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Asymmetric Synthesis of Primary Amines via the Spiroborate-Catalyzed Borane Reduction of Oxime Ethers

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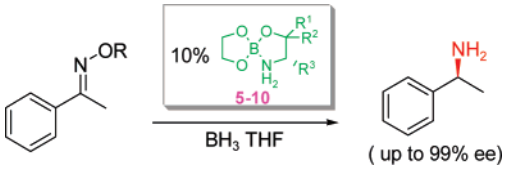
ABSTRACT



The enantioselective borane reduction of *O*-benzyloxime ethers to primary amines was studied under catalytic conditions using the spiroborate esters 5–10 derived from nonracemic 1,2-amino alcohols and ethylene glycol. Effective catalytic conditions were achieved using only 10% of catalyst 5 derived from diphenylvalinol in dioxane at 0 °C resulting in complete conversion to the corresponding primary amine in up to 99% ee.

The asymmetric reduction of oxime ethers with nonracemic chiral reducing agents represents an important synthetic route to enantiopure primary amines.[1−5] Over the past two decades, oxazaborolidines have been developed as chirality transfer reagents for the reduction of the carbonyl and imine functionality.[2] The borane-mediated catalytic reduction of ketones using 1,3,2-oxazaborolidines has been extensively investigated.[2b] These efforts have led to the synthesis of highly enantiopure alcohols using less than 10 mol % of catalyst. Applying this process to the reduction of C=N provides direct access to nonracemic primary amines which are widely used as key intermediaries in the synthesis of pharmaceuticals, chiral auxiliaries, and catalysts.[1−4] For the borane-mediated reduction of oxime ethers, a stoichiometric amount of the oxazaborolidine is usually required to obtain high enantioselectivities.[3,4] Fontaine et al.[3k] even employed 2.5 equiv of the diphenylvalinol-derived B−H oxazaborolidine to achieve complete reduction with high selectivity.

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Itsuno and co-workers[3b] reported the first catalytic borane-based reduction of acetophenone *O*-benzyl oxime. With 10 mol % of the (*S*)-diphenylvalinol oxazaborolidine, generated in situ, 52% ee was observed in the product (*S*)-1-phenylethanamine. This selectivity is much lower than the 93% ee obtained for this substrate employing 1 equiv of the catalyst.

In addition to their high cost and air and moisture sensitivity, B−H oxazaborolidines often contain impurities which diminish their effectiveness.[2c−e] This has led to the development of alternative catalytic systems for the reduction of oximes, but with only modest success.[5] In the present study, a truly catalytic and highly enantioselective process for the borane-mediated asymmetric reduction of oxime ethers is reported for the first time.

Recently, we prepared stable enantiopure spiroborate esters **5**−**10** derived from 1,2-amino alcohols, as new catalysts for the asymmetric reduction of ketones (Figure 1).[6]These

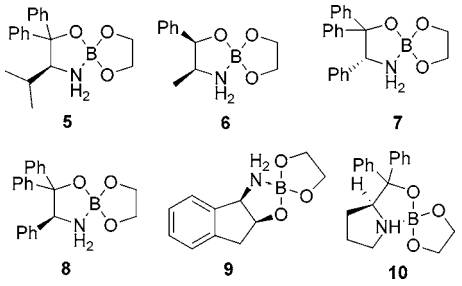
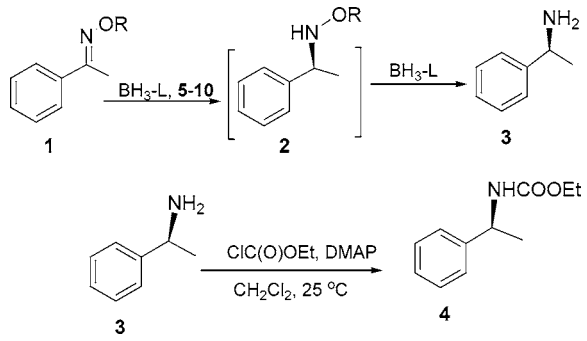


Figure 1. Spiroborate esters derived from nonracemic 1,2-amino alcohols.

spiroborates proved to be highly reactive and enantioselective catalysts for this process. Coupled with their operational convenience, we felt that they may provide effective catalysts for reduction of oxime ethers, thereby providing a new, highly useful entry to nonracemic amines (Scheme 1).[7]

Scheme 1



Initially, we examined the reduction of (*E*)-benzyl oxime ether **1a** (R = Bn) in toluene employing 50 mol % of spiroborate ester **5** and 2 equiv of BH_3·DMS at 50 °C for 12 h followed by 3 h at 110 °C. The amine product **2a** was isolated as its carbamate **4** in 75% yield and 93% ee. Seeking milder conditions, we discovered that the reduction could be conducted at 25 °C in THF solvent, and these conditions were used with varying amounts and sources of borane and **5** to determine optimal conditions for the reduction. These results are presented in Table 1.

Table 1. Spiroborate Ester **5** Catalyzed Reduction of **1a** with Different Borane Sources in THF at 25 °C

entry	cat. **5** (mol %)	borane reagents	time (h)	**2a**, **3** (%)[a]	ee[b]
1	50	1BH_3·DMS	48	0, 60	94
2	50	2BH_3·DMS	36	15, 85	96
3	50	4BH_3·DMS	12	0, 100	93
4	25	2BH_3·DMS[c]	48	17, 58	93
5	25	6BH_3·DMS	12	0, 85	89
6	20	2.4BH_3·THF[d]	36	9, 91	89
7	10	2.4BH_3·THF[d]	36	16, 44	86
8	**10**	**4BH_3·THF[d]**	**36**	**0, 100 (75)[e]**	**87**
9	10	4BH_3·DEA	36	0, 0	–

[a] The product ratio was determined by GC analysis. [b] The ee was determined by GC analysis using a Crompack Chirasil-Dex-CB column. [c] The oxime **1a** in THF was added in 10 h, then stirred for 38 h at 25 °C. [d] The borane reagent was stabilized with <0.005 M *N*-isopropyl *N*-methyl *tert*-butylamine. [e] The yield in parentheses was obtained after purification of ethoxy carbamide.

The complete conversion of **1a** to **3** under these conditions was achieved by increasing the amount of BH_3·DMS to 4 equiv (Table 1, entries 1−3) and using 50% of spiroborate **5**. The reduction of **1a** occurred faster and with complete conversion to primary amine **3**. Decreasing **5** to 25% and using 6 equiv of BH_3·DMS, the conversion was partial (85%, entry 5). Hence, we decided to use BH_3·THF stabilized by *N*-isopropyl *N*-methyl *tert*-butylamine, which has been demonstrated to be more stable and selective in carbonyl reductions.[8] Indeed, with 20% catalyst and using 2.4 equiv of BH_3·THF, we observed a nearly quantitative conversion to **3** (91%, entry 6). Remarkably, with only 10% of catalyst and 4 equiv of BH_3·THF, the reduction of oxime **1a** afforded the primary amine **3** quantitatively with only a slight decrease in ee (87%, entry 10). It must be mentioned that BH_3·DEA was unreactive in this oxime reduction.[9]

A variety of solvents, temperatures, and borane sources were screened for the reduction of **1a** under the previous optimized conditions.[10] In general, ethereal solvents lead to

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(8) See: Synthetic methods: Reduction. Aldrich *Chemfiles* **2005**, *5*, 4; Josyula, K.V. B.; Potyen, M.; Gao, P.; Hewitt, C. Patent application pending publication.

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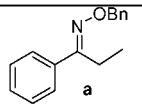
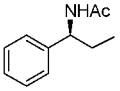
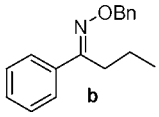
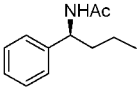
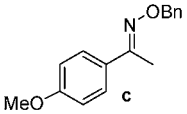
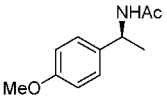
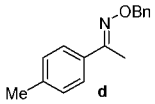
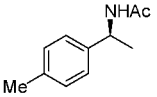
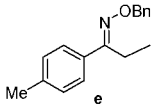
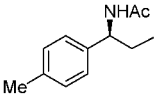
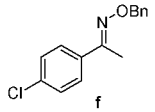
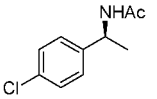
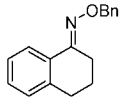
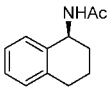
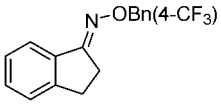
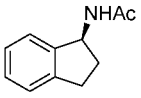
(10) The details of the results obtained using different solvents, sources of borane, temperature, mode of addition, catalysts, and oxime substituents are included in the Supporting Information.

Table 2. Asymmetric Reduction of Representative Oxime Benzyl Ethers with 0.1 Equiv of Catalyst **5**

11	12[a]	temp (°C)	yield (%)[b]	ee[c] (%)
 **a**		25	81	79
		0	89	83
 **b**		25	68	98
		0	71	99
 **c**		25	84	78
		0	90	85
 **d**		25	88	85
		0	92	98
 **e**		25	85	66
		0	91	93
 **f**		25	71	88
		0	77	94
 **g**		25	90	86
		0	85	84
 **h**		25	68	89
		0	77	97

[a] The reactions were carried out using 1 equiv of oxime ether, 0.1 equiv of catalyst **5**, and 4 equiv of borane stabilized with $NaBH_4$ in dioxane for 36 h or until the conversion was 100%. [b] Purified by column chromatography. [c] The ee was determined using a Crompack Chirasil-Dex-CB GC column.

higher ee's of the isolated product **4** with dioxane giving the best results (90% ee). The reaction temperature was also varied to further optimize the reaction conditions. At 0 °C, the reaction requires longer reaction times for the complete conversion to **3**, but the enantioselectivity is higher (96.5% ee). The BH_3·THF, stabilized with $NaBH_4$, affords **3** and after being treated with ClC(O)OEt produced **4** in 95% ee at 25 °C in dioxane. Importantly, this reagent gives 96.5% ee at 0 °C, the same result as that for the amine-stabilized BH_3·THF. The BH_3·DMS reagent proved to be a less effective borane source for this reduction. Moreover, the selectivity does not change with the addition time of the oxime ether.

The optimized reaction conditions were extended to the other spiroborate esters indicated in Figure 1. At 0 °C, the reactivity of catalysts **6**−**9** was rather low. Therefore, the reaction temperature was changed to 25 °C, except for catalyst **10**, whose reactivity was examined at 0 °C. Spiroborate ester **5** derived from diphenylvalinol shows superior enantioselectivity compared to these other systems.[10]

We further extended these studies to include the methyl and various substituted *O*-benzyl derivatives of acetophenone oxime (4-MeO−$C_6H_4CH_2$; 4-$CF_3C_6H_4CH_2$; 2-$NO_2C_6H_4CH_2$).[10] Although these all give excellent selectivities, the 4-CF_3-substituted benzyl oxime gives **4** in 99% ee.

Because similar high selectivities were observed with all of the O-benzylated acetophenone oximes, the simple (*E*)-benzyl oxime derivatives **11** of representative aryl alkyl ketones were prepared by standard methods and submitted to the optimized reductive conditions (0.1 equiv of **5**, dioxane, 25 and 0 °C). The product amines were isolated as their *N*-acetyl derivatives **12**. In general, the process gives excellent enantioselectivity (83−99%) at 0 °C. These results are summarized in Table 2.

In summary, a highly efficient new borane-based catalytic process for the asymmetric synthesis of amines from oxime ethers has been discovered. The new process employs the easily prepared and stable spiroborate ester **5** as the chiral transfer agent. Employing simple procedures, this methodology provides a convenient entry to highly versatile and important nonracemic amines. Mechanistic studies and further applications of this new process are underway.

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Supporting Information Available: Experimental procedures, full characterization for all new compounds, and ^1H spectra and GC analysis for racemic and nonracemic acetamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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