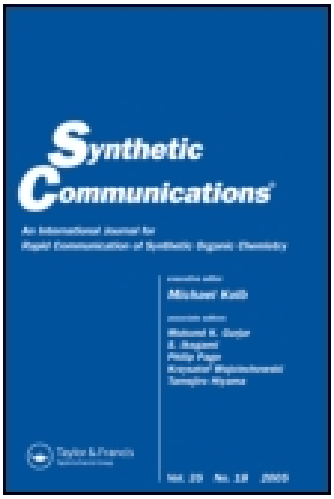

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Enantioselective Reduction of Prochiral Ketones with $NaBH_4/Me_2SO_4$/(S)-Me-CBS

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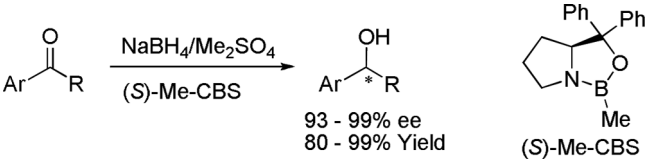
GRAPHICAL ABSTRACT



Abstract *The enantioselective reduction of prochiral ketones with $NaBH_4/Me_2SO_4/(S)$-Me-CBS is described. Borane is generated in situ* via *the reaction of $NaBH_4$ with Me_2SO_4 in tetrahydrofuran, which is as efficient as the commercial one. Such in situ–generated borane reagent was applied to reduce prochiral ketones in the presence of chiral oxazaborolidine catalyst directly. The corresponding chiral secondary alcohols were obtained with excellent enantiomeric excesses (93–99%* ee*) and good to excellent yield (80–99%).*

Keywords Asymmetric reduction; chiral alcohols; chiral oxazaborolidine; dimethyl sulfate; sodium borohydride

INTRODUCTION

Borane is among the most important reducing agents in both laboratory and industry.[1] It has been widely used in the hydroboration of unsaturated C–C bonds,[2] and reduction of carbonyl compounds,[3] oximes,[4] imines,[5] and amide.[6] One of the most important applications of borane is reducing prochiral ketones to the corresponding enantioenriched second aryl alcohols in the presence of chiral catalyst.[7] Enantiomerically pure secondary alcohols are important building blocks for the synthesis of various other organic compounds such as halides, esters, ethers, ketones, amines, and many biologically active compounds. In this context, the pioneering work of Hirao,[8] Corey,[9] and their coworkers has inspired the research interests of synthetic organic chemists, and the asymmetric reduction of prochiral ketones to optically active alcohols using chiral oxazaborolidine catalysts has become one of the most active research topics.[10]

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However, borane itself is a very harmful and unstable gas. Although the stability of borane is improved by complexing with tetrahydrofuran (THF), SMe_2, or tertiary amines, its storage still needs an inert environment such as dry nitrogen or argon atmosphere and low temperature.[11] This limitation restricts the use of borane on large scale. One of the alternative ways to overcome that limit is developing $NaBH_4$/additive systems to replace borane in organic synthesis.[12] In reported systems, the additives included chlorotrimethylsilane,[13] iodine,[14] bromine,[15] catechol,[16] phenylboronic acid,[17] Lewis acids,[18] and so on. Nevertheless, most of the $NaBH_4$/additive combinations suffered from either poor selectivity or high cost of the additives. Thus, a safe and low-cost $NaBH_4$/additive system is highly desired. Recently, we reported a convenient method to generate BH_3/THF complex (BTHF) via the reaction of $NaBH_4$ with Me_2SO_4 in THF.[19] BTHF prepared in situ is almost as effective as the commercial one. Herein, we report a novel combination of reagents $NaBH_4/Me_2SO_4$ with the chiral oxazaborolidine [(*S*)-Me-CBS] catalyst that reduces prochiral ketones with good yield and enantioselectivity under mild conditions.

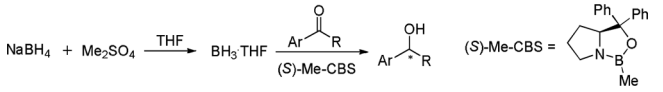
RESULTS AND DISCUSSION

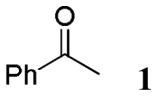
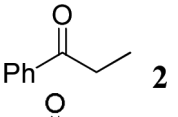
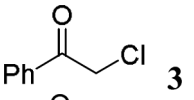
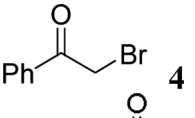
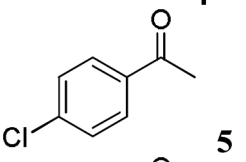
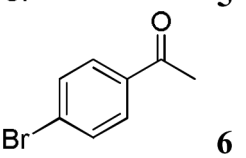
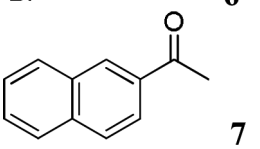
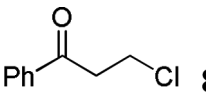
BTHF (BH_3/THF complex) was generated in situ by the reaction of $NaBH_4$ with Me_2SO_4 in THF following the method established in our laboratory, and it was applied to reduce prochiral ketones in the presence of (*S*)-Me-CBS catalyst directly. To optimize the reaction condition, acetophenone was employed as the model substrate. 1-Phenylethanol was generated in good yield when acetophenone was added dropwise into the mixture of BTHF (generated in situ from $NaBH_4/Me_2SO_4$) and (*S*)-Me-CBS catalyst (Table 1, entries 1–5). A little greater enantioselectivity was achieved at lower temperature (entries 1–3). Less BTHF resulted in the decrease of both the yield and enantioselectivity (entry 4). The reaction gave the best results with 10 mol% (*S*)-Me-CBS catalyst and 0.7 equivalent of BTHF at $-15\,^{\circ}C$ (entry 5).

Having established the optimum condition, we applied this method to a number of prochiral ketones. Good to excellent yield were achieved with high enantioselectivity (Table 1, entries 6–12). α-Chloro or α-bromo of acetophenone did not influence the yield and *ee* value (entries 7 and 8). 4-Chloroacetophenone and 4-bromoacetophenone gave lower yield (entries 9 and 10). This may be due to the effect of electron-withdrawing group *para* to the acetyl group. 2-Acetonaphthone gave the best enantioselectivity because of the great bulky distinction between the groups beside the carbonyl group (entry 11). The results were similar with those reported by Corey et al.,[9b] in which commercial BTHF was used. It indicates that the BTHF generated in situ by the reaction of $NaBH_4$ with Me_2SO_4 in THF is as effective as the commercial one in the enantioselective reduction of prochiral ketones catalyzed by Me-CBS.

Recently, Soloshonok revealed that some nonracemic enantiomeric alcohols are prone to an enantiomer self-disproportionation effect (SDE) on achiral silica gel or via sublimation.[20] We therefore confirmed that the optical purity of the products do not change after chromatographic purification using achiral silica gel. The same result was given for nonracemic enantiomeric 1-(phenyl)ethanol while it was distilled in vacuum.

Table 1. Asymmetric reduction of prochiral ketone with $NaBH_4/Me_2SO_4$ catalyzed by Me-CBS [a]



Entry	Ketone	Temp. (°C)	Catalyst loading (mol%)	Yield[b] (%)	*ee* (%)[c]
1	 **1**	25	5	98	84
2		0	5	98	86
3		−15	5	95	93
4[d]		−15	5	72	85
5		−15	10	99	96
6	 **2**	−15	10	99	98
7	 **3**	−12	10	97	96
8	 **4**	−12	10	98	98
9	 **5**	−10	10	90	97
10	 **6**	−10	10	80	97
11	 **7**	−10	10	94	99
12	 **8**	0	10	95	93

[a]Reaction conditions: $NaBH_4/Me_2SO_4$/ketone = 0.7/0.7/1.
[b]Isolated yield.
[c]Determined by HPLC with a chiral column (Daicel OD).
[d]$NaBH_4/Me_2SO_4$/ketone = 0.6/0.6/1.

EXPERIMENTAL

All reactions were performed under a nitrogen atmosphere in oven-dried glassware with magnetic stirring. Anhydrous solvents were freshly distilled from sodium and benzophenone. Column chromatography was performed on silica gel

(100–200 mesh) using petroleum ether/EtOAc (7:3) as an eluant. NMR spectra were recorded in $CDCl_3$ at 400 MHz (^1H) on a spectrometer. Chemical shift (δ) were reported in parts per million (ppm) relative to the residual solvent signal. (*S*)-Me-CBS catalyst was prepared following the procedure described by Corey et al.[9b] Other reagents were purchased from commercial sources.

Under a nitrogen atmosphere, 27.7 mg (0.7 mmol) of $NaBH_4$ (purity: 96%) and 1 mL of anhydrous tetrahydrofuran were introduced into a 10-mL, three-necked flask equipped with pressure-equalizing addition funnel, a gas inlet pipe, a thermometer, and magnetic stirring bar. The mixture was added dropwise with 89.3 mg of Me_2SO_4 (0.7 mmol) at 0 °C and stirred for 1 h in an icebath and further 4 h at room temperature until no gas generation was observed. Then 28.2 mg of (*S*)-Me-CBS was added and stirred at room temperature for 10 min. After the reaction mixture was cooled to desired temperature, a solution of the corresponding prochiral ketone (1 mmol) in anhydrous THF was added dropwise through a syringe in 1 h. After the addition, the mixture was stirred for additional 30 min; 1 mL of HCl (2 mol/L) aqueous solution was added and stirred for 30 min. Then THF was removed on a rotary evaporator. The residue was extracted with ethyl acetate (3×10 mL). The organic layers were combined and washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography on silica gel to give pure products.

Spectroscopic and characterization data of the products are provided in the Supporting Information, available online.

CONCLUSION

In conclusion, we have developed a convenient and useful method to prepare asymmetric second aryl alcohols using the combination of $NaBH_4$, Me_2SO_4, and Me-CBS. The reagent $NaBH_4/Me_2SO_4$ can be used as a cheap large-scale resource of borane in laboratory and industry. The excellent asymmetric selectivity and yields of the isolated products indicate that this is a useful and convenient method of asymmetric reduction of prochiral ketones.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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