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Asymmetric reduction of ketoxime derivatives and *N*-alkylketimines with borane–oxazaborolidine adducts

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Abstract—Oxime ethers of acetophenone, isopropyl methyl ketone, and *tert*-butyl methyl ketone were reduced to the corresponding hydroxylamine ethers of 45–94% ee with borane–oxazaborolidine **1** derived from (−)-norephedrine. A one-pot reduction of acetophenone oxime with **1** to 1-phenylethylhydroxylamine of 87% ee is described. The reduction of 6-methyl-2,3,4,5-tetrahydropyridine and *N*-methylimines of the above mentioned ketones with borane-*B*-methyloxazaborolidine adduct **2**, derived from (−)-diphenylprolinol, gave the corresponding amines of 40–74% ee.

In contrast to excellent reagents and catalysts developed for the asymmetric reduction of prochiral ketones, limited success has been achieved in the reduction of prochiral ketoximes and ketimines.[1] Boranes and borohydrides are among the reagents of choice for these reductions.[2] Although many years ago it was reported that the reduction of oximes can be controlled to produce hydroxylamines,[3] only recently, in connection with the synthesis of 5-lipoxygenase inhibitor, has the asymmetric reduction of 7-benzyloxycumaranone oxime *O*-benzyl ether with borane–oxazaborolidine adduct **1** derived from (−)-norephedrine, been achieved.[4a] The reaction depends on the ether group as indicated by unreactive hindered ethers, and mixtures of products obtained from *O*-methoxymethyl and allyl ethers.[4b] However, its scope has not been delineated. Also, little is known on the asymmetric reduction of *N*-alkylketimines with boranes. The small amount of reported data show low to moderate enantioselectivity.[5] Consequently, in continuation of our earlier studies on the reduction of oximes,[6] we decided to examine the asymmetric reduction of representative ketoxime derivatives and *N*-alkylketimines with borane-oxazaborolidine adducts **1**–**3**. The adducts **1** and **3** are prepared in tetrahydrofuran and used in situ,[2a,4b,7] whereas **2** is a stable crystalline compound, and can be used in other solvents (Fig. 1).[8]

Acetophenone oxime *O*-methyl ether **4a**, isopropyl methyl ketone oxime *O*-methyl ether **5a**, and *tert*-butyl methyl ketone oxime *O*-methyl ether **6a** were reduced with **1**. The reaction run in tetrahydrofuran at 0°C afforded mixtures of the corresponding hydroxylamine *O*-methyl ethers and amines of 45–82% ee in 31–92% yield (Table 1). The products were readily separated by flash chromatography. Enantiomeric excesses of the hydroxylamine ethers and amine products are the same, since the amines are formed by the reduction of hydroxylamine ethers not affecting the stereogenic centre. The reduction of **4a** proceeded in a high yield to give a mixture of 1-phenylethylhydroxylamine *O*-methyl ether **7a** and 1-phenylethylamine **10** of 55% ee in a 54:46 ratio. Oxime ethers **5a** and **6a** were reduced with **1** to the corresponding hydroxylamine *O*-methyl ethers **8a** and **9a** with higher chemoselectivity, 87 and 77%, respectively. Enantioselectivity increased to 82% ee for **8a**, but decreased to 45% ee for the more hindered **9a**.

The reduction of *O*-benzyl ether **4b** with **1** showed higher chemo- (77%) and enantioselectivity (94% ee) as compared with **4a**, whereas a slight decrease in selectiv-

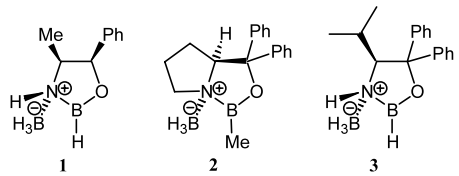

Figure 1.

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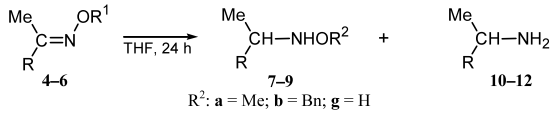
Table 1. Asymmetric reduction of **4–6**, and the reduction of **4c–f** with BH_3/THF and BMS[a]



4–6 7–9 10–12

R^2: **a** = Me; **b** = Bn; **g** = H

Oxime derivative			Reducing agent[b]	Temp. (°C)	Product			
4–6	R	R^1			**7–12**	Comp.[c] (%)	Ee[d] (%) (conf.)[e]	Yield[f] (%)
4a	Ph	Me	**1**	0	**7a**/**10**	54:46	55 (*S*)	92
4b	Ph	Bn	**1**	0	**7b**/**10**	77:23	94 (*S*)	88
5a	*i*-Pr	Me	**1**	0	**8a**/**11**	87:13	82	61
5b	*i*-Pr	Bn	**1**	0	**8b**/**11**	75:25	74	58
6a	*t*-Bu	Me	**1**	0	**9a**/**12**	77:23	45	31
6b	*t*-Bu	Bn	**1**	0	No r.			
4a			A[g]	20	**10**		0	12
4a			B[g]	20	**10**		9 (*S*)	37
4a			C[g]	20	**10**		62 (*S*)	62
4a			D[g]	20	**10**		0	92
4a			E[g]	20	**10**		60 (*S*)	60
4c	Ph	BBN	BH_3/THF	0	**7g**/**10**	3:97	0	57
4c			BMS	0	**7g**/**10**	14:86	0	60
4d	Ph	$BChx_2$	BH_3/THF	0	**7g**/**10**	40:60	0	55
4d			BMS	0	**7g**/**10**		0	52
4e	Ph	B^dIpc_2[h]	BH_3/THF	0	**7g**/**10**	67:33	0	50
4e			BMS	0	**7g**/**10**	83:17	0	50
4f	Ph	$B(2\text{-}^dIcr)_2$[i]	BH_3/THF	0	**7g**/**10**	81:19	21 (*R*)	40
4d			**1**[j]	0	**10**		85 (*S*)	60
4d			**1**	0	**7g**/**10**	71:29	84 (*S*)	56
4e			**1**	0	**7g**/**10**	88:12	87 (*S*)	52
4e			**2**	0	**7g**/**10**	71:29	0	45
4d			**3**	0	**7g**/**10**	67:33	71 (*S*)	39
4e			**3**	0	**7g**/**10**	73:27	72 (*S*)	40

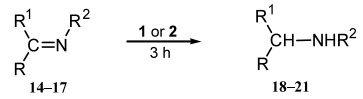
[a] For representative procedures, see Refs. 9 and 10.
[b] One molar equivalent was used, if not otherwise stated.
[c] Determined by GC analysis on a Supelco SPB-5, 30 m×0.32 mm, column.
[d] TFA derivatives of **10–12** and **7g** were analyzed by GC on Chiraldex G-PN, 20 m×0.25 mm, or Supelco Beta-DEX 325, 30 m×0.25 mm, chiral columns.
[e] Configurations were established by comparing the signs of rotation with the literature data,[11,12] and GC comparison with an authentic sample of (*S*)-1-phenylethylamine TFA derivative.
[f] Isolated yields.
[g] A–D = $NaBH_4/MCl_2$/(−)-norephedrine (4:1:1), MCl_2: A = $NiCl_2$; B = $CoCl_2$; C = $TiCl_4$; D = bis(cyclopentadienyl)titanium dichloride. E = $NaBH_4/TiCl_4$/(−)-1,1-diphenylprolinol (4:1:1).
[h] Derived from (+)-α-pinene, >99% ee.
[i] Derived from (+)-2-carene, >99% ee.
[j] Two molar equivalents.

ity was observed for **5b** as compared with **5a**. *O*-Benzyl ether **6b** was unreactive under the same conditions. The decreasing yields of products obtained from **4a**>**4b**>**5a**>**5b**>**6a**>**6b** reflect the increasing steric hindrance exerted both by the ketone R group and the ether R^1 substituent (Table 1).

Itsuno,[13] introduced the sodium borohydride–zirconium(IV) chloride mixture, modified with chiral amino alcohols derived from L-valine, for the asymmetric reduction of ketoxime *O*-ethers. We used mixtures of nickel(II), cobalt(II), and titanium(IV) chlorides (1 molar equiv.) with sodium borohydride (4 equiv.) in the presence of (−)-norephedrine or (−)-1,1-diphenylprolinol (1 equiv.). The reduction of **4a** with the first two mixtures produced 1-phenylethylamine **10** in low yield and low enantiomeric excess (Table 1). In contrast, the reduction of **4a** with sodium borohydride-titanium(IV) chloride in the presence of (−)-norephedrine or (−)-1,1-diphenylprolinol produced **10** of 60–62% ee in ~60% yield. Interestingly, **10** was obtained from **4a** in much higher yield when bis(cyclopentadienyl)titanium dichloride was substituted for titanium(IV) chloride, however, the product was racemic. In spite of changes in the molar ratio of components of the reducing mixtures, **7a** was not detected among the products of these reactions.

Next, the reduction of acetophenone oxime **13** with diisopinocampheylborane ($^dIpc_2BH$) was attempted. The reagent transformed the oxime into the corresponding borinate **4e** (Table 1), and no further reaction was observed at room temperature. However, the addi-

Table 2. Asymmetric reduction of **14–16** and 6-methyl-2,3,4,5-tetrahydropyridine (**17**) with **1** and **2**[a]



Imine[b]				Reducing agent	Solvent	Temp. (°C)	Product		
14–17	R	R^1	R^2				**18–21**	Ee[c] (%) (conf.)[e]	Yield[d] (%)
14	Ph	Me	Me	**1**	THF	0	**18**	38 (*S*)	58
14				**2**	Toluene	0	**18**	74 (*S*)	60
14				**2**	Toluene	20	**18**	41 (*S*)	78
15	*i*-Pr	Me	Me	**1**	THF	0	**19**	13	71
15				**2**	Toluene	0	**19**	60	79
16	*t*-Bu	Me	Me	**1**	THF	0	**20**	40	55
16				**2**	Toluene	0	**20**	5	85
17	Me	$-(CH_2)_4-$		**1**	THF	0	**21**	21	70
17				**2**	Toluene	0	**21**	50	92

[a] Representative procedure, see Ref. 14.
[b] *N*-Methylketimines were prepared from the corresponding ketones and methylamine according to Ref. 15.
[c] Determined by GC analysis of TFA derivatives on a Chiraldex G-PN, 20 m×0.25 mm, chiral column.
[d] Isolated yields.
[e] Configuration was determined by comparing the sign of rotation with the literature data.[16]

tion of borane–tetrahydrofuran to **4e** at 0°C produced a mixture of racemic 1-phenylethylhydroxylamine **7g** and **10** (83:17) in 64% yield. Borinates derived from **13** and 9-borabicyclo[3.3.1]nonane (9-BBN) or dicyclohexylborane (Chx_2BH) were also reduced with borane–tetrahydrofuran, producing **7g**/**10** in the ratio 3:97 and 40:60, respectively. The reduction of **4f** with BMS produced **7g**/**10** (81:19) of 21% ee. The results demonstrate the possibility of directing the reduction of oximes with borane, either to hydroxylamine or amine, depending on steric requirements of the dialkylboryl group. However, asymmetric induction exerted by chiral dialkylboryl groups (2-$^{d}Icr_2B$ and $^{d}Ipc_2B$) in these reactions was low, or none. Fortunately, when a chiral reducing agent **1** (2 molar equiv.) was used, **4d** was transformed into **10** of 85% ee. One molar equiv. of **1** reduced **4d** and **4e** mainly to **7g** of 84% and 87% ee, respectively (Table 1). The reaction of **4d** and **4e** with **3** in the same molar ratio showed lower enantioselectivity, and the reduction of **4e** with **2** produced a mixture of racemic **7g**/**10**.

Finally, *N*-methylketimines **14–16** and 6-methyl-2,3,4,5-tetrahydropyridine **17** were reduced with **1** and **2** (Table 2). The imines reacted in much shorter time than the corresponding oxime derivatives.

Imines **14** and **16** reacted with **1** producing **18** and **20** of 38–40% ee. The non-aromatic imines **15** and **17** reacted with lower selectivity. The reagent **2** was more selective reducing **14**, **15**, and **17** to **18**, **19**, and **21** of 74, 60, and 50% ee, respectively. Enantioselectivity of **2** in these reactions is among the highest achieved in the reduction of *N*-alkylimimines of non-aromatic ketones with boranes.[5b] However, **2** reacted with the most hindered **16** with low selectivity. The reduction of **14**, **15** and **17** with borane in the presence of catalytic amounts (up to 10% molar) of **1** and **2** was less selective as compared to the stoichiometric reactions.

In conclusion, the asymmetric reduction of **4d** and **4e** with **1** and **3** to give **7g** demonstrates for the first time a direct one-pot transformation of an oxime into the corresponding hydroxylamine in high enantiomeric excess with a borane reagent. *O*-Benzyl ethers **4b–6b** are reduced with **1** to the corresponding hydroxylamine *O*-benzyl ethers of high to moderate ee. Adduct **2** is more enantioselective than **1** in the reduction of ketimines **14**, **15**, and **17**.

Acknowledgements

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9. **Representative procedure. (*S*)-(−)-1-Phenylethylhydroxylamine *O*-benzyl ether 7b**: **A** borane–THF solution (2 M, 2.5 mL, 5 mmol) was added to a stirred solution of (−)-norephedrine (0.76 g, 5 mmol) in THF (5 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred at this temperature until hydrogen evolution ceased (0.5–1 h). A borane–THF solution (2 M, 2.5 mL, 5 mmol) was added and stirring was continued for 3 h. A solution of **4b** (1.01 g, 4.5 mmol) in THF (2 mL) was added dropwise and the stirring was continued for 24 h. The mixture was cooled in an ice-bath and 3 M HCl (10 mL) was added. After stirring the mixture at room temperature for 5 h, THF was evaporated under reduced pressure. The mixture was alkalized with 6 M sodium hydroxide and extracted with diethyl ether (3×15 mL). The extract was washed with brine, and dried with anhydrous magnesium sulphate. Removal of the solvent provided a crude product. GC analysis on a Supelco SPB-5, 30 m×0.32 mm, column, revealed **7b**/**10**, 77:23. Flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2), afforded **7b** (0.69 g, 68%), $[\alpha]_D^{20}=-29.16$ (*c* 1.16, $CHCl_3$), and **10** (0.11 g, 20%), identified by GC comparison with an authentic sample, $[\alpha]_D^{20}=-33.1$ (*c* 1.05, $CHCl_3$), lit.:[11] $[\alpha]_D^{20}=+34.5$ (*c* 1.0, $CHCl_3$), 98% ee for the (*R*)-isomer. Derivatization of **10** (20 mg) with trifluoroacetic anhydride and GC analysis on a Supelco Beta-DEX 325, 30 m×0.25 mm, column showed 94% ee. **7b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (d, $J=6.6$ Hz, 3H, CH_3), 4.18 (m, 1H, CH), 4.60 (d, $J=11.7$ Hz, 1H, OCH_2), 4.66 (d, $J=11.5$ Hz, 1H, OCH_2), 5.64 (s, 1H, NH), 7.26–7.40 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 19.86 (CH_3), 60.57 (CH), 76.73 (CH_2), 127.17 (2×CH), 127.29 (CH), 127.62 (CH), 128.23 (2×CH), 128.30 (2×CH), 128.37 (2×CH), 138.02 (C), 143.01 (C).
10. **(*S*)-(−)-1-Phenylethylhydroxylamine 7g**: A solution of acetophenone oxime (**13**) (1.35 g, 10 mmol) in THF (5 mL) was carefully added to a suspension of ^{d}Ipc$_2$BH (2.91 g, 10.4 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred until hydrogen evolution ceased (1–1.5 h) and a clear solution was obtained. The solution was cooled in an ice-bath, and a solution of **1**, prepared from (−)-norephedrine (1.81 g, 12 mmol) and a borane–THF solution (2 M, 12 mL, 24 mmol), was added dropwise. The stirring was continued for 20 h. The reaction mixture was cooled in an ice-bath and 3 M HCl (20 mL) was added. After stirring the mixture at room temperature for 5 h, layers were separated. The aqueous layer was extracted, with diethyl ether (2×10 mL), alkalized with solid sodium carbonate, and extracted with chloroform (4×20 mL). The chloroform extracts were combined and dried with magnesium sulphate. Removal of the solvent provided a crude product. GC analysis on a Supelco SPB-5, 30 m×0.32 mm, column revealed **7g**/**10**, 88:12. Crystallization from petroleum ether (40–60°C) afforded **7g** (0.71 g, 52%), mp 90–91°C, $[\alpha]_D^{20}=-30.1$ (*c* 4.25, $CHCl_3$), lit.:[12] $[\alpha]_D^{20}=-34.6$ (*c* 4.93, $CHCl_3$) for the (*S*)-isomer. GC analysis of **7g** on a Supelco Beta-DEX 325, 30 m×0.25 mm, column showed 87% ee. **7g**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (d, $J=6.0$ Hz, 3H, CH_3), 4.11 (q, $J=6.0$ Hz, 1H, CH), 5.19 (s, 2H, OH, NH), 7.26–7.35 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 19.25 (CH_3), 61.76 (CH–N), 127.11 (2×CH), 127.49 (CH), 128.44 (2×CH), 142.34 (C).
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14. **(*S*)-(−)-*N*-Methyl-1-phenylethylamine 18**: A solution of **2** (0.55 g, 2 mmol) in toluene (5 mL), was slowly added to a stirred solution of **14** (0.27 g, 2 mmol) in toluene (3 mL) at 0°C under a nitrogen atmosphere. After 3 h, a 3 M sodium hydroxide (5 mL) was added dropwise, and stirring was continued for 1 h. Layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The extracts were combined and dried with magnesium sulphate. Evaporation of the solvents and flash column chromatography on silica gel (petroleum ether/ethyl acetate, 8:2), afforded **18** (0.16 g, 60%), identified by comparison (GC, ^{1}H NMR) with an authentic sample, $[\alpha]_D^{20}=-55.2$ (*c* 1.22, $CHCl_3$), lit.:[16] $[\alpha]_D^{20}=+74.9$ (*c* 1.02, $CHCl_3$), 99% ee for the (*R*)-isomer. Derivatization of **18** (20 mg) with trifluoroacetic anhydride, and GC analysis on a Chiraldex G-PN, 20 m×0.25 mm, column showed 74% ee.
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