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Enantioselective reduction of aliphatic ketones using $NaBH_4$ and TarB–NO_2, a chiral boronic ester

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Abstract—High enantioselectivities are obtained using a tartaric acid-derived boronic ester (TarB–NO_2) in combination with $NaBH_4$ for the asymmetric reduction of aliphatic ketones. The resulting alcohols are obtained in enantiomeric excesses ranging from 56% to 94%.

Asymmetric reduction of prochiral ketones to optically active secondary alcohols is one of the most powerful methodologies in organic synthesis.[1] A number of effective asymmetric reducing agents have been reported, but few have offered a route to enantioselective reduction of aliphatic substrates. Asymmetric reducing agents generally give high enantioselectivities in the reduction of aromatic ketones. For example, reductions involving CBS[2] and DIP-Cl[©3] reagents routinely give very high enantioselectivities for aromatic alkyl ketones. However, enantioselective reductions of aliphatic substrates have proven to be more challenging.[4] Very few reducing agents are known to give good asymmetric induction with a wide range of ketone substrates. Recently, 2-octanone was reduced using tris-mentholoxyborohydride to give 2-octanol in 85% ee.[5]

Many asymmetric reducing agents utilize reagents derived either from borane (H_3B:L) or borohydride (MBH_4). Among these reagents, $NaBH_4$ modified compounds are of particular interest. $NaBH_4$ modified reagents have been explored for several years with varying degrees of success over a wide range of experimental conditions. Chiral modifications have been made with amino acids,[6,7] monosaccharides,[8–10] and phase transfer catalysts[11] for the reduction of aromatic and hindered ketones. Mukaiyama devised a catalytic cobalt(II) system that was able to reduce ketones and imines with $NaBH_4$ in high enantiomeric excess.[12–14] However, the system was not tested on aliphatic substrates. Modification of $NaBH_4$ with carboxylic acids has been used in the reduction of various nitrogen and oxygen-based functionalities.[15,16] The use of tartaric acid and $NaBH_4$ has been previously reported with varying degrees of success.[17] Tartaric acid offers a unique conjugate with $NaBH_4$. Such conjugates are bifunctional asymmetric reducing reagents, combining the activities of carboxylic acids and Lewis acids.

We have previously reported that the chiral reducing agent TarB–NO_2 (**1**), which consists of a tartaric acid-derived boronic ester, achieves excellent enantioselectivity in the reduction of aryl ketones.[18,19] TarB–NO_2 is easily prepared by mixing 3-nitrophenylboronic acid with the appropriate isomer of tartaric acid and refluxing in THF over CaH_2 (Scheme 1). Subsequent removal of CaH_2 yields the TarB–NO_2 reagent, which is stored and used as a molar solution in THF. Adding $NaBH_4$ (2 equiv) to a solution of pre-mixed TarB–NO_2 and ketone in THF gives a heterogeneous mixture. It is presumed that hydride delivery occurs via an acyloxyborohydride intermediate (**2**), which is formed by complexation of $NaBH_4$ with the carboxylic acid of TarB–NO_2 (Scheme 2).[20] While $NaBH_4$ is essentially insoluble in THF, the acyloxyborohydride has increased solubility in THF. This difference in solubility is advantageous because it prevents achiral hydride delivery from free $NaBH_4$ to the ketone.

While aryl ketones have been reduced by various methods with excellent enantioselectivity, aliphatic ketones continue to show poor asymmetric reduction.[2] Aliphatic

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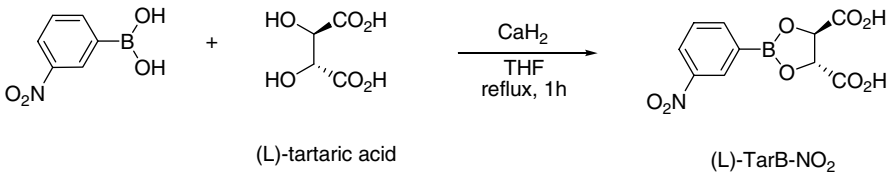
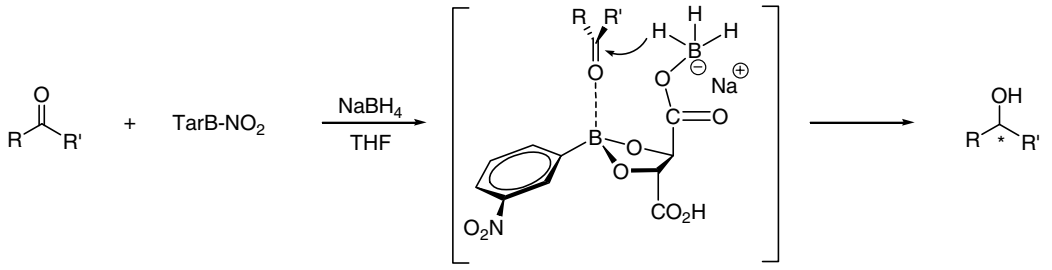


(L)-tartaric acid

(L)-TarB-NO_2

1

Scheme 1. Synthesis of (L)-TarB–NO_2.



2

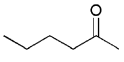
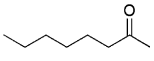
Scheme 2. Asymmetric reduction of prochiral ketones via the proposed acyloxyborohydride intermediate.

acyclic ketones present a challenge because they are more reactive than aromatic ketones and there is little difference in the steric bulk on either side of the ketone. CBS catalyst has been used in the reduction of aliphatic substrates with some success, particularly with *tert*-alkyl and *sec*-alkyl ketones.[2,21] Asymmetric reduction declines with methyl *n*-alkyl ketones, however. DIP-Cl© has also shown excellent enantioselectivity in the reduction of hindered aliphatic substrates, but limited success with *n*-alkyl or even *sec*-alkyl methyl ketones.[4] TarB–NO_2 has proven to be comparable to these reducing agents in the reduction of aromatic ketones, but we were curious to see whether it could successfully reduce aliphatic substrates with high enantioselectivity.

Using TarB–NO_2 for the asymmetric reduction of aliphatic substrates has produced promising results. Asymmetric induction ranged from moderate to excellent, depending on the steric bulk of the groups flanking the ketone (Table 1). The *tert*-alkyl ketones, pinacolone and 2,2-dimethyl-cyclopentanone, showed excellent enantioselectivity, yielding 94% and 95% ee, respectively of the *R*-isomer (entries 1 and 2). Even *sec*-alkyl substrates showed high degrees of selectivity (entries 3–6). We were pleased to find that the *n*-alkyl ketones, 2-octanone and 2-hexanone, were reduced with moderate enantioselectivity (entries 7 and 8).

In comparison to other boron-based chiral reducing agents, such as DIP-Cl© and CBS catalyst, TarB–NO_2 performed very well. Table 2 shows previously reported results for the reduction of various aliphatic ketones with these two reagents compared to TarB–NO_2. It can be seen that TarB–NO_2 achieved comparable enantioselectivities to DIP-Cl© for the *tert*-alkyl substrates (entries 1 and 2), and markedly higher enantioselectivities with the *sec*-alkyl and *n*-alkyl substrates (entries 3–5). In comparison to CBS catalyst, TarB–NO_2 produced comparable results for the reported aliphatic substrates.

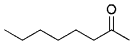
Table 1. Reduction of aliphatic ketones with TarB–NO_2 and $NaBH_4$[a]

Entry	Ketone	Isolated yield[b] (%)	% ee[c] (config)
1		80	94 (*R*)[d]
2[e]		—	95 (*R*)
3		80	80 (*R*)
4		86	83 (*R*)
5		62	62 (*R*)
6		82	82 (*R*)
7		65	56 (*R*)
8		83	60 (*R*)

[a] Reactions carried out as described in Ref. 22.
[b] All reactions gave >99% conversion by GC analysis. Isolated yield for entries 5 and 7 are low due to high volatility of the alcohols.
[c] Calculated by chiral GC analysis of the acetylated alcohols.
[d] Determined by comparison of optical rotation with literature value, and all others assigned by analogy.
[e] Results previously reported.[20]

In conclusion, we have disclosed a method for the enantioselective reduction of various aliphatic ketones using the chiral reducing agent TarB–NO_2 and $NaBH_4$. This

Table 2. Comparison of CBS catalyst, DIP-Cl©, and TarB–NO_2 for the enantioselective reduction of aliphatic ketones

Entry	Ketone	% ee		
		CBS Catalyst	DIP-Cl©	TarB–NO_2
1		98[a]	95[b]	94
2		92[a]	98[b]	95
3		91[a]	32[b]	80
4		84[a]	26[c]	82
5			7[b]	60

[a] See Ref. 2.
[b] See Ref. 4.
[c] See Ref. 23.

method is inexpensive and mild, as TarB–NO_2 is easily prepared from 3-nitrophenylboronic acid and tartaric acid, and $NaBH_4$ is used as the hydride source. Asymmetric reduction of aliphatic ketones produced the corresponding alcohols in enantiomeric excesses of 56–94%. The utility of this reagent for the reduction of a wide range of substrates, as well as the low cost and ease with which it is prepared, make it attractive for both academic and industrial applications.

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22. *General procedure for the reduction of aliphatic ketones. The reduction of pinacolone is representative.* An oven dried 50 mL round bottom flask was cooled under argon and charged with 3,3-dimethyl-2-butanone (0.62 mL, 5 mmol) and TarB–NO_2 (10 mL of a 0.5 M solution in THF, 5 mmol) and allowed to stir for 10 min. $NaBH_4$ (0.377 g, 10 mmol) was added in a single portion to the ketone/TarB–NO_2 solution, causing rapid evolution of H_2 gas. The reaction was allowed to stir for 30 min. Water was added dropwise to quench the reaction until gas evolution ceased. The mixture was brought to pH 12 with solid NaOH and stirred. The solution was extracted with pentane (10 mL) and the organic layer washed with 3 M NaOH (10 mL), brine (10 mL), and dried over $MgSO_4$. Evaporation under reduced pressure gave (*R*)-(−)-3,3-dimethyl-2-butanol (0.403 g, 80% yield), $[\alpha]_D^{20}$ −6.3 (*c* 4.3, MeOH). The alcohol was then acetylated using acetyl chloride in CH_2Cl_2 and pyridine. Enantiomeric excess of the acetylated alcohol was determined to be 94% by chiral GC analysis using a Supelco β-cyclodextrin 120 column (30 m × 0.25 mm).
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