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

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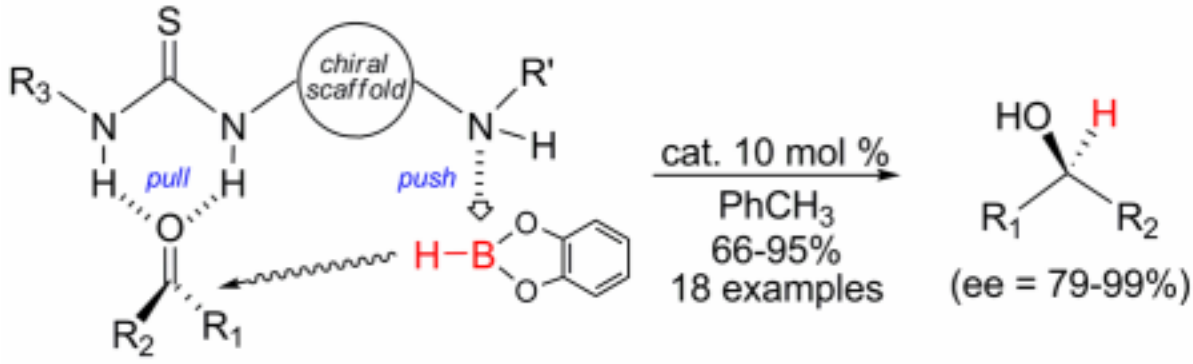
Abstract



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] towards 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]

Whilst chiral ureas and thioureas have emerged as efficacious catalysts for a variety of nucleophilic conjugate additions[11] and 1,2-carbonyl additions, e.g., hydrocyanation,[12] Henry reaction,[13] and Baylis-Hillman reaction,[14] there are few examples of highly

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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.

enantioselective hydride additions.[15,16] However, the insights gained developing asymmetric oxy-Michael additions of boronic 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 of 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 upwards 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, e.g., 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 just steric differences, although alternative explanations, e.g., π-π 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 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 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 catayst 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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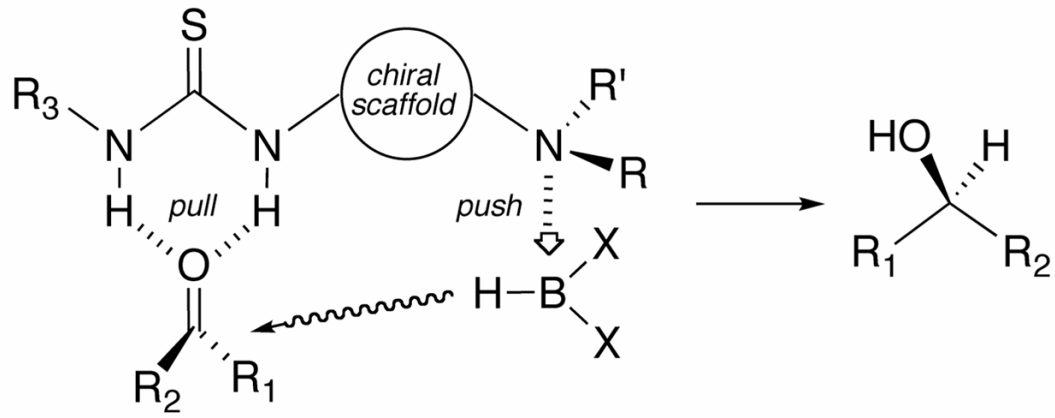
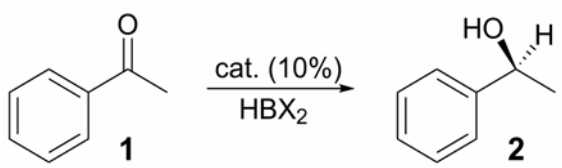


Figure 1.
Proposed asymmetric catalysis

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	catechol borane (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.

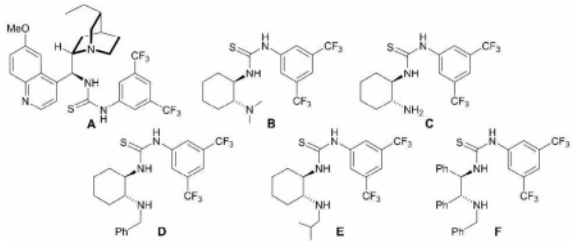
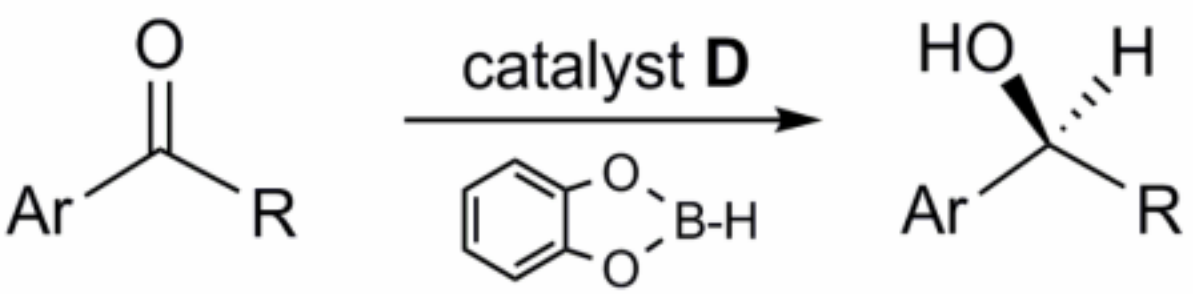


Table 2

alcohol	time (h)	yield[b] (%)	ee[c] (%)
4	24	86	99



alcohol	time (h)	yield[b](%)	ee[c](%)
 **6**	24	86	99

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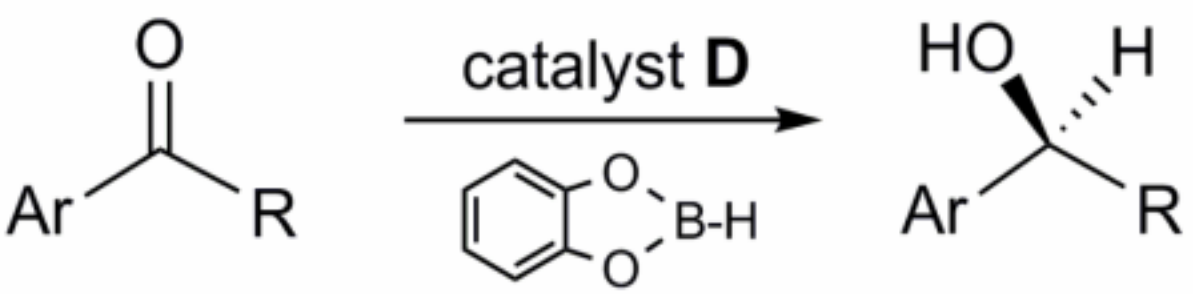
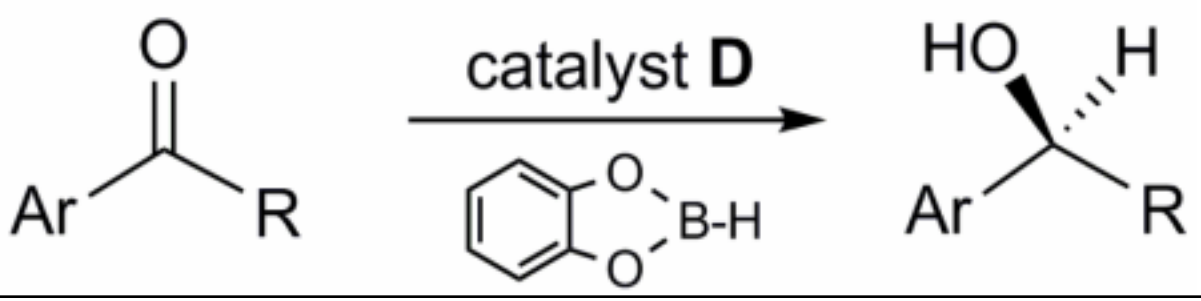
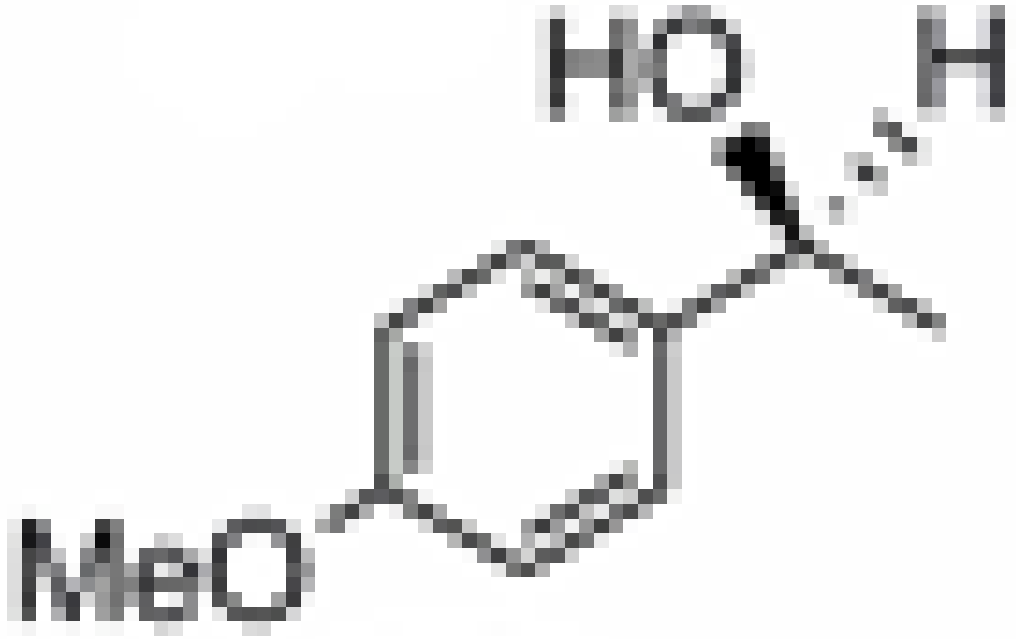
	alcohol	time (h)	yield[b](%)	ee[c](%)
8		26	71	95



alcohol	time (h)	yield[b](%)	ee[c](%)
 **10**	22	92	96



alcohol	time (h)	yield[b](%)	ee[c](%)
	36	80	97

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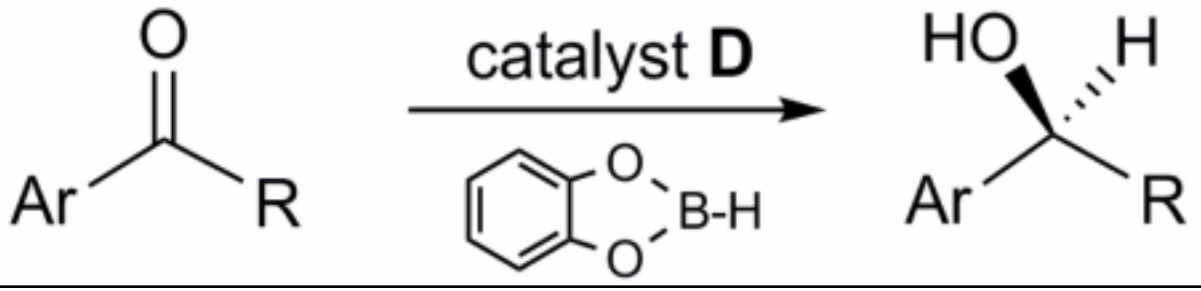
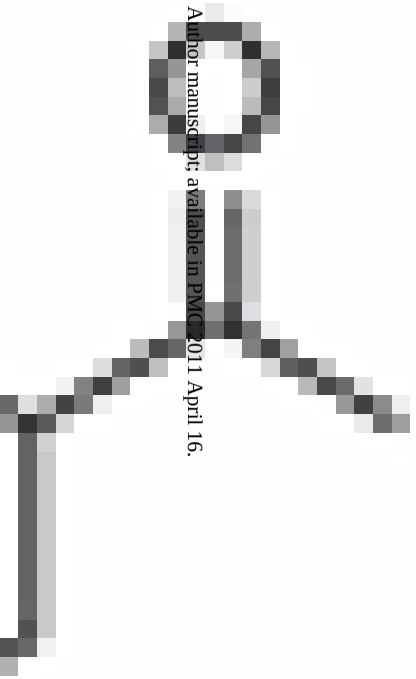
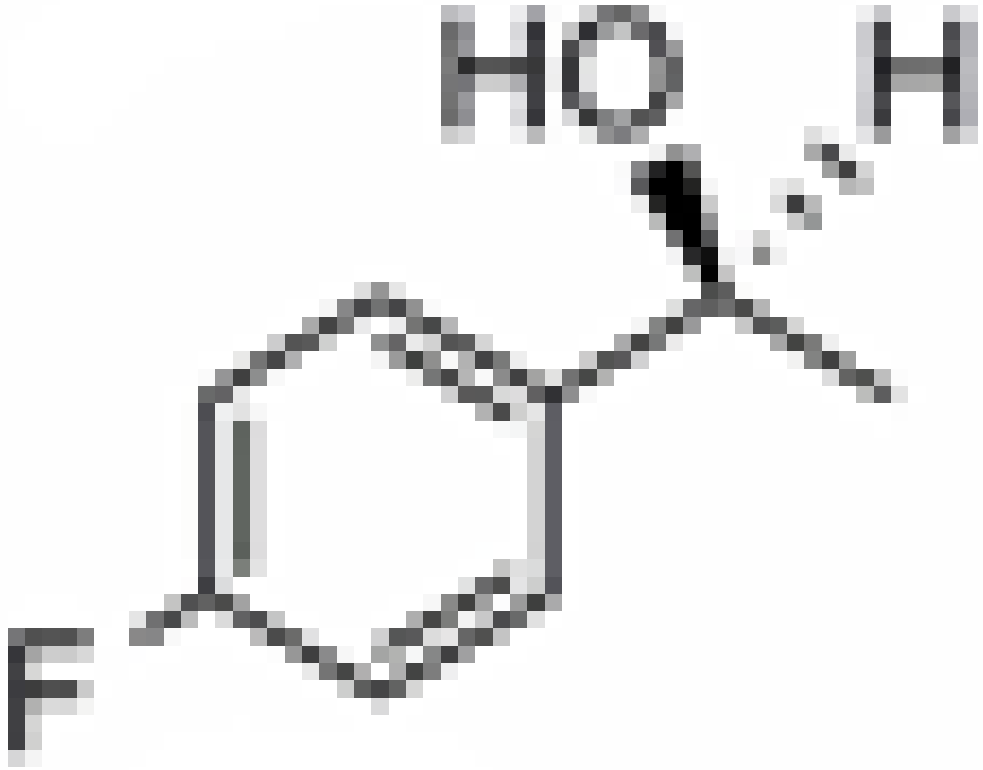


	alcohol	time (h)	yield[b](%)	ee[c](%)
		20	84	99





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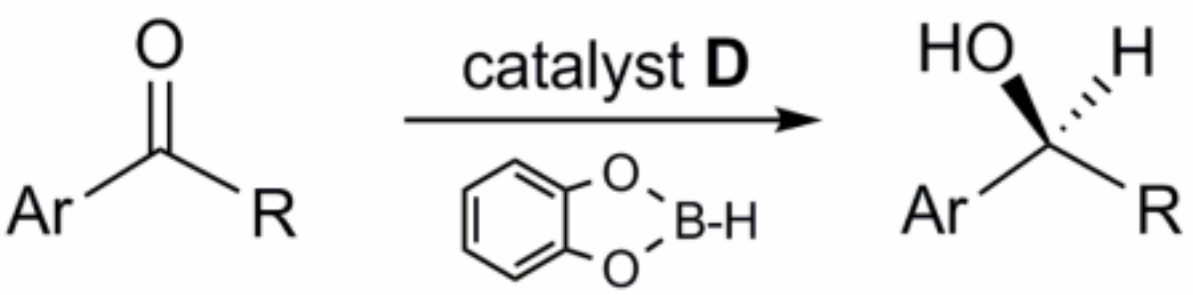
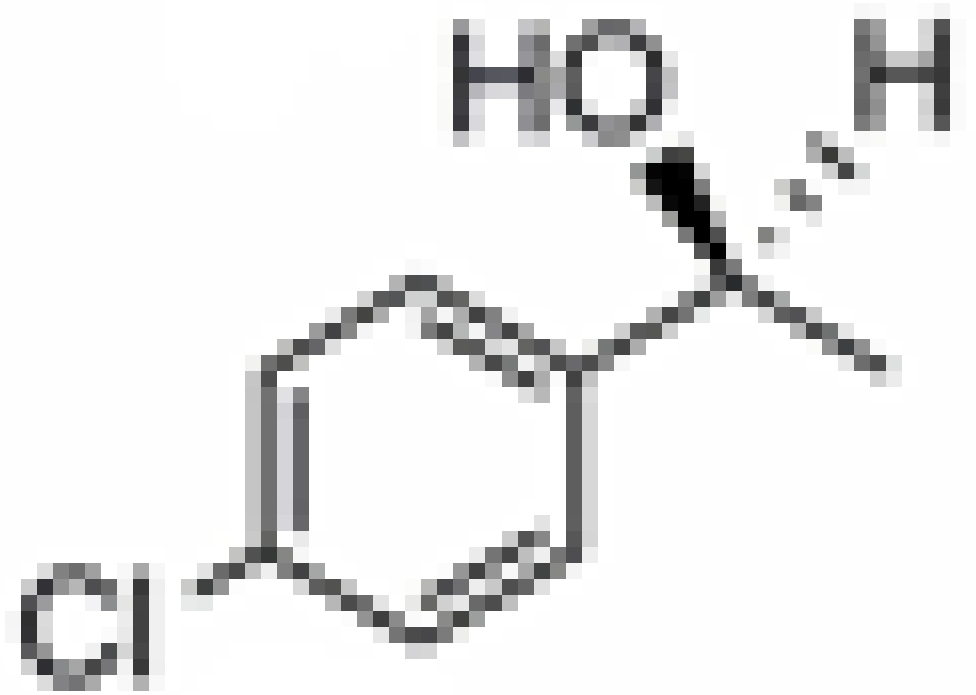


alcohol	time (h)	yield[b](%)	ee[c](%)
	22	94	99

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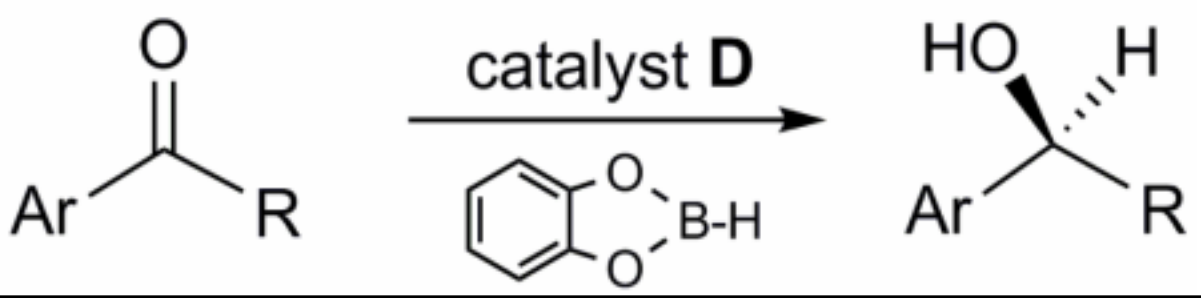
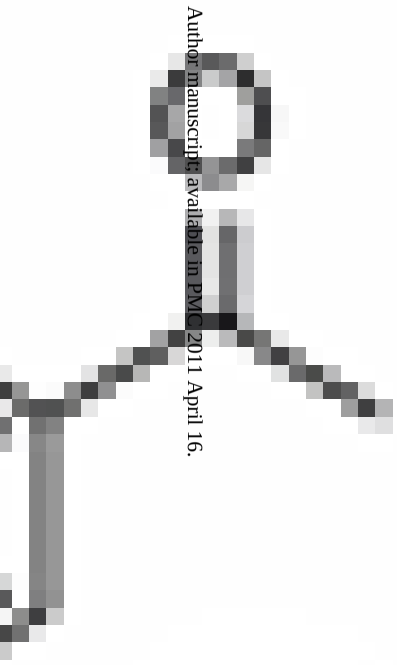
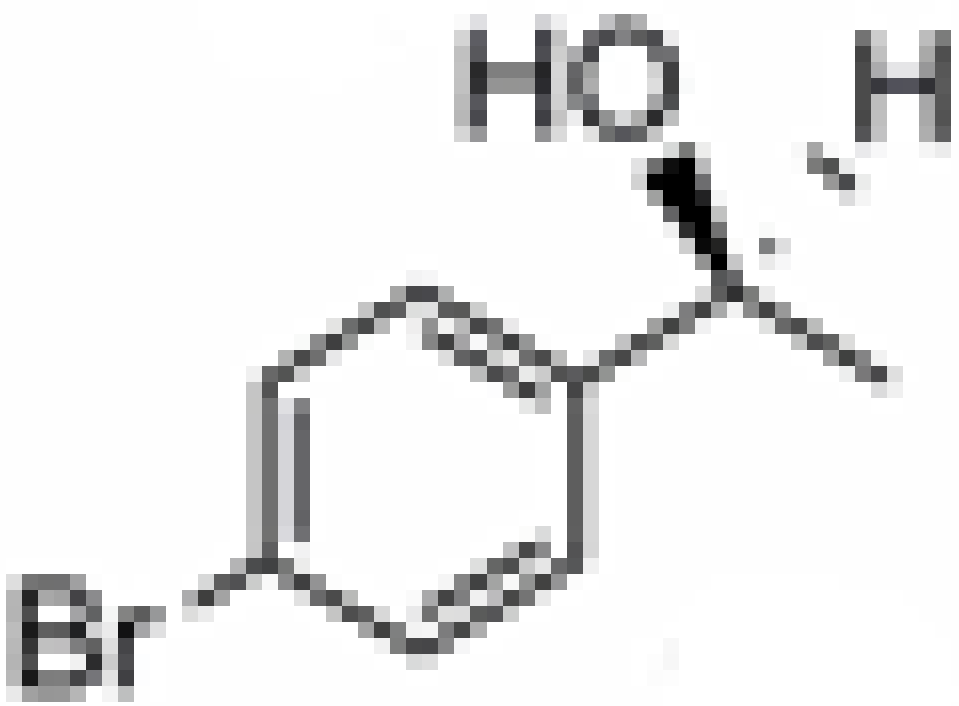


	alcohol	time (h)	yield[b](%)	ee[c](%)
		22	95	99





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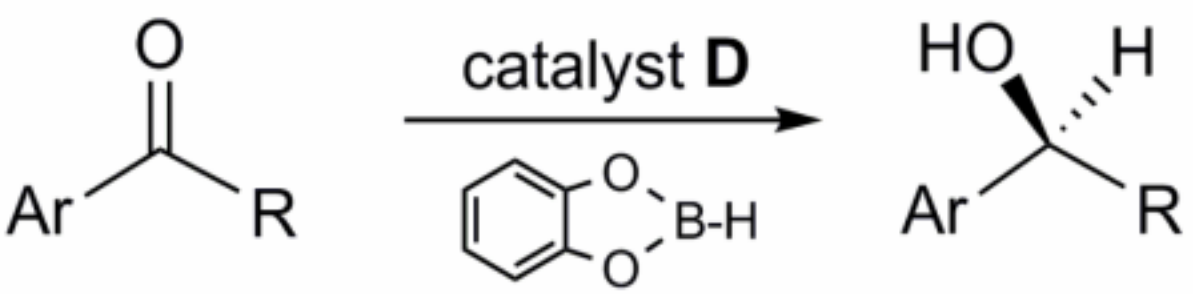

alcohol	time (h)	yield[b](%)	ee[c](%)
 **20**	24	86	99

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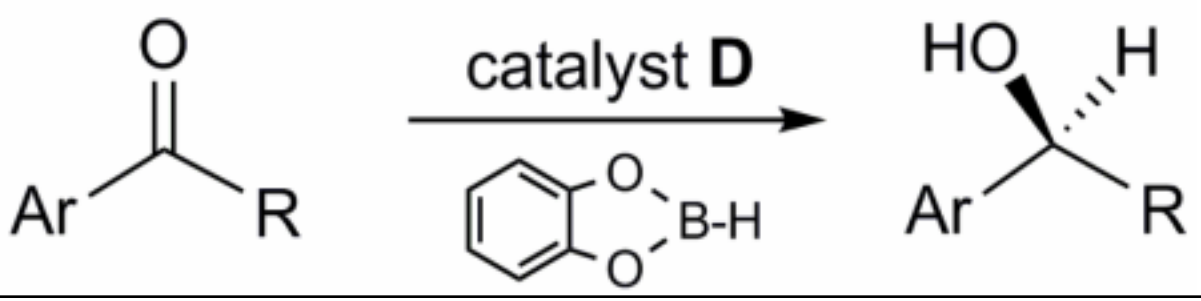
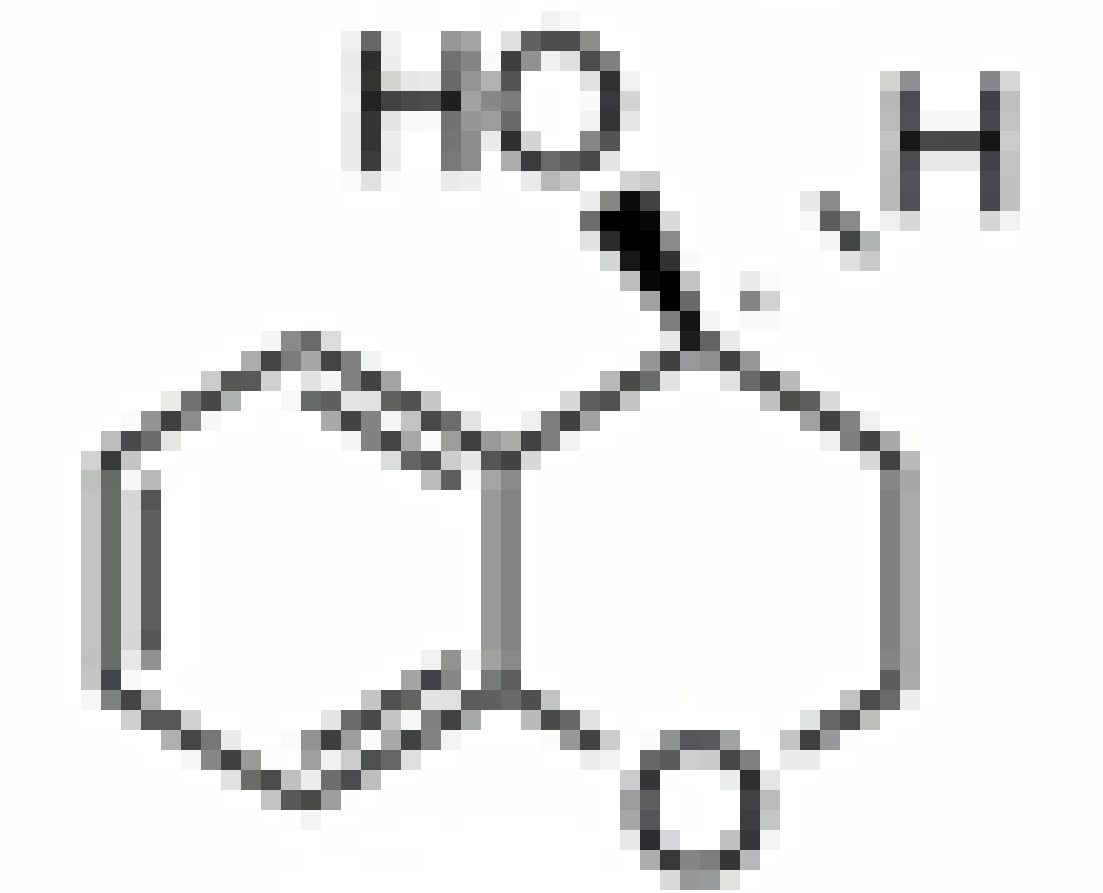


alcohol	time (h)	yield[b](%)	ee[c](%)
	24	95	98

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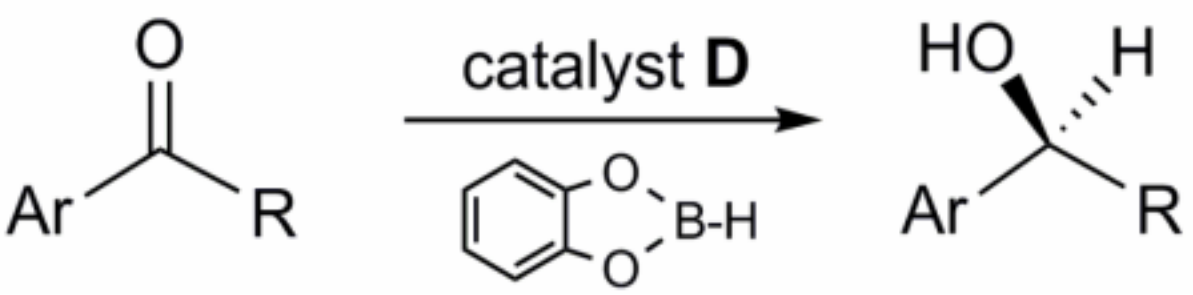
alcohol	time (h)	yield[b](%)	ee[c](%)
24	24	93	98



	alcohol	time (h)	yield[b](%)	ee[c](%)
26		30	66	97

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[a] Reaction conditions: catalyst **D** (10 mol %), catecholborane (1.6 equiv), 4 Å molecular sieves, toluene, −46 °C, argon atmosphere.

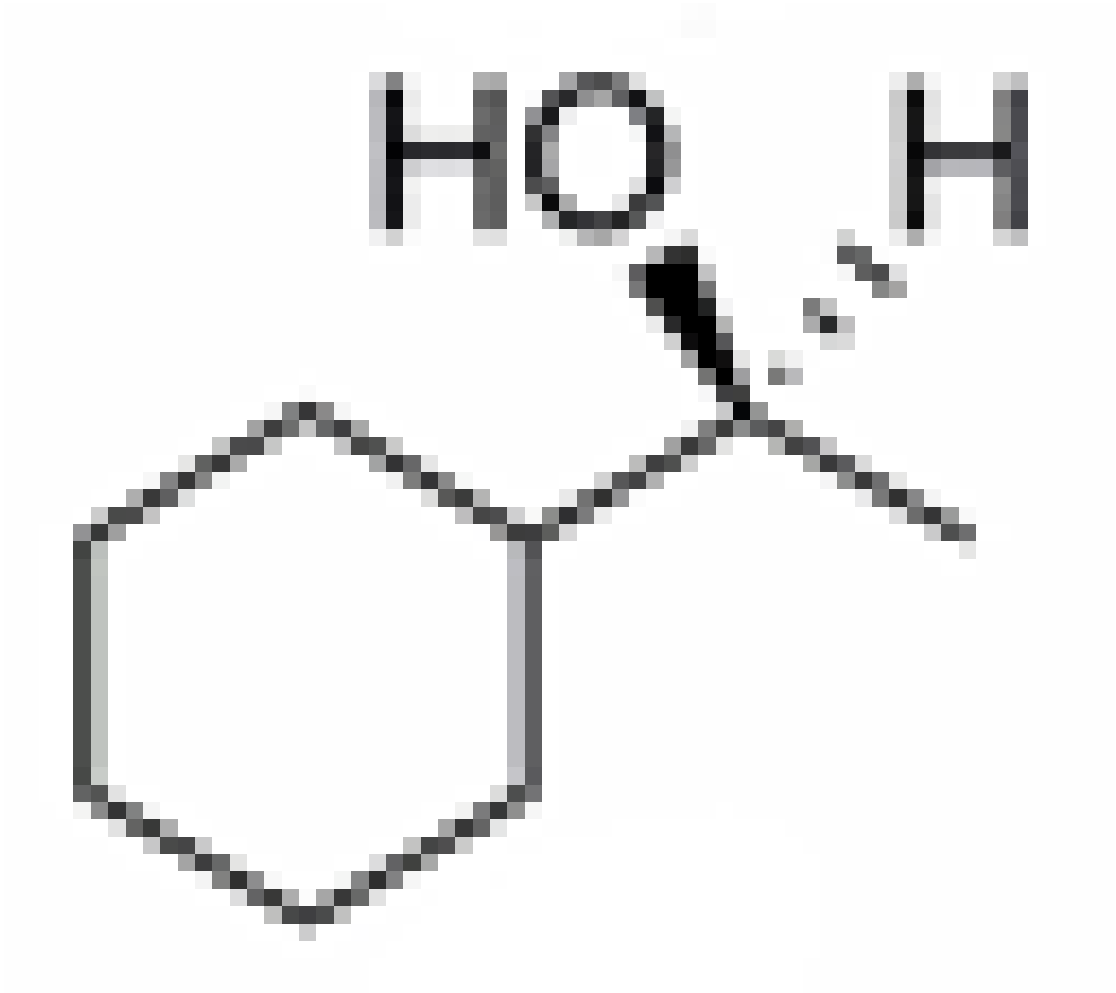
[b] Isolated yield.

[c] Measured by chiral HPLC.

Table 3

alcohol	catalyst	yield[b](%)	%ee[c]
28	**D**	78	90
30	**D**	88	86

alcohol	catalyst	yield[b](%)	%ee[c]
	D	82	97
	D	81	47
	G	84	63

alcohol	catalyst	yield[b](%)	%ee[c]
34	**H**	92	79
34	**I**	90	67
	D	60	89
			
36			
36	**H**[d]	68	91

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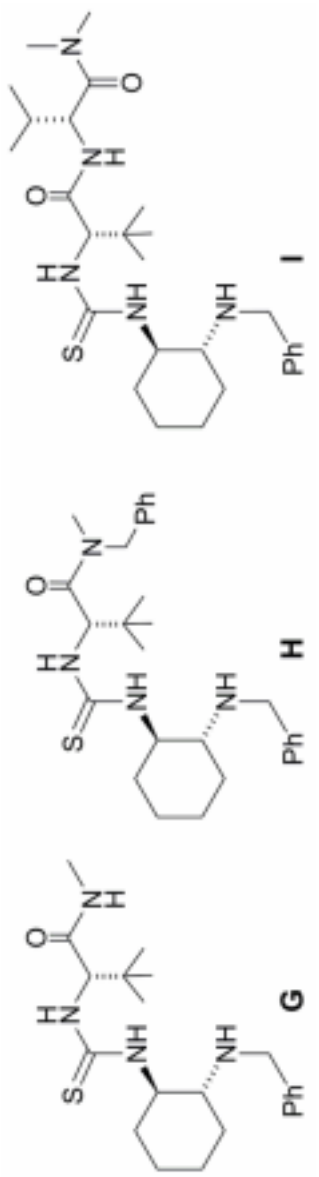

[a] Reaction conditions: catalyst (10 mol %), catecholborane (1.6 equiv), 4 Å molecular sieves, toluene, −46 °C, 24 h.

[b] Isolated yield.

[c] Measured by chiral HPLC.

[d] 36 h.