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Enantioselective reduction of α-substituted ketones mediated by the boronate ester TarB-NO_2

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ABSTRACT

A facile and mild reduction procedure is reported for the preparation of chiral secondary alcohols prepared from α-substituted ketones using sodium borohydride and the chiral boronate ester (L)-TarB-NO_2. Direct reduction of substituted ketones bearing Lewis basic heteroatoms generally provided secondary alcohols of only modest enantiomeric excess likely due to either competition between the target carbonyl and the functionalized sidechains at the Lewis acidic boron atom in TarB-NO_2 or the added steric bulk of the α-sidechain. As an alternative method, these substrates were synthesized using TarB-NO_2 via a two-step procedure involving the reduction of an α-halo ketone to a chiral terminal epoxide, followed by regioselective/regiospecific epoxide opening by various nucleophiles. This procedure provides access to a variety of functionalized secondary alcohols including β-hydroxy ethers, thioethers, nitriles, and amines with enantiomeric excesses of 94% and yields up to 98%.

1. Introduction

β-Functionalized optically active secondary alcohols are ubiquitous in both naturally occurring bioactive compounds and modern synthetic intermediates. Optically active β-hydroxyamines have been reported as intermediates in many synthetic methodologies[1] and can also be found in a variety of compounds which affect the central nervous system (CNS) and the respiratory system. These compounds include the β-adrenoceptor agonist Arfomoterol[2] (Brovana) used for the treatment of chronic obstructive pulmonary disease (COPD), and the recently isolated CNS depressant (+)-11-hydroxyethratidine.[3] Optically active β-hydroxyethers have been used in a variety of applications as well, such as biological probes,[4] molecular switches,[5] and synthetic intermediates.[6] Enantioenriched β-hydroxythioethers have been utilized as intermediates in a variety of synthetic schemes, including the total synthesis of abyssomicin C[7] and several insect pheromones.[8] Optically active β-hydroxysulfones possess a range of biological activity, including recent reports of anti-tumor[9] and metalloproteinase inhibition activity.[10] They are also a useful functional handle in synthetic methodology, especially in the Julia Olefination,[11] and have been utilized as intermediates in the synthesis of a diverse array of compounds.[12]

One of the most direct methods of preparing β-functionalized optically active secondary alcohols is via the asymmetric reduction of a prochiral α-substituted ketone. Given the versatility of these compounds, it is of no surprise that a number of reagents have been developed for this application. Optically active β-hydroxyamines have been prepared from the enantioselective reduction of α-aminoketones by a variety of reagents including ruthenium catalysts,[13] rhodium catalysts,[14] copper hydrides,[15] enzymes,[16] oxazaborolidines,[17] and the DIP-Cl reagent.[18] The enantioselective reduction of α-alkoxyketones to β-hydroxyethers has been reported using ruthenium catalysts,[19] a rhodium catalyst,[20] enzymes,[21] and a spiroborate.[22] Enantioenriched β-hydroxythioethers have been prepared from the enantioselective reduction of α-thioketones using the CBS catalyst,[23] an iridium catalyst,[24] and several enzymes.[25] Optically active β-hydroxysulfones have also been prepared from α-sulfonylketones using the CBS catalyst[26] and enzymes,[27] as well as a ruthenium hydrogenation catalyst.[28]

Though many reagents have been developed for the enantioselective reduction of α-substituted ketones, many obstacles still prevent their widespread use. Heavy transition metals are difficult to remove and their associated toxicity precludes their use in the synthesis of many pharmaceutical reagents. Enzymes are non-toxic but they are extremely substrate dependant and not suitable for the reduction of many ketones. Boron based reagents, however, eschew many of these complications. DIP-Cl and the CBS catalyst, in particular, have shown exceeding promise in the reduction of a wide variety of substituted ketones.[29] However, both reagents often require low temperatures (−78 °C) and/or superstoichiometric quantities to achieve maximal induction. In contrast, the TarB-NO_2 reagent has demonstrated the ability to reduce a variety of aliphatic and aromatic ketones to highly enantioenriched

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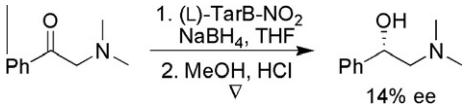
secondary alcohols at room temperature in 1 h utilizing only $NaBH_4$.[30] A TarB-NO_2 analog has also achieved excellent induction with various ketones without requiring a dry or inert atmosphere.[31] Given these promising results, we sought to expand the scope of the TarB-NO_2 reagent by investigating the asymmetric reduction of various prochiral α-substituted ketones.

2. Results and discussion

Previous reduction studies of aromatic and aliphatic substrates with the TarB-NO_2 reagent indicated that the enantioselectivity of the reaction was strongly correlated to the sterics about the carbonyl center. Carbonyl groups bearing a sterically demanding group on one side and a significantly smaller group on the other consistently gave the best results.[31] On the basis of this trend, it was decided to first investigate the asymmetric reduction of aromatic α-aminoketones, since the reduction of simple aromatic ketones by TarB-NO_2 gives superb results and the molecule bears a convenient fluorophore. Several of these substrates were synthesized and reduced with 1 equiv of TarB-NO_2 and 2 equiv of $NaBH_4$ at room temperature for 1 h. NMR studies showed that the initial reduction product isolated from the reaction mixture was the β-hydroxyamine borane. The undesired borane product was removed in acidic refluxing methanol to yield the desired product as confirmed by ^1H and ^{13}C NMR spectra. Subsequent analysis of the product β-hydroxyamines by HPLC and/or the corresponding Alexakis esters[32] revealed only poor enantioselectivity. Reductions performed at lower temperatures (0 °C, −78 °C) and/or with an excess of TarB-NO_2 also produced alcohols of poor optical purity (Scheme 1).

The results obtained from the reduction of α-aminoketones suggested that these substrates behaved very differently than simple aromatic and aliphatic ketones. ^{11}B NMR studies were performed on the initial reaction mixtures prior to the addition of $NaBH_4$ to determine if a new binding paradigm was present. As a 0.5 M solution in THF, TarB-NO_2 exhibits two signals in the ^{11}B spectrum. One signal, typically at about 31 ppm, corresponds to the free TarB-NO_2 molecule in solution. Another less intense signal is also observed around 9 ppm. This signal corresponds to a tetrahedral boronate of the form $ArB(OR)_3$, and is assumed to be either a THF coordination complex or a dimer of TarB-NO_2. A 1:1 molar mixture of TarB-NO_2 and acetophenone in THF yields the same spectrum as TarB-NO_2 alone. Since an acetophenone/TarB-NO_2 complex would come at the same chemical shift as a TarB-NO_2 dimer or a THF complex, this result suggests that acetophenone binds only very weakly to TarB-NO_2 despite the fact that it is reduced with $NaBH_4$ to the product alcohol with a 99% ee. A 1:1 molar mixture of TarB-NO_2 and 2-(piperadinyl)-1-phenyethanone also yields a similar spectra, but the 9 ppm signal corresponding to a TarB-NO_2 complex is much stronger than the free TarB-NO_2 molecule or a 1:1 mixture of TarB-NO_2 and acetophenone.[33] This suggests that a new complex has formed between the substrate and TarB-NO_2. Since the α-aminoketone bears a tertiary nitrogen atom, it is hypothesized that the Lewis basic lone pair of the amine is responsible for the formation of an amine–TarB-NO_2 borane complex. Since α-aminoketones give very poor enantioselective induction, it is surmised that formation of this amine–TarB-NO_2 complex provides an alternative achiral reduction pathway that is responsible for the poor induction observed with these substrates.

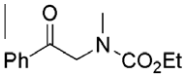
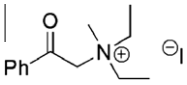
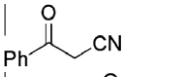
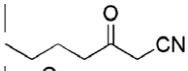
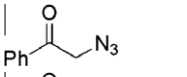
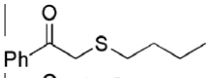
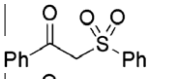
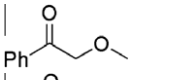
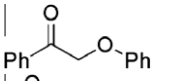
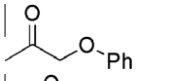
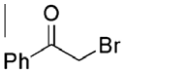


Scheme 1. α-Aminoketone reduction with (L)-TarB-NO_2.

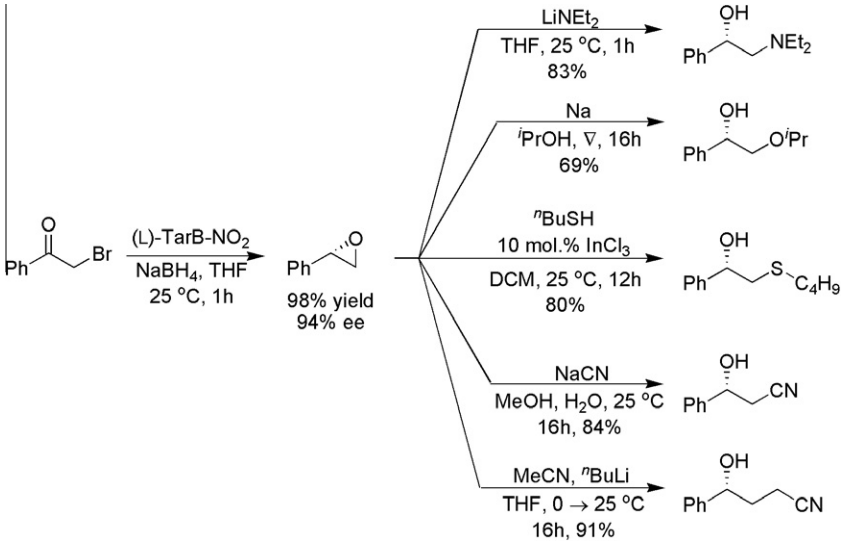
Following the results of the reduction of α-aminoketones with TarB-NO_2, a variety of other α-substituted ketones were reduced to further quantify the role of the heteroatom in these reactions. The results are summarized in Table 1.

The optical purity of the isolated secondary alcohol varied widely depending on the nature of the substrate. Reduction of a prochiral carbamate and amine salt gave minimal induction (Table 1, entries 1 and 2), but a moderate induction was observed for 2-cyano- and 2-azidoacetophenone (entries 3 and 5). Reduction of an *n*-alkyl cyano derivate gave very poor induction, presumably due to the lack of any steric difference between the sidechains flanking the carbonyl (entry 4). Reduction of a thioether resulted in a racemic product, while reduction of a sulfone gave slight enantioenhancement (entries 6 and 7). Reduction of 2-methoxyacetophenone gave the corresponding (*S*) alcohol with a good enantiomeric excess of 80% (entry 8), but reductions of α-phenoxyketones were less successful (entries 9 and 10). The higher enantioselectivity observed in the reduction of 2-methoxyacetophenone and the inversion of configuration observed for 1-phenoxy-2-propanone suggests that the steric bulk of the phenyl ether greatly influences the interaction between the ketone substrate and TarB-NO_2. The lack of enantioselectivity observed with 2-phenoxyacetophenone also suggests that the phenoxyether moiety serves as a sterically demanding group, since the TarB-NO_2 reagent has demonstrated the best enantioselectivity in the reduction of ketones bearing one small and one sterically demanding group attached to the carbonyl. The reduction of α-haloketones such as 2-bromoacetophenone, however, proceeds smoothly to give chiral epoxides of high optical purity with TarB-NO_2 as reported previously (entry 11).[34]

Table 1
Reduction of α-substituted ketones with (L)-TarB-NO_2

Entry	Ketone	% ee[a]	Yield (%)	Config.[b]
1		6	42	—
2		4	88	—
3		74	85	(*R*)
4		6	62	—
5		61	94	(*S*)
6		0	53	—
7		35	86	—
8		80	92	(*S*)
9		0	87	—
10		31	85	(*R*)
11		94	98	(*S*)

[a] Determined via HPLC, GC or analysis of the corresponding Alexakis ester. See Supplementary data.
[b] Determined via optical rotation values in comparison to literature values. See Supplementary data.



Scheme 2. Preparation of β-functionalized secondary alcohols utilizing (L)-TarB-NO_2.

Though functionalized chiral alcohols of sufficient optical purity could not be prepared via the direct reduction of α-substituted amino-, thio-, sulfonyl-, cyano-, alkoxy-, or phenoxyketones, they can be prepared indirectly using TarB-NO_2 via optically active epoxides. Starting from (*S*)-styrene oxide prepared from the reduction of 2-bromoacetophenone by (L)-TarB-NO_2 and $NaBH_4$, a variety of β-substituted secondary alcohols were prepared in high optical yield (Scheme 2).

A β-hydroxyamine was prepared using a regiospecific epoxide opening procedure reported previously by our lab via the reaction of (*S*)-styrene oxide with an in situ generated lithium amide in THF.[35] Preparation of a β-hydroxyether was achieved using isopropanol and sodium metal, providing the desired secondary alcohol along with some of the undesired primary alcohol formed via the attack of the isopropoxide nucleophile at the benzylic carbon in an 87:13 mixture. Separation of the two isomers via column chromatography with a dichloromethane/ethyl acetate 6:1 eluent provided the desired product in 69% yield. While thiolysis of styrene epoxides are known to generally favor attack at the β-carbon, the addition of indium (III) chloride has been shown to give excellent regioselectivity for the α-carbon.[36] Using a modification of these previously reported conditions, (*S*)-styrene oxide was reacted with 1-butanethiol and a catalytic amount of indium (III) chloride to provide the product β-hydroxythioether as a single regioisomer. This thiolysis reaction is also a potential precursor to β-hydroxysulfones, since several methods for the selective oxidation of the sulfur atom in the presence of an optically active secondary alcohol are known.[37] A β-hydroxynitrile was prepared using a simple regiospecific opening with sodium cyanide, and a γ-hydroxynitrile was prepared via the regiospecific opening of the epoxide with a lithiated acetonitrile carbanion.[38]

3. Conclusion

Asymmetric reductions of α-substituted amino-, cyano-, azido-, thio-, sulfonyl-, alkoxy-, and phenoxyketones with (L)-TarB-NO_2 were investigated as a potential route for the preparation of β-functionalized optically active secondary alcohols. Unfortunately, TarB-NO_2 was found to reduce most of these compounds with poor to modest enantioselectivity. Comparing the enantioselectivities observed with TarB-NO_2-mediated reductions from these and previous studies, the general trend observed for substitutions at the alpha position of acetophenone derivatives is as follows: H > alkyl > Br,Cl > CN,OR > SO_2R > CO_2R,SR,NR_2. Experimental evidence suggests that competition at the Lewis acidic boron atom in TarB-NO_2 between the target carbonyl and the functionalized sidechains or the added steric bulk of the α-sidechain is responsible for the poor enantioselectivity of the reaction. Despite these challenges, several functionalized and highly enantioenriched secondary alcohols were prepared via regioselective and regiospecific epoxide opening reactions of (*S*)-styrene oxide prepared with TarB-NO_2. These reactions offer a simple two-step alternative to the direct reduction of α-substituted ketones to prepare bioactive and synthetically useful β-functionalized secondary alcohols of high optical purity.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.146.

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