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Chiral styrene oxides from α-haloacetophenones using $NaBH_4$ and TarB-NO_2, a chiral Lewis acid

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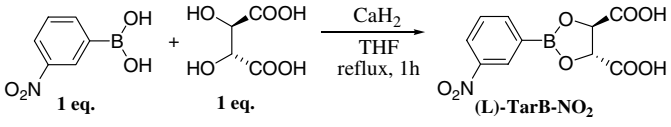
Abstract—High enantioselectivities are obtained for the preparation of chiral styrene oxides through reduction of α-haloacetophenones using TarB-NO_2 reagent and the inexpensive and mild reducing agent $NaBH_4$. The epoxides are easily obtained in up to 95% ee through routine acid–base workup of the product alcohols. Either the (*R*) or (*S*) epoxide can be obtained by using the appropriate L- or D-tartaric acid starting material in the TarB-NO_2 reagent.

The utility of chiral epoxides in organic synthesis provides considerable impetus for the development of high yielding and enantioselective methods for their preparation. Styrene oxides are particularly useful as they present convenient building blocks for pharmaceutically important compounds such as the antidepressant Sertraline and the adrenergic blockers Nifenalol and Salmeterol.[1,2] Notable among the approaches developed for the preparation of chiral styrene oxides are Sharpless's asymmetric dihyroxylation of styrenes,[3,4] Jacobsen's direct epoxidation of styrenes using (salen)Mn complexes,[5,6] and various schemes for the kinetic resolution of racemic epoxides.[7–10] An additional method for obtaining chiral styrene oxides used by several groups involves the reduction of α-haloacetophenones to the α-halophenylethanol followed by base catalyzed S_N2 closure to give the chiral epoxide.[11,12] With this approach, we have found that styrene oxides can be obtained from α-haloacetophenones under mild conditions and in high enantiomeric excess using the chiral Lewis acid reagent TarB-NO_2 with inexpensive $NaBH_4$.

Previously, we have reported the use of TarB-NO_2 with sodium borohydride ($NaBH_4$) for the reduction of aromatic and aliphatic ketones to their corresponding alcohols.[13] The enantioselective reduction takes place through the intermediacy of a chiral acyloxyborohydride formed in situ from the TarB-NO_2 and $NaBH_4$ reagents. TarB-NO_2 and related reagents are easily prepared as indicated in Scheme 1.

For ketone reductions, TarB-NO_2 and related reagents are most conveniently and effectively used as THF solutions. For the preparation of chiral styrene oxides, we premixed the α-haloacetophenone substrate with TarB-NO_2/THF solution. We then added this mixture to a suspension of $NaBH_4$ in THF. Sodium borohydride is essentially insoluble in THF, but the chiral acyloxyborohydride reducing species that forms in situ after mixing



Scheme 1. Preparation of TarB-X reagents.

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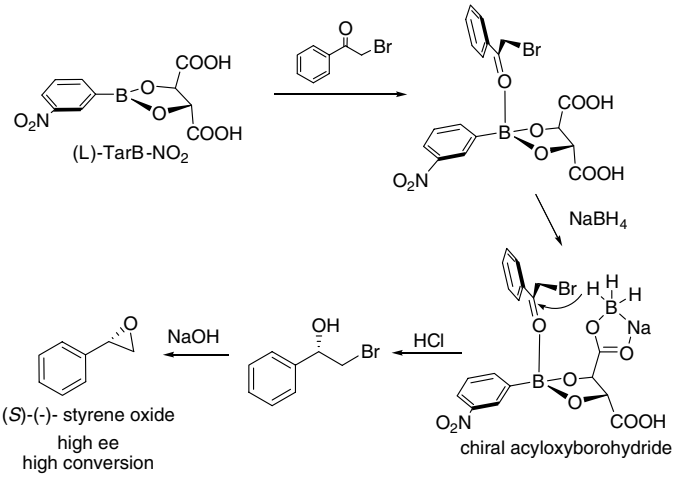


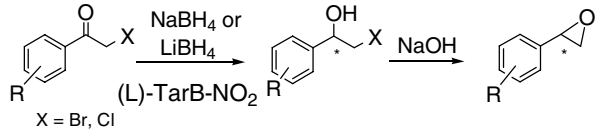
Scheme 2. Mechanism of acyloxyborohydride mediated reduction of α-haloacetophenone and subsequent S_N2 ring closure to form the epoxide.

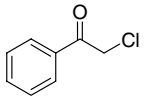
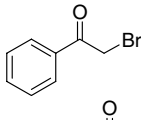
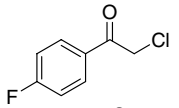
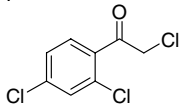
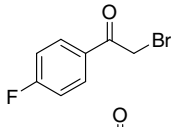
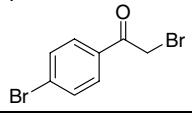
is soluble in THF. This situation effectively prevents the achiral and unmodified $NaBH_4$ from carrying out achiral reduction and only the chiral reduction pathway is opened. After reduction of the α-haloacetophenone to its corresponding alcohol, treatment with 3 M NaOH base for 1 h during workup allows for S_N2 closure of the epoxide ring.[14] The suggested mechanisms are shown in Scheme 2.

We used the combination of 2 equiv each of TarB-NO_2 and $NaBH_4$ to prepare styrene oxides from several α-chloro- and α-bromoacetophenone substrates at room temperature. Additionally, we also examined the TarB-NO_2-mediated reduction using $LiBH_4$ in place of $NaBH_4$. Lithium borohydride is soluble in THF and we used it to examine what effects improved solubility of borohydride would have on our selectivity. Generally, with both $NaBH_4$ and $LiBH_4$ we found that the reduction was complete in 30 min or less and that the enantiomeric excesses of the epoxide products were on the order of good to excellent. Better enantiomeric excesses were usually obtained using insoluble $NaBH_4$. Results for several of the substrates are given in Table 1.

As in our studies on the reduction of simple aromatic and aliphatic ketones, we generally found that combination of TarB-NO_2 and $NaBH_4$ provided superior results to those obtained using $LiBH_4$. While ees were high for most substrates, the 2′,2,4-trichloroacetophenone substrate gave exceptionally low 26% and 36% ees, respectively, for $LiBH_4$ and $NaBH_4$ reductions. We were curious as to whether this low induction could be explained by steric crowding by the ring substitutent in the 2-position, which might interfere with carbonyl coordination to the Lewis acidic boron of the TarB-NO_2 reagent. Alternatively, we suspected that the simple electron withdrawing effect of the chloro- substituents might activate the reactivity of the ketone carbonyl towards hydride reduction and, thus, reduce the selectivity normally observed in this system. To investigate these possibilities, we examined the effects of electron withdrawing and donating groups on the enantioselectivity observed in styrene oxide preparation from α-bromoacetophenones. The selected substrates and ees are shown in Table 2.

Table 1. Enantioselectivities obtained for preparation of chiral styrene oxides from α-chloro- and α-bromoacetophenone substrates at 25 °C



Substrate	$LiBH_4$	$NaBH_4$ (yield)	Config
	84	93 (94)	*S*[a]
	91	94 (80)	*S*[a]
	89	86 (87)	*S*[b]
	26	36 (95)	*S*[b]
	90	95 (89)	*S*[b]
	86	94 (84)	*S*[b]

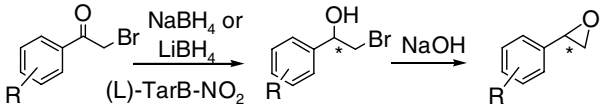
Isolated yields for reactions done using $NaBH_4$ are given in parentheses. All ees determined from chiral GC analysis using a Chiral BetaDex 120 column. All products were observed to display a (−) optical rotation.

[a] Configuration determined by comparison with the literature values.

[b] Configuration based on mechanistic model.

As indicated in Table 2, the presence of substituents in the 2-position of the α-bromoacetophenone substrates

Table 2. Enantioselectivities obtained for preparation of chiral styrene oxides from substituted α-bromoacetophenone substrates at 25 °C



Substrate	$LiBH_4$	$NaBH_4$	Configuration/ sign of rotation
R = *o*-NO_2	13	35	*S*[b]/(−)
m-NO_2	73	83	*S*[c]/(−)
p-NO_2	71	73	*S*[b]/(+)
o-OMe	86[a]	80[a]	*S*[b]/(+)
m-OMe	90	94	*S*[b]/(−)
p-OMe	85[a]	95[a]	*S*[b]/(+)

All ees determined from chiral GC analysis using a Chiral BetaDex 120 column. According to the GC results, the conversion was greater than 99% for all substrates.

[a] Determined using HPLC with Chiracel OB/OB-H column (99 hex:1IPA).

[b] Configuration based on mechanistic model.

[c] Configuration determined by comparison with the literature values.

does appear to cause a significant decrease in the observed enantioselectivity giving only 13% and 35% ee, respectively, for the $LiBH_4$ and $NaBH_4$ reductions of the 2-nitro-substituted substrate. Similarly, among the methoxy-substituted compounds, the lowest ee was recorded with the methoxy substituents in the 2-position. More generally, the presence of the electron-withdrawing nitro groups gave lower ee as compared to those obtained with substrates substituted with electron-donating methoxy groups. These results suggest that enantioselectivity in the TarB-NO_2/borohydride reduction system is sensitive to both electron-withdrawing effects and substitution at the 2-position.

In summary, we have demonstrated that chiral styrene oxides can be obtained under mild conditions in high enantiomeric excess and good yield using the chiral Lewis acid TarB-NO_2 with metal borohydrides. Generally, we observed that superior results are obtained when using mild and inexpensive $NaBH_4$ as the borohydride reagent. Substitution with electron-withdrawing groups tends to produce lower enantioselectivity, while substitution with any group in the 2-position of the substrate also tends to give lower ees. Enantiomeric excesses as high as 95% were observed with substituents in the 4-position. We are currently investigating the applicability of this reaction for the preparation of other epoxides.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.011.

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14. Representative isolation scale procedure: A 200-mL round-bottomed flask was flame dried, cooled under N_2, then charged with α-bromoacetophenone (1.99 g, 10 mmol) and TarB-NO_2 (40 mL of a 0.5 M solution in THF, 20 mmol) and allowed to stir for 10 min. $NaBH_4$ (0.755 g, 20 mmol), was then added in a single portion to the ketone-TarB-NO_2 solution causing rapid gas evolution. The reaction was left to stir for 1 h and then slowly quenched with 3 M HCl until gas evolution was no longer observed. The mixture was brought to pH 12 with 3 M NaOH and stirred for 1 h and extracted with ether (3 × 50 mL). The combined ether extracts were combined and washed with DI H_2O (2 × 50 mL) and dried over $MgSO_4$. GC analysis on a Supelco Beta-Dex 120 column revealed >99% conversion and 94% ee of (*S*)-(−)-styrene oxide. After solvent removal, the crude alcohol product was distilled under reduced pressure to afford the pure product in 80% yield. Alternatively, the pure epoxide could be obtained by column chromatography (SiO_2, hexane/EtOAc 7:1) followed by removal of solvent under reduced pressure.