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Synthesis of optically-active benzylic amines; asymmetric reduction of ketoxime ethers with chiral oxazaborolidines

Evelyne Fontaine,* Claudie Namane, Jérôme Meneyrol, Michel Geslin, Laurence Serva, Eliane Roussey, Stéphanie Tissandié, Mohamed Maftouh and Pierre Roger

Recherche Exploratoire, Sanofi-Synthélabo Recherche, 195 rte d'Espagne, 31036 Toulouse, France

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Abstract—The preparation of novel optically active benzylic amines by the enantioselective reduction of phenone oximes using chiral oxazaborolidine is described. The choice of the chiral 1,2-amino alcohol (*S*)-diphenylvalinol as chiral inducer and that of the benzyl group for the *O*-oxime substituent is explained. 23 primary amines are obtained, with high enantioselectivity (e.e. = 98%), good yield (74%) on preparative scale. A mechanistic explanation is proposed.

1. Introduction

Much attention has focussed on the asymmetric synthesis of optically active amines because they play an important role as starting materials for the synthesis of many biologically active compounds[1] and resolving agents.

One of the easiest ways to obtain optically active amines is by the asymmetric reduction of the C=N double bond of ketoximes.[2] The use of an oxazaborolidine formed by condensation of a chiral 1,2-amino alcohol with borane is one of the most successful methods of enantioselective ketone reduction. Itsuno[3] adapted this method to oxime reduction and the first amino alcohols were those provided by the reduction of the amino acids valine and proline. The next optimisation of the ligand design furnished a diphenyl derivative of valine, which was highly effective in the enantioselective reduction of acetophenone methyl oxime.[4] In 1988, Sakito et al.[5] described the efficiency of norephedrine as a chiral ligand in the reduction of several oxime ethers. Another aspect of the optimisation of the reduction of ketoxime ethers is the nature of the oxime ether *O*-substituents.[4,5]

Herein, we describe, in the first part, the study of the effect of the oxime ether *O*-substituent on the enantioselectivity of the reduction using norephedrine as a chiral inducer. In the second part, norephedrine is replaced by the Itsuno ligand, (*S*)-diphenylvalinol. 24 examples are described. The third part deals with the optimisation of the reaction and proposes a mechanistic explanation of the high enantioselectivity.

2. Results

2.1. Effects of the oxime substituent

The oximes were classically prepared from the ketones by addition of hydroxylamine.[6] The mixture of (*Z*)- and (*E*)-isomers obtained (in a ratio of 3:1) was easily separated by simple chromatography purification and then alkylated (NaH, RHal)[4] to furnish *O*-alkylated oximes **1a 1d**. It is essential for the further reduction to have pure isomer, as the two geometric isomers give the opposite enantiomer.[5] The results of the experimental optimisation have been described,[4,5] they imply the ratio: 1 equiv. oxime:2.5 equiv. amino alcohol:5 equiv. BH_3. The reduction of oximes **1a**–**1d** with the oxazaborolidine of norephedrine gives a mixture of the required amine **3** and hydroxylamines **2a**–**2d** (readily converted to amine **3** in the presence of lithium aluminium hydride).

* Corresponding author. E-mail: evelyne.fontaine@sanofi-synthelabo.com

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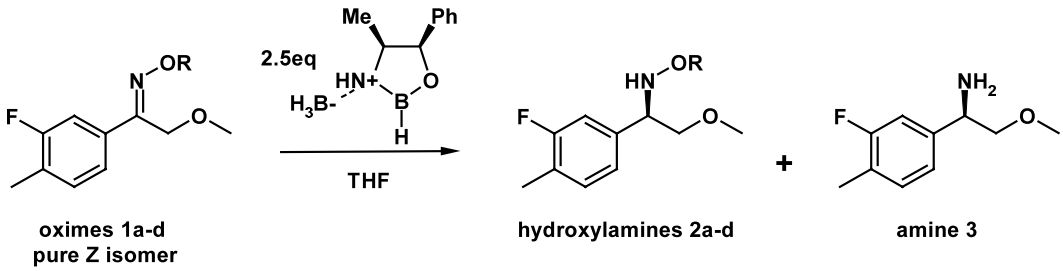


The results of the enantioselective reduction of oximes **1a**–**1d** using the oxazaborolidine prepared from (−)-norephedrine are summarised in Table 1.

Independent of the nature of the oxime substituent, the reduction using (−)-norephedrine generally gives the hydroxylamines **2** with an average yield of 42%. The yield of the amine **3** is significantly increased in the case of benzylic oximes **1c** and **1d** (20 and 30%) compared with the alkyl homologue **1a** and **1b** (8 and 2%), and the enantiomeric excess (e.e.) remains almost constant (between 90 and 93%). Dougherty et al. described, in their cyclic oxime case, the higher enantiomeric purity of the *ortho*-nitrobenzyl analogue over the benzyl analogue.[7] In our case, the e.e. of the product from *ortho*-nitrobenzyl substituted oxime **1d** is nearly identical to that formed from the benzyl analogue **1c**.

2.2. (*S*)-Diphenylvalinol results

According to Itsuno's procedure,[4] (*S*)-diphenylvalinol was prepared from (*S*)-valine. By the addition of 6 equivalents of commercial phenylmagnesium bromide, we obtained (*S*)-diphenylvalinol, in 87% yield. The comparison of the two α-amino alcohols in the reduction of oximes **1c** and **1d** is shown in Table 2.

The reduction using diphenylvalinol is more complete than that using norephedrine, giving amine **3** (60% yield) preferentially over hydroxylamines **2**. The e.e. is increased markedly in the cases of oximes **1c** and **1d**, from 90 to 98% and 91 to 99%, respectively. The benzyl group is preferred to the *ortho*-nitrobenzyl group for the next applications for practical aspects (availability and chemical resistance to reducing agent).

These conditions were applied to three families of phenone benzyloximes on a larger scale.

In the three families; alkyl (propyl and butyl), cycloalkylmethyl (cyclopropyl and cyclobutyl) and methoxymethyl the primary amines are obtained with high optical purity, the Rb substituent could be either an halogen (fluorine, chlorine or bromine), an alkyl (methyl), a methoxy or a methylene dioxy group.

We can see from Table 3 that 24 different benzylic amines were prepared by this method, Of these, 23 have e.e. of >96%, (with a mean e.e. of 98%) and the average yield is 74%. In the case of the fluorobutylbenzylamine (entry **m**) the e.e. could not be measured. This reaction sequence constitutes an excellent synthetic method for the preparation of diverse chiral benzylic amines on preparative scale (up to 20 g).

The (*S*)-diphenylvalinol ligand is easily recovered in the last stage of the synthesis by precipitation of its hydrochloride salt. The recycling proposed by Itsuno et al.[4] was tested with success in several cases and then applied in all our syntheses.

Table 1. Asymmetric reduction of oximes **1a 1d** using (−)-norephedrine

Oxime	R	Time (h)	Yield (%) of hydroxylamines **2**	Yield (%) of amine **3**	E.e. (%)[a] of amine **3**
1a	Me	70	45	8	90
1b	*iso*-Pr	70	48	2	93
1c	Bn	16	43	20	91
1d	*o*-NO_2Bn	16	33	30	90

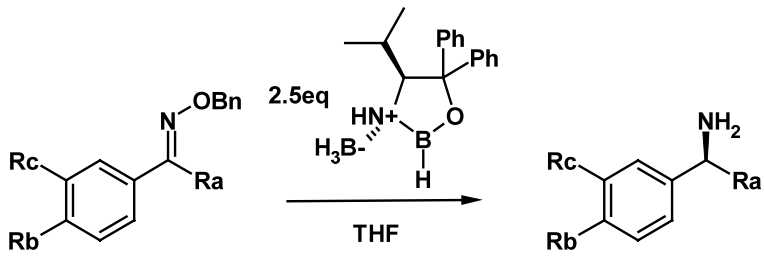
[a] E.e.s were determined by reversed-phase HPLC using crown-ether (Crownpak CR column) as chiral selector, the reference racemic amine was obtained by reduction of oxime **1a** with $LiAlH_4$.

Table 2. Enantioselective reduction of oximes **1c** and **1d** using (−)-norephedrine or (*S*)-diphenylvalinol

1,2-Amino alcohol	Oxime	Yield (%) of amine **3**	E.e. (%)[a] of amine **3**
(−)-Norephedrine	**1c**	20	91
	1d	30	90
(*S*)-Diphenylvalinol	**1c**	60	99
	1d	60	98

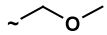
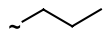
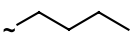
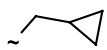
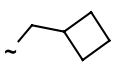
[a] E.e. was determined by reversed-phase HPLC using crown-ether (Crownpak CR column) as chiral selector, the racemic amine was obtained by reduction of oxime **1a** with $LiAlH_4$.

Table 3. Asymmetric reduction of benzyloximes using (*S*)-diphenylvalinol



oximes
pure anti isomer

benzylic amines

Ra	Rb	Rc	Benzylic amines		Entry
			E.e. (%)[a]	Yield (%)	
	Cl	H	98	78	**a**
	Et	H	>99[b]	76	**b**
		H	>99[b]	75	**c**
	Cl	F	98	85	**d**
	Me	F	99	68	**e**
			>99[b]	87	**f**
	H	H	97	>42	**g**
	F	H	98	61	**h**
	Me	H	98	68	**i**[d]
	MeO	H	97	96	**j**[d]
		H	97	78	**k**
	Me	F	99	75	**l**
	F	H	nd[c]	43	**m**
		H	97	86	**n**
	Me	F	97	43	**o**
	H	H	96	73	**p**
	F	H	97	76	**q**
	Cl	H	99	64	**r**
	Br	H	>99[b]	74	**s**
	Me	H	97	72	**t**[d]
	Me	F	97	84	**u**
	F	Me	99	68	**v**
			97	89	**w**
	F	H	99	85	**x**

[a] E.e.s were determined by reversed-phase HPLC using crown-ether (Crownpak CR colum) as chiral selector, capillary electrophoresis using cyclodextrin as chiral selctor or supercritical fluid chromatography using cellulose (Chiracel OD) and amylose (Chiralpak AD) as chiral selector on amine or amine derivative (eg acetamid). The reference racemic amine was obtained by reduction of the corresponding oxime with $LiAlH_4$

[b] only one enantiomer was detected

[c] the racemic mixture was not separated in usual conditions

[d] The solvent used is diethyl ether.

2.3. Further optimisation

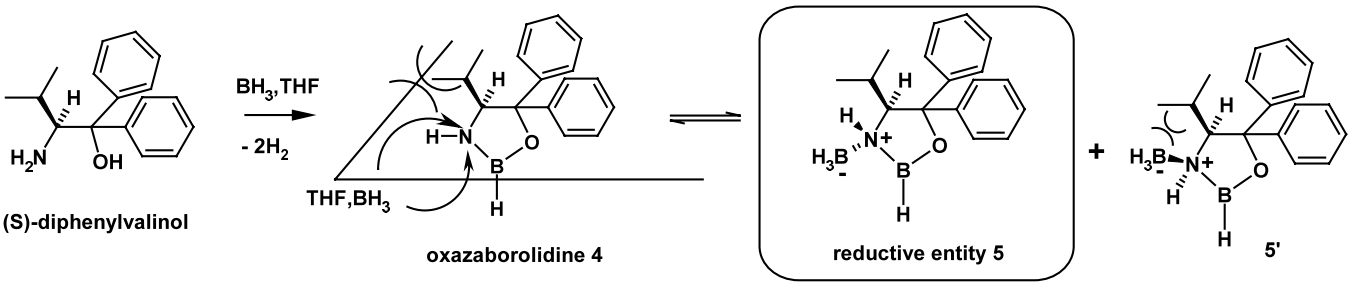
In order to improve the experimental procedure of the asymmetric reduction of *O*-benzyloxime with (*S*)-diphenylvalinol complex, two parameters were considered.

- *Solvent*. In the case of the *para*-fluorinated cyclopropylmethyl oxime (entry **q**) the replacement of tetrahydrofuran by diethyl ether improved the optical purity of the amine formed (from an e.e. of 96.6 to 98.7%), the yield of the reaction remaining constant.
- *Molar ratio of oxime: reducing agent complex*. Itsuno et al.[8] unsuccessfully investigated the catalytic use of the chiral complex. In our case, the cyclopropylmethyl oxime (entry **u**) was treated with one equivalent of diphenylvalinol complex instead of the 2.5 equivalents usually observed. The e.e. remained excellent (98%) but the yield of the reaction decreased (from 84 to 52%).

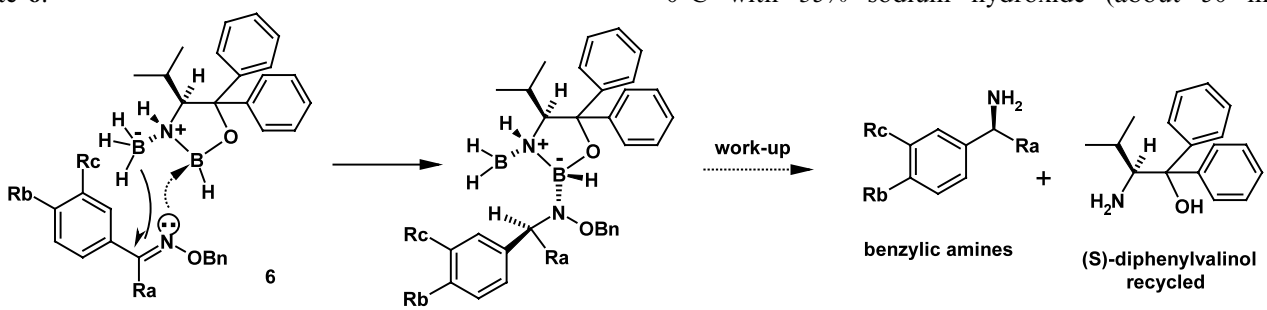
3. Discussion

3.1. Mechanistic consideration

In 1987, Corey et al.[9] reported ^{1}H NMR, ^{11}B NMR and infrared spectroscopic evidence of the structure of valinol chiral cycle **4**. The oxazaborolidine **4** is unable to reduce oximes.[9] The addition of a second equivalent of borane at the opposite site of the *iso*-propyl group gives the effective chiral reducing agent **5**. The complex **5′** is sterically unfavourable.



Our adaptation of the mechanism for the reduction of ketone[9] to amines agrees with the high enantioselectivity observed. The nitrogen of the anti-geometric isomer is complexed by the endocyclic borane allowing the chiral hydrogen transfer via a six-membered cyclic transition state **6**.



At this stage, the stereogenic centre is formed, benzylic amines and (*S*)-diphenyl valinol are obtained after work-up. This hypothetical mechanism illustrates a general feature of the reaction.

4. Conclusion

In conclusion, in the enantioselective reduction of phenone oximes, (*S*)-diphenylvalinol oxazaborolidine is distinctly more effective than (−)-norephedrine. 23 primary benzylic amines were prepared by this method; the average e.e. is excellent (98%), the mean yield 74%. The (*S*)-diphenylvalinol is easily recovered in the last step of the reaction. Most of the amines prepared are novel compounds. The mechanistic explication proposed correlates with the observed high e.e.s.

5. Experimental

All reactions were carried out under inert atmosphere.

5.1. Preparation of the ligand: (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol

A solution of phenylmagnesium bromide (3.0 M, 600 mL, 1790 mmol) in diethyl ether was stirred at 0°C and diluted with THF (300 mL), followed by portionwise addition of L-valine methyl ester hydrochloride (50 g, 298 mmol) while keeping the temperature below 10°C. After stirring for 3 h at rt, the reaction mixture was poured slowly into ice-cold ammonium chloride solution. Diethyl ether (500 mL) and ethyl acetate (500 mL) were added to the mixture. After separation of the phases, the aqueous phase was re-extracted with TBME (*tert*-butyl methyl ether, 1 L). The combined organic phases were stirred at 0°C and acidified slowly with 35% hydrochloric acid (about 40 mL) in water. The hydrochloride precipitate thus formed was filtered off and rinsed with TBME. The mixture was then taken up in dichloromethane (1 L) and water (1 L) and basified at 0°C with 35% sodium hydroxide (about 50 mL). After separation of the phases, the aqueous phase was re-extracted with dichloromethane (1 L). The combined organic phases were washed with water and then with brine, dried over sodium sulphate and concentrated.

After crystallisation from *iso*-propyl ether, (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol was obtained (61 g, 87%). $[\alpha]_D^{25} = -127.8$ ($c = 0.639$, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz), δ ppm, J Hz 7.00–7.60 (**Ar**, m, 10H); 5.24 (-O**H**, s, 1H); 3.66 (-C**H**-N, d, $J = 1.5$, 1H); 1.53 (-C**H**-CH_3, hept d, $J = 1.5$ and 7, 1H); 1.16 (-N$\mathbf{H_2}$, s, 2H); 0.81 (-C$\mathbf{H_3}$, 2d, $J = 7$, 6H).

5.2. Synthesis of the enantiomeric amines: typical procedure

A solution of (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (330 mmol) in tetrahydrofuran (600 mL) was stirred at a temperature below 30°C, followed by slow addition of borane–tetrahydrofuran solution (1 M, 670 mL). The temperature was allowed to rise to room temperature over 2 h. The reaction medium was then stirred at 0°C and a solution of pure *anti*-benzyl oxime (132 mmol) in tetrahydrofuran (100 mL) was added. After stirring the mixture for 20 h at room temperature, the reaction mixture was cooled to 0°C and treated with aqueous hydrochloric acid (2N, 1 L). The mixture was stirred for 16 h then basified at 0°C by addition of 35% sodium hydroxide, followed by extraction with ethyl acetate. This extract was washed with water and saturated aqueous sodium chloride solution, then dried over sodium sulphate and evaporated to dryness. The residue obtained was chromatographed on a column of silica gel.

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