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Tetrahedron: *Asymmetry* 16 (2005) 751–754

# Enantioselective reduction of ketones with $NaBH_4$/diglyme possibly catalysed by trialkyl borate: optically active *sec*-alcohols from prochiral ketones with catalytic (−)-menthol: autocatalysis option

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Received 25 October 2004; accepted 15 November 2004
Available online 21 January 2005

**Abstract**—Ketones can be reduced with $NaBH_4$ in diglyme without an apparent proton source, but putatively catalysed by a trialkyl borate. This can be initially derived in situ from $NaBH_4$ and an alcohol, although the reaction becomes increasingly autocatalytic with time. With (−)-menthol as the initiating alcohol, the enantioselective reductions of a range of prochiral ketones in quantitative yields and moderate ees (generally 58–87%) were realised (the autocatalysis was demonstrated in two cases; catalysis by tris-(−)-menthyl borate was demonstrated in one case). The mechanism may involve either the activation of the substrate (electrophilically) or of the hydride reagent (nucleophilically). This method offers a relatively simple and inexpensive approach to a key transformation in asymmetric synthesis.


## 1. Introduction

The reduction of ketones with sodium borohydride ($NaBH_4$) is an important transformation in organic synthesis, which is characterised by its effectiveness and simplicity. It is generally believed to require a proton source, usually water or an alcohol such as ethanol, that is employed as a solvent for the reaction.[1–4] The role of the proton source is mechanistically unclear: importantly, the activation of the carbonyl group via protonation at the ketone oxygen atom may be ruled out, given the large difference in the p$K_a$'s of ketones (∼−7) and alcohols (∼+16).[5] Also, $NaBH_4$ reacts competitively with the hydroxylic solvent employed (to produce borate species)—and yet, the reduction reaction works excellently in practice.[1–4]

An interesting possibility is that the reaction is catalysed by the trialkyl borate **I**, which is formed as a by-product (Scheme 1); in fact, the reducing species may also be the trialkoxyborohydride **IV** (Scheme 2). It is known that borohydride reactions are electrophilically catalysed by metal ions ($Li^+$ or $Mg^{2+}$),[4] and that alkoxyborohydrides are better hydride donors than $NaBH_4$ itself.[6] Thus, the $NaBH_4$ reduction of ketones may apparently be promoted either by the electrophilic activation of the substrate or the nucleophilic activation of the reagent—or, of course, both. This, in fact, leads to a possible asymmetric variant of the borohydride reaction, catalysis by an optically active alcohol in an inert solvent. The design of asymmetric variants of the complex metal hydride reductions has attracted much interest and continues to be a challenge.[7–12]

## 2. Results and discussion

We explored the above possibility in diethyleneglycol dimethyl ether (diglyme, an aprotic solvent, which has been recommended[1] for $NaBH_4$). When a variety of prochiral ketones **1** was treated with a solution of $NaBH_4$ in dry diglyme, which had been pre-treated with 0.05 M equiv (relative to $NaBH_4$) of (1*R*)-menthol, the corresponding alcohols **2** were produced over a period of 24–40 h, in essentially quantitative yields and generally moderate ees (Scheme 3 and Table 1; note that the ees are ⩾80% in two cases). Also, no detectable reaction occurred without the above pre-treatment with the menthol. The scope of the reaction is demonstrated by its success with aliphatic, alicyclic and aromatic substrates (Table 1).

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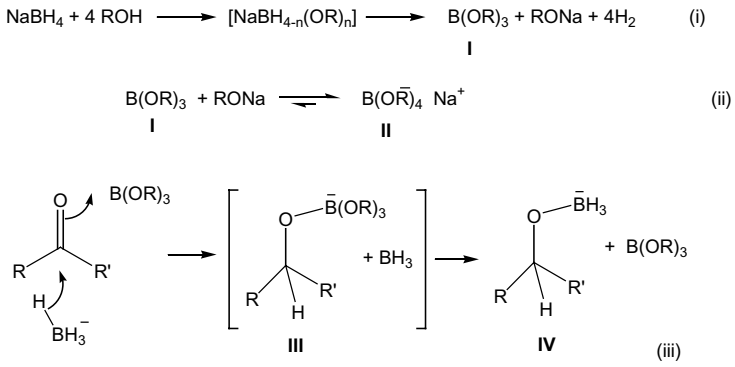
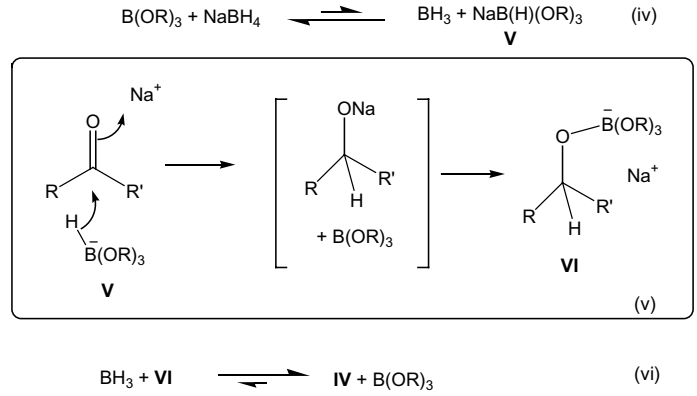
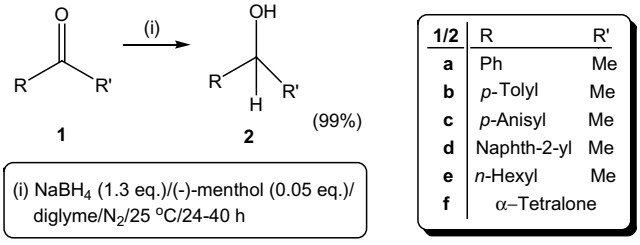
doi:10.1016/j.tetasy.2004.11.078




**Scheme 1.** Possible catalysis by trialkyl borate **I** of the reduction of a ketone with $NaBH_4$. Borate **I** is produced by the reaction of added alcohol with $NaBH_4$, as in (i), and subsequently may form the 'ate complex' **II**, as in (ii): this equilibrium, however, would considerably favour **I** as $NaBH_4$ is in large excess relative to ROH (catalyst). Possible electrophilic catalysis by **I** of the reduction reaction is shown in (iii). The **III** converts to **IV** as $BH_3$ is more electrophilic than $B(OR)_3$.[7] Further reaction occurs with **IV** and its higher alkoxy analogues (instead of $NaBH_4$), under catalysis by $B(OR)_3$.




**Scheme 2.** Possible reduction of a ketone by a trialkoxyborohydride **V**. This may be formed by the reaction of a trialkyl borate with $NaBH_4$, as in (iv); **V** may transfer hydride to a ketone more efficiently than $NaBH_4$ does itself, as in (v); for the reaction in (vi), cf. Scheme 1; **IV** may react with $B(OR)_3$ as in (iv) to regenerate **V**.




| 1/2 | R | R' |
|---|---|---|
| a | Ph | Me |
| b | *p*-Tolyl | Me |
| c | *p*-Anisyl | Me |
| d | Naphth-2-yl | Me |
| e | *n*-Hexyl | Me |
| f | α–Tetralone | |

**Scheme 3.** Enantioselective reduction of the prochiral ketones **1** to the corresponding secondary alcohols **2**, catalysed by (−)-menthol (cf. Table 1).

The assumption that the reactions are possibly catalysed by the trimenthyl borate is supported by the observation that the reduction of acetophenone **1a**, with $NaBH_4$ in diglyme in the presence of tris-(1*R*)-menthyl borate, afforded the corresponding alcohol **2a** in 69% ee. Also, chiral catalysis by an alcohol other than (−)-menthol was demonstrated by the reduction of naphthyl ketone **1d** in the presence of the (−)-octanol **2e**: it is noteworthy that different enantiomers of **2d** were obtained in two cases (entries 5 and 6).

Mechanistically, however, the reaction sequences in Schemes 1 and 2 would need to be modified in the case of the above reactions initiated by menthol: even if it presumed that the reaction is initially catalysed by tris-(1*R*)-menthyl borate, the trialkyl borate derived from the product alcohol, which is indeed the primary product prior to work-up, would itself act as a catalyst. Clearly, as the reaction proceeds, it would increasingly be autocatalysed. This is apparently advantageous in that the reaction can be initiated by the product alcohol itself (presuming its availability), thus eliminating the need to separate it from menthol or any other initiating alcohol that may be employed.

On the other hand however, an autocatalytic process severely limits the possibilities for stereocontrol (as the chiral auxiliary is invariable), and the observed levels of induction would have to be accepted as they are. In other words, a chiral autocatalytic reaction would be useful only if the induction is 'naturally high'. It should be noted that the product alcohol may not always be available, so that the initiation may have to be performed with an available chiral alcohol, for example, (1*R*)-menthol. Interestingly, it would be possible to avoid autocatalysis, if the initiating trialkyl borate is

**Table 1.** Enantioselective reduction of the ketones **1** to the alcohols **2** with $NaBH_4$/diglyme, catalysed by (−)-menthol (Scheme 3)[a]

| Entry | Ketone **1** | Time (h) | Product **2** | Configuration–rotation | Ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | 24 | **2a** | 1*S*-(−) | 62 (62) |
| 2 | **1a** | 24 | **2a** | 1*S*-(−) | 58 |
| 3 | **1b** | 24 | **2b** | 1*S*-(−) | 63 (63) |
| 4 | **1c** | 24 | **2c** | 1*S*-(−) | 23 (43) |
| 5 | **1d** | 36 | **2d** | 1*S*-(−) | 80 (74) |
| 6 | **1d** | 36 | **2d** | 1*R*-(+) | 63 |
| 7 | **1e** | 40 | **2e** | 2*R*-(−) | 87 |
| 8 | **1f** | 30 | **2f** | 1*R*-(−) | 58 (57) |

[a] Entries 2 and 7 refer to autocatalysis: the reaction was performed not with (−)-menthol, but with added **2a** and **2d**, respectively; entry 6 refers to catalysis by (−)-octan-2-ol **2e** instead of (−)-menthol.

[b] Polarimetrically determined values, with the corresponding chiral HPLC values in parenthesis. *Typical procedure*: $NaBH_4$ (1.3 mmol) in dry diglyme (5 mL) was treated with (−)-menthol (0.05 mmol), under dry $N_2$. The (effervescent) mixture was stirred for 15 min/25 °C, and treated with prochiral ketone **1** (1.0 mmol, in one portion) for 24–40 h; the progress of the reaction was followed by TLC. The mixture was worked-up by quenching with saturated $NH_4Cl$ solution (5 mL), concentrating in vacuo to remove most of the diglyme, adding water (20 mL) and extracting the mixture with $Et_2O$, etc. The resulting crude product **2** was purified by flash column chromatography ($SiO_2$/eluent: 20% EtOAc–hexane). The resulting pure **2a**–**f** were identified spectrally (IR, 300 MHz $^1H$ NMR and MS); the specific rotations were determined (on a JASCO DIP-370 digital polarimeter), and compared with reported values to obtain the configurations and the ees.[13–15] It was demonstrated that the reaction of **1a** could be catalysed by tris-(−)-menthyl borate[16] (0.2 equiv) rather than by (−)-menthol itself: a nearly quantitative yield of **2a** in 69% ee was realised.

The polarimetric ee values were also confirmed by chiral HPLC analysis, except in the case of octanol **2e**, which could not be resolved. A cellulose carbamate based Chiralcel OD column (250 × 4.6 mm) was employed on a Shimadzu LC-10AS instrument, eluting with hexane–isopropanol (90:10 v/v) at a flow rate of 0.8 mL/min, and monitoring at 260 nm (315 nm in the case of **2d**).

far more electrophilic than the product trialkyl borate. The autocatalytic possibility has been demonstrated in the case of two substrates, acetophenone and octan-2-one (58% and 87% ee, respectively); it is clear that only the octanone case is viable.

Asymmetric reductions of ketones by complex metal hydride reagents have attracted much attention by several groups in recent years, although apparently with mixed results.[7–12] The results have been particularly disappointing so far in the case of $NaBH_4$, although an $LiBH_4$/*N*-benzoylcysteine reagent is quite efficient.[9] The related oxazaborolidine-based reductions are both efficient and act at catalytic levels,[7–9] but are less accessible than $NaBH_4$. Moreover, other unsaturated functionalities would interfere to varying extents with these borane based reactions. The present work employing the relatively simple and highly chemoselective $NaBH_4$, represents an important departure from previous approaches to the enantioselective reduction of ketones.

Previous approaches have employed $NaBH_4$ modified by a chiral acid or alcohol, for example L-tartaric acid[10] or a monosaccharide,[11,12] in an aprotic solvent (benzene or THF). However, the reactions are mechanistically unclear and their scope limited with the chiral auxiliary also being used at stoichiometric levels. Presumably, the reductions are mediated by an alkoxyborohydride species, for example, $H_nB(RCO_2)_{4-n}$, where $RCO_2$ represents L-tartrate, cf. Scheme 2. Thus, the present method offers considerable improvements in terms of both procedure and scope.

## 3. Conclusion

In conclusion, we have developed an asymmetric version of the well-known $NaBH_4$ reduction of ketones that is catalytic in the chiral auxiliary: when the enantiopure alcohol product is available, the process can be performed entirely autocatalytically. The yields are quantitative and the ees generally moderate (good in two cases). The process also offers insights into the mechanism of the reaction of $NaBH_4$ with ketones (notably, a plausible explanation for the necessity of a 'proton source'). Further work to elaborate the interesting results obtained is planned.

## Acknowledgements

We thank the CSIR (New Delhi) for generous financial support of this work. We are most grateful to Prof. S. Chandrasekaran for access to the HPLC facility in his group, without which this work could not have been completed.

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