta, S.; Krause, J.; Mandal, T.; Zhao, C. *Org. Lett.* **2007**, *9*, 2745. (i) Xie, H.; Zu, L.; Oueis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1923. (j) Han, B.; Li, J.; Ma, C.; Zhang, S.; Chen, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971. (k) Ramachary, D. B.; Reddy, Y. V.; Prakash, B. V. *Org. Biomol. Chem.* **2008**, *6*, 719. (l) Han, B.; He, Z.; Li, J.; Li, R.; Jiang, K.; Liu, T.; Chen, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474. (m) Wu, L.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196. (n) Ramachary, D. B.; Mondal, R.; Venkaiah, C. *Org. Biomol. Chem.* **2010**, *8*, 321. (o) Jia, Z.; Jiang, H.; Li, J.; Gschwend, B.; Li, Q.; Yin, X.; Grouleff, J.; Chen, Y.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053.

(6) (a) Shen, J.; Nguyen, T. T.; Goh, Y. P.; Ye, W.; Fu, X.; Xu, J.; Tan, C. H. *J. Am. Chem. Soc.* **2006**, *128*, 13692. (b) Wang, Y.; Li, H.; Wang, Y.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364. (c) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. (d) Goia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236.

(7) (a) Wittkopp, A.; Schreiner, P. R. *Org. Lett.* **2002**, *4*, 217. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407. (c) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (d) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (e) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336. (f) Liu, H.; Cun, L.; Mi, A.; Jiang, Y.; Gong, L. *Org. Lett.* **2006**, *8*, 6023. (g) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796. (h) Mori, K.; Maddaluno, J.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Synlett* **2009**, 2346. (i) Chen, H.; Trewyn, B.; Wiench, J.; Pruski, M.; Lin, V. *Top. Catal.* **2010**, *53*, 187. (j) Wang, X.; Chen, J.; Cao, Y.; Cheng, H.; Xiao, W. *Org. Lett.* **2010**, *12*, 1140.

(8) (a) Bond, R. F.; Boeyens, J. C. A.; Holzapfel, C. W.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1751. (b) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573. (e) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63.

(9) (a) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058. (b) King, F. D.; Brown, A. M.; Gaster, L. M.; Kaumann, A.; Medhurst, A. D. *J. Med. Chem.* **1993**, *36*, 1918. (c) Bonjoch, J.; Sole, D.; Garcia-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230. (d) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455. (e) Kato, D.; Sasaki, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3685.

(10) (a) Bencivenni, G.; Wu, L.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (b) Wei, Q.; Gong, L. *Org. Lett.* **2010**, *12*, 1008. (c) Jiang, K.; Jia, Z.; Chen, S.; Wu, L.; Chen, Y. *Chem. Eur. J.* **2010**, *16*, 2852. (d) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem. Eur. J.* **2010**, *16*, 12541. (e) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473.

(11) (a) Chen, X.; Wei, Q.; Luo, S.; Xiao, H.; Gong, L. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (b) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem. Eur. J.* **2010**, *16*, 12541. (c) Zhang, X.; Cao, S.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, *47*, 1548. (d) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4675.

(12) Recent examples: (a) Ramachary, D. B.; Kishor, M.; Reddy, Y. V. *Eur. J. Org. Chem.* **2008**, 975. (b) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437. (c) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425. (d) Tan, B.; Chua, P. J.; Zeng, X.; Lu, M.; Zhong, G. *Org. Lett.* **2008**, *10*, 3489. (e) Cabrera, S.; Aleman, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121. (f) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2008**, *14*, 4788. (g) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539. (h) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187. (i) Tan, B.; Shi, Z.; Chua, P.; Li, Y.; Zhong, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 758. (j) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (k) Jiang, K.; Jia, Z.; Wu, L.; Chen, Y. *Org. Lett.* **2010**, *12*, 2766. (l) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682. (m) Ramachary, D. B.; Mondal, R.; Venkaiah, C. *Eur. J. Org. Chem.* **2010**, 3205. (n) Jui, N. T.; Lee, E. C. Y; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015. (o) Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas, C. F., III. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20672. (p) Ramachary, D. B.; Prasad, M. S.; Madhavachary, R. *Org. Biomol. Chem.* **2011**, *9*, 2715.

(13) Selected reviews of hydrogen-bonding catalysis: (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.

(14) For selected uses of this catalyst, see: (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (b) Zhang, Y.; Liu, Y.; Kang, T.; Hu, Z.; Chen, Y. *J. Am. Chem. Soc.* **2008**, *130*, 2456. (c) Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron* **2008**, *64*, 9423. (d) Kanta De, C.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. For a pioneering report on thiourea catalysis, see: (e) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

(15) The product was stable during NMR analysis but not during chiral-phase chromatography. Thus, a [1,3]-H shift transformation was performed prior to HPLC analyses.

(16) (a) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (b) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064.

(17) Ricci[6d] obtained good results using a cinchonia alkaloid derivative as a bifunctional tertiary amine−thiourea catalyst. For recent examples, see: (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (b) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967. (c) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (d) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558. (e) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758.

(18) (a) Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785. Computational studies concerning hydrogen-bond-catalyzed D−A reactions: (b) Gordillo, R.; Dudding, T.; Anderson, C. D.; Houk, K. N. *Org. Lett.* **2007**, *9*, 501. (c) Fu, A.; Thiel, W. J. *THEOCHEM* **2006**, *765*, 45. (d) Linder, M.; Brinck, T. *Org. Biomol. Chem.* **2009**, *7*, 1304.