ORGANIC LETTERS

2010
Vol. 12, No. 8
1756−1759

Enantioselective, Organocatalytic Reduction of Ketones using Bifunctional Thiourea-Amine Catalysts

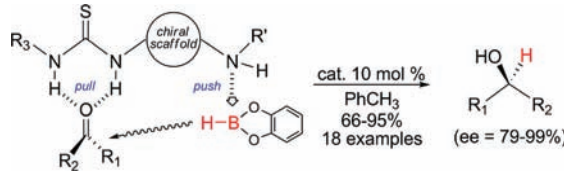
De Run Li, Anyu He, and J. R. Falck*

Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75390

j.falck@utsouthwestern.edu

Received February 11, 2010

ABSTRACT



Prochiral ketones are reduced to enantioenriched, secondary alcohols using catecholborane and a family of air-stable, bifunctional thiourea−amine organocatalysts. Asymmetric induction is proposed to arise from the in situ complexation between the borane and chiral thiourea−amine organocatalyst resulting in a stereochemically biased boronate−amine complex. The hydride in the complex is endowed with enhanced nucleophilicity while the thiourea concomitantly embraces and activates the carbonyl.

The enantioselective reduction of prochiral ketones is a mainstay in the production of enantioenriched, secondary alcohols.[1] As in other areas of chiral synthetic methodology, the trend has been away from stoichiometric reductants[2] toward more economic and environmentally friendly catalytic processes[3] and, in recent years, has embraced organocatalysis.[4,5] One of the most prominent and frequently applied members of this latter category is the Corey−Bakshi−Shibata (CBS) catalyst, a chiral oxazaborolidine pioneered by Itsuno[6] and further developed by Corey[7] and other investigators.[8] However, the sensitivity of oxazaborolidines to oxygen and moisture as well as the need in conjunction with a current project for a highly enantioselective reducing agent compatible with a challenging combination of highly sensitive functionality, prompted us to explore the utility of urea-/thiourea-based organocatalysts as an alternative to CBS oxazaborolidines.[9,10]

While chiral ureas and thioureas have emerged as efficacious catalysts for a variety of nucleophilic conjugate additions[11] and 1,2-carbonyl additions, for example, hydrocyanation,[12] Henry reaction,[13] and Baylis−Hillman reaction,[14] there are few examples of highly enantioselective hydride additions.[15,16] However, the insights gained developing asymmetric oxy-Michael additions of boronic

(1) Review: (a) Itsuno, S. *Org. React.* **1998**, *52*, 395–576. (b) Noyori, R.; Takeshi, O.; Sandoval, C. A.; Muniz, K. *Asymmetric Synth.* **2007**, 321–325.

(2) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley-Interscience: New York, 2001; pp 355−367.

(3) (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2005; pp 314−322. (b) Cho, B. T. *Chem. Soc. Rev.* **2009**, *38*, 443–452.

(4) Review: Kagan, H. B. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007; pp 391−401.

(5) Alternative methodology for enantioselective ketone reductions: (a) Wu, X.; Xiao, J. *J. Chem. Soc., Chem. Commun.* **2007**, 2449–2466. (b) Nakamura, K.; Matsuda, T. *Curr. Org. Chem.* **2006**, *10*, 1217–1246. (c) Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun* **2007**, 2977–2979.

(6) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, *8*, 469–470.

(7) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.

(8) Review Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(9) Li, Derun; Falck, John R., U.S. Pat. Appl. 2009253919, 2009; CAN 151:425227, AN 2009:1231134.

(10) Recent example using borane-amine complex Zhou, Y.; Wang, Y.-W.; Dou, W.; Zhang, D.; Liu, W.-S. *Chirality* **2009**, *21*, 657–662.

(11) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743.

10.1021/ol100365c
Published on Web 03/24/2010

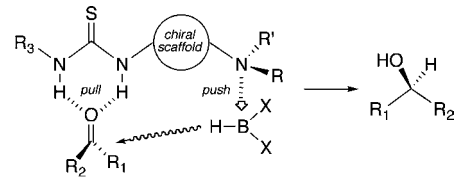
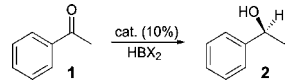


Figure 1. Proposed asymmetric catalysis.

acids with α,β-unsaturated ketones[17] revealed several unique attributes that we felt could be harnessed for enantioselective carbonyl reductions. Specifically, we envisioned that the union between a borane and a chiral thiourea−amine organocatalyst would result in a stereochemically biased boronate−amine complex.[18] The hydride in the complex is endowed with enhanced nucleophilicity (the push) while the thiourea concomitantly embraces and activates the carbonyl (the pull) (Figure 1). As proof-of-concept, we developed a family of robust, bifunctional thiourea−amine catalysts and describe herein their exploitation for the stereodefined reduction of prochiral ketones to enantioenriched, secondary alcohols.

Despite its outstanding performance catalyzing the aforementioned oxy-Michael additions,[17] thiourea catalyst **A**[19] furnished (*S*)-(−)-1-phenylethanol (**2**) in poor yield and low enantioselectivity at room temperature in THF (Table 1, entry 1) using acetophenone (**1**) and BH_3·THF as the model substrate and hydride source, respectively. Reasoning that the cinchona alkaloid moiety might be responsible, it was replaced with the simpler (*R*,*R*)-*trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine. The resultant monobasic catalyst **B** provided a modest improvement in yield and enantioselectivity, albeit delivering the *R*-enantiomer of **2** (entry 2). A survey of commercial boranes showed catecholborane delivered the best performance and that toluene was superior to other common solvents. In concert with the temperature dependency displayed by CBS catalysts,[20] both yield and optical purity improved using this combination as the temperature was lowered to around −46 °C (entry 3), but then declined as the temperature was lowered still further (entry 4). Primary amine catalyst **C** (entry 5) was disappointing in all respects and was not further pursued. In contrast, the corresponding *N*-benzyl secondary amine catalyst **D** at −78 °C boosted the stereoselectivity upward to 73% ee, albeit at the expense of yield (entry 6). Mindful of the preceding temperature dependency, catalyst **D** was evaluated over a wider temperature range (see Supporting Information). At −46 °C, the yield of **2** jumped to 88% and the enantioselectivity to 98% ee (entry 7); thereafter, the stereoselectivity slowly declined as the temperature was raised, for example, 85% ee at −30 °C (entry 8). The biphasic behavior of the thiourea catalysts might be attributed to the slow breakdown of the catalyst-product complex below approximately −46 °C; presumably, the catalyst-product complex is functionally catalytic, but less enantioselective than the catalyst alone.[20] Catalyst **E**, which differs from **D** by having an N-isobutyl substituent instead of an N-benzyl, showed a significant loss of enantioselectivity under otherwise identical reaction conditions (entry 9 vs 7). This might be attributed to

Table 1. Influence of Select Reaction Parameters on Yield and Enantioselectivity[a]



entry	catalyst	borane (equiv)	solvent	temp (°C)	yield[b](%)	ee[c](%)	config
1	A	BH_3·THF (0.7)	THF	23	10	5	S
2	B	BH_3·THF (0.7)	THF	23	40	13	R
3	B	catecholborane (1.6)	toluene	−46	88	43	R
4	B	catecholborane (1.6)	toluene	−78	65	27	R
5	C	catecholborane (1.6)	toluene	−78	25	20	S
6	D	catecholborane (1.6)	toluene	−78	24	73	S
7	**D**	**catecholborane (1.6)**	**toluene**	**−46**	**88**	**98**	**S**
8	D	catecholborane (1.6)	toluene	−30	88	85	S
9	E	catecholborane (1.6)	toluene	−46	85	65	S
10	F	catecholborane (1.6)	toluene	−46	83	96	S

[a] Reaction conditions: catalyst (10 mol %), 24 h, argon atmosphere. [b] Isolated yield. [c] Measured by chiral HPLC.

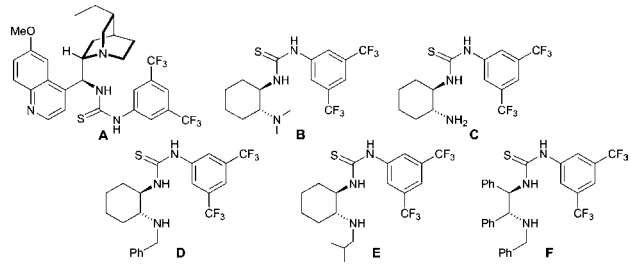
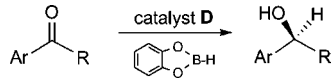


Table 2. Enantioselective Reduction of Aryl Ketones[a]



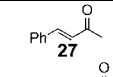
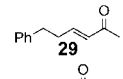
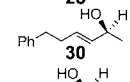
entry	aryl ketone	alcohol	time (h)	yield[b](%)	ee[c](%)
1	 **3**	 **4**	24	86	99
2	 **5**	 **6**	24	86	99
3	 **7**	 **8**	26	71	95
4	 **9**	 **10**	22	92	96
5	 **11**	 **12**	36	80	97
6	 **13**	 **14**	20	84	99
7	 **15**	 **16**	22	94	99
8	 **17**	 **18**	22	95	99
9	 **19**	 **20**	24	86	99
10	 **21**	 **22**	24	95	98
11	 **23**	 **24**	24	93	98
12	 **25**	 **26**	30	66	97

[a] Reaction conditions: catalyst **D** (10 mol %), catecholborane (1.6 equiv), 4 Å molecular sieves, toluene, −46 °C, argon atmosphere. [b] Isolated yield. [c] Measured by chiral HPLC.

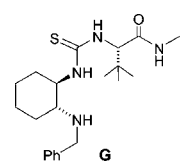
just steric differences, although alternative explanations, for example, $\pi-\pi$ bonding between the N-benzyl of **D** and the electron-rich catechol of the borane, warrant investigation. A comparison of catalyst **F** with **D** is also instructive. The former was prepared from a commercial, chiral acyclic-diamine, yet furnished results comparable to **D** (entry 10), indicating a wide latitude in the design of future catalysts.

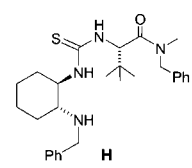
Catalyst **D** proved useful for the enantioselective reduction of a wide range of aryl ketones (Table 2). Simple phenyl alkyl ketones **3** and **5** were smoothly reduced with excellent stereocontrol to (*S*)-alcohols **4** (entry 1) and **6** (entry 2), respectively. Importantly, the presence of an ortho-substituent did not alter the level of enantioselectivity (entry 3, **7** → **8**) nor did electron-withdrawing (entry 4) or electron-donating (entry 5) groups, although the latter did require a longer reaction time. Other functionality was also well tolerated including *p*-fluoro (entry 6), *p*-chloro (entry 7), and *p*-bromo (entry 8). The cyclic ketones 1-tetralone (**19**) and 4-chromanone (**21**) were likewise well behaved and furnished alcohols **20** (entry 9) and **22** (entry 10) in high yield and optical purity. Comparable results were obtained using

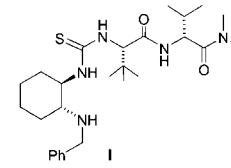
Table 3. Enantioselective Reduction of Alkenyl and Alkyl Ketones[a]

entry	ketone	alcohol	catalyst	yield[b](%)	%ee[c]
1	 **27**	 **28**	**D**	78	90
2	 **29**	 **30**	**D**	88	86
3	 **31**	 **32**	**D**	82	97
4	 **33**	 **34**	**D**	81	47
5	**33**	**34**	**G**	84	63
6	**33**	**34**	**H**	92	79
7	**33**	**34**	**I**	90	67
8	 **35**	 **36**	**D**	60	89
9	**35**	**36**	**H**[d]	68	91

[a] Reaction conditions: catalyst (10 mol %), catecholborane (1.6 equiv), 4 Å molecular sieves, toluene, −46 °C, 24 h. [b] Isolated yield. [c] Measured by chiral HPLC. [d] Thirty-six hours.


G


H


I

2-acetonaphthone (**23**, entry 11) and the heterocycle 2-acetylthiophene (**25**, entry 12).

As an extension of our survey of structurally diverse prochiral carbonyls, α,*β*-unsaturated ketones **27**, **29**, and **31** were transformed in good yields and stereoselectivities to alcohols **28**, **30**, and **32**, respectively, using catalyst **D** (Table 3, entries 1−3). The latter example deserves comment since it was obtained in appreciably better optical purity (97% ee) than that reported using the CBS catalyst (81% ee).[21] Unsymmetrical dialkyl ketones, of course, were more challenging. While alcohol **34** was produced from ketone **33** in good yield using catalyst **D**, the chiral induction was quite modest (entry 4). Drawing inspiration from the recent work of Zuend and Jacobsen,[22] we sought to improve catalytic performance with the introduction

(12) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

(13) Shibasaki, M.; Groger, H.; Kanai, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 2003; Supp. 1, Chapter 29.3.

(14) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.

(15) Procuranti, B.; Connon, S. J. *J. Chem. Soc., Chem. Commun.* **2007**, 1421–1423.

(16) Thioureas with metals: (a) Touchard, F.; Fache, M. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3319–3326. (b) Bernard, M.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *Eur. J. Org. Chem.* **2001**, 1589–1596.

(17) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* 2008*130*, 46–48.

(18) For similar chiral Lewis Base catalyzed silane additions, see: (a) Kocovsk, P.; Malkov, A. V. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007; pp 255−286. (b) Malkov, A. V.; Stewart-Liddon, A. J. P.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kocovsk, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432–1435. (c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021–12022.

of an additional chiral center. Indeed, after extensive study of the structure−activity relationships of the catalyst scaffold (see Supporting Information for details), catalysts **G** and **H** were found to raise the stereoselectivity for the reduction of **33** to 63% ee (entry 5) and 79% ee (entry 6), respectively, validating this approach. Yet, catalyst **I** was less successful despite having a fourth chiral center. In the case of cycloalkyl alkyl ketone **35**, catalysts **D** and **H** were comparable and furnished **36** with high enantioselectivity (entries 8 and 9).

In summary, we describe a family of air-stable, bifunctional amino-thiourea cataysts for the enantioselective reduction of prochiral ketones using echolborane. Yields and % ee using aryl and α,β-unsaturated ketones rival or exceed those achievable using extant reagents. Promising results were also seen using unsymmetrical dialkyl ketones and a strategy for future catalyst optimization was demonstrated.

Acknowledgment. Financial support provided by the Robert A. Welch Foundation and NIH (GM31278, DK38226).

Supporting Information Available: Synthetic procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100365C

(19) Vakulya, B.; Varga, S.; Csa′mpai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967–1969.
(20) Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465–472.
(21) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614.
(22) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883.