Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4607–4618

TETRAHEDRON:
ASYMMETRY

Highly stereoselective reduction of acyclic α-sulfinyl ketimines: synthesis of enantiomerically pure β-aminosulfoxides

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Received 5 November 1999; accepted 18 November 1999

Abstract

The DIBAL reduction of enantiomerically pure α-sulfinyl ketimines can be achieved almost completely stereoselectively under ZnX_2 catalysis, regardless of the alkyl or aryl substituent at nitrogen and the aliphatic (cyclic or acyclic) or aromatic character of the imine. Steric factors as well as the electrophilic character of the hydride are responsible for the stereochemical course of the reduction.

1. Introduction

Enantiomerically pure β-aminosulfoxides are interesting building blocks in asymmetric synthesis.[1] Different approaches have been described for the synthesis of these compounds. Asymmetric oxidation of β-aminosulfides,[2] Mitsunobu type amination of enantiopure β-hydroxysulfoxides,[3] and Michael addition of amines to vinyl sulfoxides,[4] have been occasionally used. Some of the most studied processes are those involving both condensation of arylsulfinyl carbanions with compounds bearing C=N bonds and reduction of α-sulfinyl ketimines. The low reactivity of imines with stabilised carbanions determines that only arylimines were moderately efficient in the first processes.[5,6] Better results were achieved with compounds exhibiting higher reactivity of the C=N bonds, such as fluoroalkyl aldimines[7] or nitrones,[8] but in most cases the ability of the sulfinyl group to control the stereoselectivity was only moderate.[9] Concerning the stereoselective reduction of α-sulfinyl ketimines, moderate stereoselectivity was observed upon the use of $NaBH_4$[10,11] and $NaCNBH_3$[12] as reducing agents on endocyclic imines to give rise to bicyclic alkaloids, whereas one paper related to the reduction of imines derived from α-sulfinyl cyclohexanone[13] evidenced the almost completely stereoselective evolution of the *N*-phenyl derivatives with both nucleophilic ($NaBH_4$ and $LiAlH_4$) and electrophilic (DIBAL) hydrides (only DIBAL proved to be efficient with *N*-benzylimines). L-Selectride gave high stereoselectivity but low

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00523-6

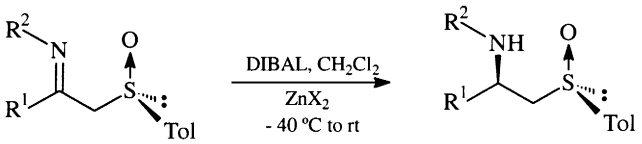
yields with sulfinyl enamines derived from primary amines[14] but it did not affect those compounds derived from secondary ones. $NaBH_4$ and Selectrides have been used on polyfluorinated *N*-aryl α-sulfinyl imines,[15] the $NaBH_4$/MeOH being the best reducing system on 1-naphthylsulfinyl derivatives (the substrates evolve with almost complete stereoselectivities in a quantitative yields).[16] In contrast with this behaviour, borohydrides are not efficient for achieving the stereoselective reduction of acyclic α-sulfinyl ketimines,[17] even though moderate to high diastereoselectivities have been reported in the reduction of some *N*-unsubstituted enamino sulfoxides with 1-benzyl-1-azonia-4-azabicyclo[2,2,2]octane tetrahydroborate.[18]

In 1992 the almost completely stereoselective reduction of some acyclic *N*-benzylimines with DIBAL in the presence of $ZnBr_2$ was published.[17] This reducing agent, which also proved to be efficient with endocyclic α-sulfinyl imines,[19] seems to be the most suitable for reducing any α-sulfinylated C=N bond. However, in order to check the general scope of the method it was necessary to widen the number and structural variety of the substrates under study. This goal was restricted since a general method to prepare enantiomerically pure starting α-sulfinyl ketimines was not available in the literature. Recently, we have described such a general method[20] and thus we report in this paper the complete results obtained in the reduction of different *N*-alkyl- and *N*-aryl-substituted α-sulfinyl alkyl and aryl ketimines.

2. Results and discussion

The synthesis of the starting acyclic α-sulfinyl imines **1**–**9** (Table 1) and **11**–**13** (Table 2) has been previously described.[20] Endocyclic sulfinyl imine **10** was prepared by *N*-acylation of δ-valerolactam with di-*t*-butyl dicarbonate,[21] followed by opening of the lactam ring with the lithium anion of (*R*)-methyl *p*-tolyl sulfoxide and final cyclisation to the deprotected NH_2 group generated by treatment of the carbamate derivative with TFA (Scheme 1).

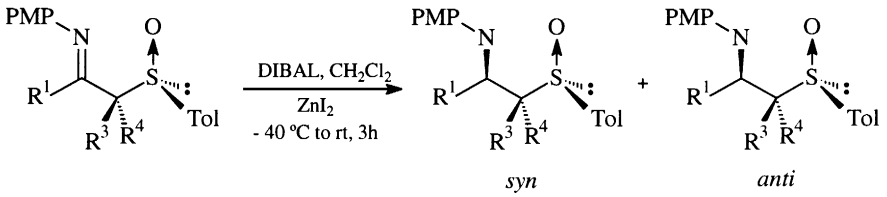
Table 1
Results obtained in the reduction of the α-sulfinyl imines **1**–**10** with DIBAL/ZnX_2



Subst.	R^1	R^2	ZnX_2	time(h)	Product	Yield(%)[a]
1	Me	Bn	$ZnBr_2$	2	**14**	94
2	*n*-Pr	Bn	$ZnBr_2$	3	**15**	70
3	*i*-Pr	Bn	$ZnBr_2$	3	**16**	90
4	*t*-Bu	Bn	$ZnBr_2$	24	**17**	10
5	Ph	Bn	$ZnBr_2$	2	**18**	75
6	*n*-Pr	PMP	ZnI_2	1.5	**19**	95
7	*i*-Pr	PMP	ZnI_2	1.5	**20**	84
8	*t*-Bu	PMP	ZnI_2	12	**21**	83
9	Ph	PMP	ZnI_2	1.5	**22**	70
10	—$(CH_2)_4$—		$ZnBr_2$	52	**23**	65

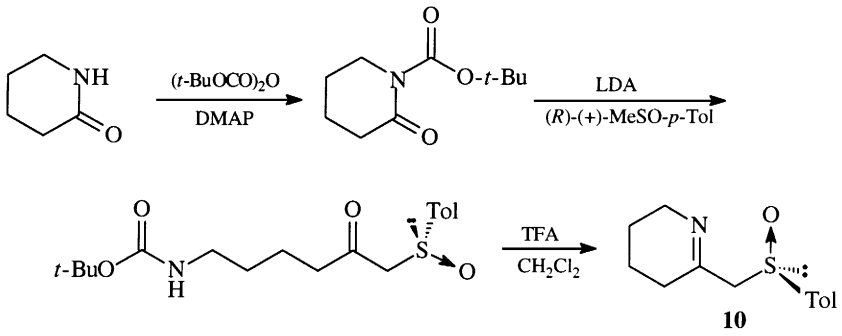
[a] Isolated product after chromatography and crystallisation (of solids).

Table 2
Results obtained in the reduction of the α-alkyl α-sulfinyl imines **11**–**13** with DIBAL/ZnI_2



Subst.	R^1	R^3	R^4	Product	*syn*:*anti* ratio	Yield(%)[a]
11	Ph	Me,H [b]		**24**	50:50	80
12	Me	H	Et	**25**	8:92	90
13	Me	Et	H	**26**	92:8	90

[a] Isolated product after chromatography and crystallisation (of solids). [b] Mixture of 2*R*,(S)*R* and 2*S*,(S)*R* epimers.

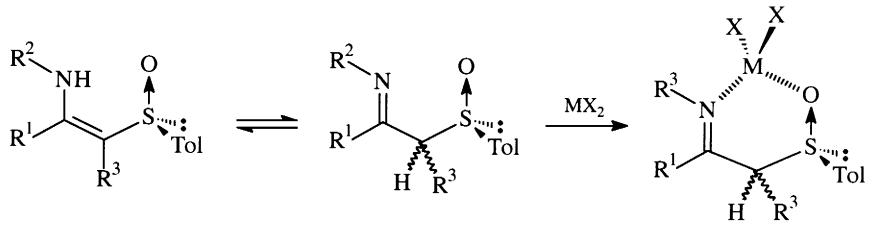


Scheme 1.

The reaction of *N*-benzyl imines **2** and **5** with DIBAL or DIBAL/$ZnCl_2$ were initially investigated under the conditions reported for reduction of α-sulfinyl ketones[22] and cyclic α-sulfinyl imines.[13] However, all attempts proved to be unsuccessful for recovering the unchanged starting materials. The use of an excess of the reagent (up to 8 equiv.) in the presence of $ZnCl_2$ in CH_2Cl_2 caused the reduction of both imine and sulfinyl groups affording the corresponding optically inactive aminosulfides as the only reaction products, which proved that the sulfur function must be first reduced. This was not an unexpected result taking into account that compounds **2** and **5** only exist as enaminic tautomers[20] (hence inert to the reduction). On the other hand, the $NaBH_4$ reduction of sulfinyl imine **4**, which is present as the imine tautomer,[20] afforded its corresponding aminosulfoxide in good yield as a mixture of the two possible diastereoisomers, epimeric at the aminic carbon, but with scarce (CH_3CN as the solvent) or no (MeOH) stereoselectivity. The change of the hydride (DIBAL, DIBAL/$ZnCl_2$, or $LiEt_3BH$) did not give better results.

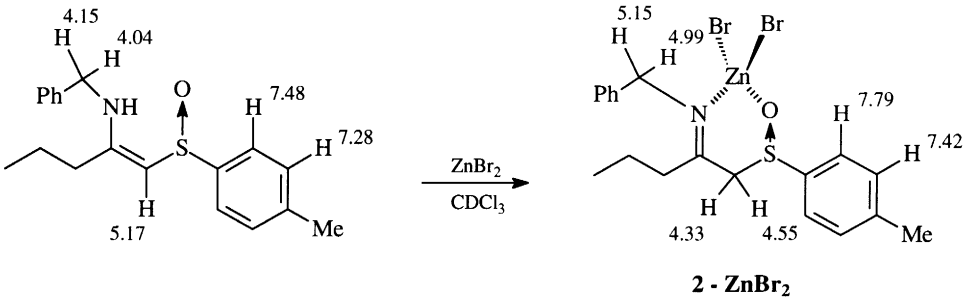
In order to shift the enamine–imine equilibrium towards the reactive imine tautomer, different Lewis acids ($MgBr_2$, $ZnCl_2$, $ZnBr_2$, and ZnI_2) in non-coordinating solvents, such as CH_2Cl_2 or toluene–CH_2Cl_2 mixtures, were studied (Scheme 2). Moreover, Lewis acids must also enhance the electrophilic character of iminic carbon, thus increasing the reactivity of the substrates.

The best results were attained under $ZnBr_2$ (*N*-alkyl imines) and ZnI_2 (*N*-*p*-methoxyphenyl imines, *N*-PMP) catalysis. As could be expected, these Lewis acids were insoluble in the selected solvents, but they quickly dissolved when the sulfinyl imine was added, regardless of the initial composition of their



Scheme 2.

imine–enamine equilibria, thus suggesting the formation of the corresponding chelates, which can be observed by ^{1}H NMR analysis. As an example, Scheme 3 shows the significant changes induced in the chemical shifts of the protons at compound **2** as a consequence of its association with $ZnBr_2$ (δ_H ppm). These changes suggest that the addition of the Lewis acid leads to the shift of the imine–enamine equilibrium towards the iminic form, which is the tautomer involved in the formation of the chelates.



2 - ZnBr$_2$

Scheme 3.

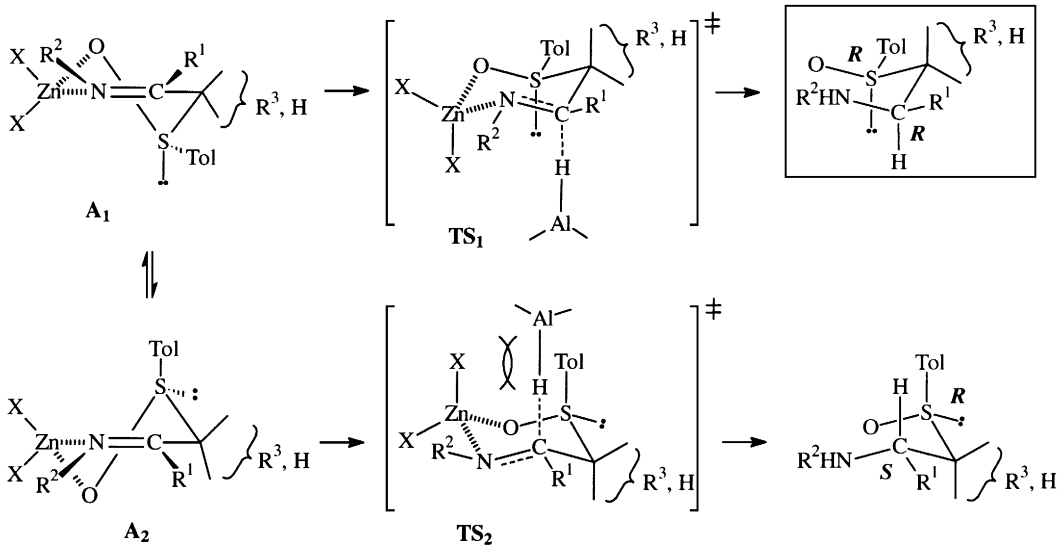
Supporting this conclusion, the reactivity of all substrates with hydrides clearly improved under these conditions. The best stereochemical results were obtained with DIBAL as the reducing agent in CH_2Cl_2 as the solvent at –48°C (Tables 1 and 2).

As can be seen, the reduction of all substrates (except **4**) takes place in good yields and complete stereoselectivities. The low conversion of *N*-benzyl imine **4** can be due to the difficulty to adopt the *E*-configuration (as a consequence of the steric interaction between the benzyl and *t*-butyl groups) required to form the **4**–$ZnBr_2$ complex in the chelated species (see Scheme 2). In fact, in this case the complete solubilisation of Lewis acid ($ZnBr_2$ or ZnI_2) in the reaction mixture, which occurred with all the other substrates, was not observed. As expected, *N*-arylimines required shorter reaction times than the corresponding *N*-alkylderivatives, even though the influence of the substituent at nitrogen is rather low in these catalysed reactions. The clearly lower reactivity of compound **10** could be a consequence of the difficulties associated with the formation of a bicyclic chelated species.

In compounds **11**–**13** (Table 2) two stereogenic centres could compete in the control of the stereoselectivity of the reduction. Nevertheless, the obtained results suggest the predominant role of the sulfinyl group, which is exclusively responsible for the stereochemical course of the hydride attack, regardless of the configuration at C-2. Thus, compound **11**, which only exists in its enaminic form, was transformed into a 1:1 mixture of epimers at C-2 of **24**, but with the same configuration at the aminic carbon. The study of the ^{1}H NMR spectrum of **11** in the presence of Lewis acid revealed the formation of an equimolecular mixture of two chelates, both derived from iminic forms (two doublets for the methyl group at 2.10 and 1.44 ppm in the mixture, in contrast with the singlet at 1.69 ppm observed in the absence of the catalyst). This suggests that the formation of *syn* and *anti* epimers must be a consequence of the completely stereoselective reduction of both chelates governed by the sulfinyl configuration. The formation of mixtures of **25** and **26** observed in the reactions of diastereoisomerically pure **12** and **13**

was initially attributed to a slight epimerisation at C-2, prior to the reduction, produced by the Lewis acid. However, we could not obtain any evidence supporting this assumption from ^{1}H NMR studies. Thus, the spectra of the chelated species **12**–ZnI_2 and **13**–ZnI_2, which remained unaltered up to 4 h in CD_2Cl_2 solution (conditions identical to those used in the reduction reactions), revealed the presence of signals corresponding to only one diastereoisomer. Nevertheless, compounds **25** and **26** exhibited identical configuration at the iminic carbon (see later) but different at the sulfur carbon, which suggests that reduction of both epimers **12** and **13** was completely stereoselective.

The above results suggest that the reduction of α-sulfinyl imines with DIBAL in the presence of ZnX_2 are 1,3-induction processes, the stereochemistry at the new chiral centre being exclusively controlled by the configuration at the sulfinyl sulfur (substrates with *R*-configuration at sulfur always evolve into products with *R*-configuration at the aminic carbon). A mechanistic proposal similar to that used to explain the stereoselectivity of the reduction of sulfinyl ketones with DIBAL/$ZnCl_2$[22] can also be invoked in this case (Scheme 4).



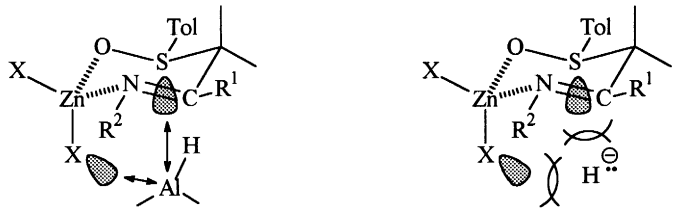
Scheme 4.

The chelates formed by association of the Lewis acid to the basic centres at the sulfinyl imines (which must be easier than in the case of sulfinyl ketones due to the higher basic character of nitrogen) can exist as two half-chair species $\mathbf{A_1}$ and $\mathbf{A_2}$ in equilibrium. From a steric point of view, the favoured approach of the hydride in both cases is to yield the chair-like transition states ($\mathbf{TS_1}$ and $\mathbf{TS_2}$, respectively) because its attack from the faces opposite to those depicted in Scheme 4 would yield less stable twist-like transition states (see Ref. 22). The higher stability of $\mathbf{TS_1}$ (*syn*-1,3-diaxial X/lone pair interaction) as compared with $\mathbf{TS_2}$ (*syn*-1,3-diaxial X/Tol interaction), would determine the preferred formation of the 1*R*,(S)*R* epimer.

Substitution at C-2 in sulfinyl imines **11**, **12** and **13** ($R^3 \neq H$, Scheme 4) scarcely affected the relative stability of the transition states and, therefore, the stereochemical pathway of their reactions must be identical to that suggested for unsubstituted compounds.

In order to understand the feasible contribution of the stereoelectronic factors to the relative stability of the transition states and therefore to the stereoselectivity of the reactions, we have studied the behaviour of some substrates with a nucleophilic hydride such as $NaBH_4$ in the presence of $ZnBr_2$. Thus, compounds **1**, **4** and **10** were first treated with the Lewis acid and then with the nucleophilic

hydride. Under these conditions, mixtures of two diastereomeric amine epimers at the aminic carbon were obtained in all cases, thus revealing that the almost complete stereoselectivity observed with DIBAL must be due to the electrophilic character of this hydride, able to give favourable stereoelectronic interaction of the lone electron pairs at sulfur and/or halogen with the empty orbital at the aluminium (**A** in Scheme 5), thus reinforcing the steric tendency shown in Scheme 4. By contrast, the electrostatic repulsion between the negatively charged nucleophilic hydride and the lone electron pairs at sulfur and/or halogen (**B** in Scheme 5) would relatively destabilise $\mathbf{TS_1}$, which decreased the stereoselectivity observed in these reactions.



Scheme 5.

2.1. *Configurational assignment of sulfinyl amines*

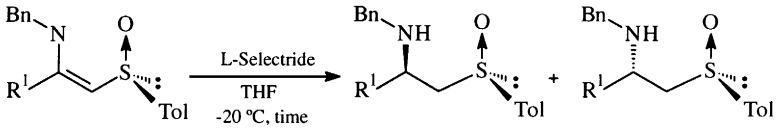
The configuration at sulfur in aminosulfoxides **14**–**26** (Tables 1 and 2) must be *R* since they were obtained from sulfinyl imines exhibiting such a configuration at this centre, which is not likely to be affected under the reduction conditions. On the other hand, the high stereoselectivity observed in the reductions of all the studied sulfinyl imines suggests the same stereochemical pathway for all substrates and, therefore, identical configuration at the new aminic chiral carbon. This configuration was unequivocally established as *R* for compound **18** by chemical correlation with 1-phenylethylamine. Thus, desulfurisation of **18** with Raney-Ni afforded (*S*)-*N*-benzyl-1-phenylethylamine with a negative sign of its specific rotation, $[\alpha]_D^{20}=-56$ (*c* 1.07, EtOH). It was of similar magnitude but opposite sign to that reported for the *R* enantiomer, $[\alpha]_D^{20}=+57$ (*c* 1.07, EtOH).[23] Consequently, we must assign the configuration 1*R*,(S)*R* to compound **18**, and similarly to the rest of compounds **14**–**23**.

Ogura et al. have described the synthesis of *N*-benzylamine (1*R**,(S)*R**)-**14** by reduction of the racemic imine **1** with L-Selectride.[14] The comparison of the spectroscopic parameters of the so-obtained compound with those of (1*R*,(S)*R*)-**14** obtained by us in the reduction of (*R*)-**1** showed that they must be different diastereoisomers. In order to clarify this point we performed the reduction of compounds **1**, **2** and **5** with this hydride obtaining the results shown in Table 3.

In our hands, the reduction of compound **1** (R^1=Me) took place with moderate yield, which became even lower for **2** (R^1=*n*-Pr) and inexistent for **5** (R^1=Ph). In the two first cases we obtained mixtures of both isomers **A** and **B**, the relative configuration of which was tentatively assigned as indicated in Table 3, by comparison of their ^{1}H NMR spectroscopic parameters with those of other epimeric β-aminosulfoxides[24] and β-hydroxysulfoxides[25] previously studied by us. The minor components of these mixtures (**A** isomers) were identified as those obtained as exclusive in DIBAL/ZnX_2 reactions (Table 1, compounds **14** and **15**, respectively), thus confirming the configuration 1*R*,(S)*R* assigned on the spectroscopic basis. The major isomers obtained from **1** (**B** isomers, Table 3), which therefore must exhibit the 1*S*,(S)*R* configuration, could be identified as the compound described by Ogura et al.[14] These results demonstrate that the operating mechanism of the reductions with both hydrides must be different.

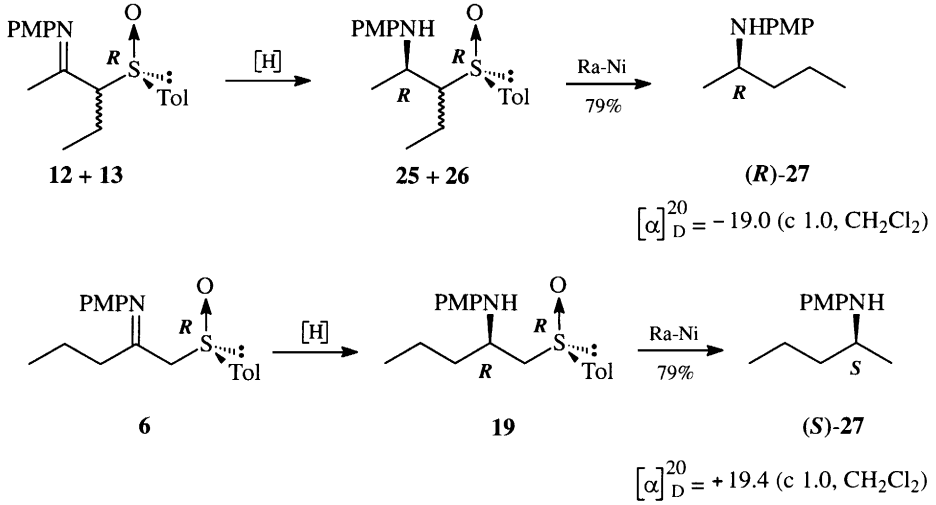
Configurational assignment at the stereogenic aminic carbon in major diastereoisomers of amino derivatives **25** and **26** (Table 2), obtained in the reductions of imines **12** and **13**, respectively, was

Table 3
Results obtained in the reduction of compounds **1**, **2** and **5** with L-Selectride



			A		B
Subst.	R^1	time (h)	Product	**A**:**B** ratio	Yield(%)
1	Me	12	**14**	9:91	50
2	*n*-Pr	12	**15**	<9:>91	10
5	Ph	48	**18**		0

established as follows (Scheme 6). Desulfinylation of compound (*R*,*R*)-**19** (obtained from **6**) with Raney-Ni yielded (*S*)-**27**. This compound is the enantiomer of that obtained by desulfinylation of an equimolecular mixture of **25**+**26** (obtained from the epimeric mixture **12**+**13**), which allowed us to identify it as compound (*R*)-**27**. These stereochemical results confirm that the sulfinyl group is the main controller of the stereochemical course of the reductions of α-sulfinyl ketones containing two stereogenic centres. Further evidence concerning the configuration of aminosulfoxides **25** and **26** was obtained from their independent transformation into enantiomerically pure *cis* and *trans* 2,3-dialkyl aziridines.[26]



Scheme 6.

Enantiomeric purities of (*R*)-**27** and (*S*)-**27** were determined to be higher than 97% by NMR analysis in the presence of the chiral paramagnetic shift reagent $Yb(tfc)_3$. Racemic **27** (required for the NMR study) was prepared in 98% yield by reduction of *N*-*p*-methoxyphenyl imine derived from 2-pentanone with $NaBH_4$/*i*-PrOH.

As a conclusion, we have demonstrated that reduction of α-sulfinyl imines with DIBAL (electrophilic hydride) in the presence of Lewis acids like ZnX_2 evolves with a complete stereoselectivity, which is controlled by the configuration of the sulfinyl group. This reaction seems to be general for *N*-alkyl and *N*-aryl imines, regardless of their aliphatic (cyclic or acyclic) or aromatic structure. As in the case of reduction of α-sulfinyl ketones with DIBAL, the contribution of both steric and electronic factors is significant for determining the stereoselectivity of the processes.

3. Experimental

3.1. General methods

All moisture sensitive reactions were performed in flame-dried glassware equipped with a rubber septum under a positive pressure of argon and monitored by TLC. Solvents were dried according to literature procedures.[27] Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM); eluents are indicated in brackets. Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23°C) (concentration in g/100 ml). The NMR spectra were recorded in $CDCl_3$ solutions at 200.1 and 50.3 MHz for ^1H and ^{13}C NMR, respectively. The IR spectra were obtained as CH_2Cl_2 solutions.

3.2. Synthesis of (R)-2-(p-tolylsulfinylmethyl)-3,4,5,6-tetrahydropyridine **10**

3.2.1. N-t-Butoxycarbonyl-δ-valerolactam

To a solution of 8.9 g (89.0 mmol) of δ-valerolactam in 20 ml of anhydrous CH_2Cl_2, 22.2 g (100.0 mmol) of di-*tert*-butyl dicarbonate in 10 ml of CH_2Cl_2 and 12.2 g (99.0 mmol) of 4-dimethylaminopyridine in 10 ml of CH_2Cl_2 were added. The mixture was stirred at room temperature for 24 h and was then washed with HCl 1N (2×50 ml), aqueous $NaHCO_3$ (2×50 ml), and aqueous NaCl (2×50 ml). The solvent was evaporated under reduced pressure. An *N-t*-butoxycarbonyl derivative was obtained as an oil in 48% yield, after chromatography (CH_2Cl_2); δ_H 3.65 (m, 2H), 2.50 (m, 2H), 1.82 (m, 4H), 1.51 (s, 9H); δ_c 170.5, 151.8, 81.8, 45.5, 30.6, 27.2, 22.2, 19.8.

3.2.2. (R)-(4-t-Butoxycarbonylamino)butyl p-tolylsulfinylmethyl ketone

To a cold (−78°C) solution of LDA in 40 ml of anhydrous THF, a solution of 3 g (19.0 mmol) of *(R)*-methyl *p*-tolyl sulfoxide in 40 ml of THF was added, and the mixture was stirred at 0°C for 30 min. The resulting mixture was slowly cannulated under argon into a cold (–78°C) solution of 4 g (20.0 mmol) of *N-t*-butoxycarbonyl-δ-valerolactam in 40 ml of THF. The mixture was stirred at –78°C for 1 h and then the reaction was quenched with 20 ml of aqueous NH_4Cl and extracted with CH_2Cl_2 (2×20 ml). The extracts were dried over $MgSO_4$ and the solvent was evaporated under vacuo. Sulfinyl ketone was obtained as a white solid in 89% yield after chromatography (ethyl acetate:hexane, 8:1) of the crude reaction. It was crystallised from acetone:hexane; mp 78–80°C; $[\alpha]_D$=+134.9 (*c* 1.0, chloroform); δ_H 7.40 and 7.26 (AA′BB′ system, 4H), 4.55 (b s, 1H), 3.66 and 3.58 (AB system, 2H, *J*=12.5 Hz), 3.19 (m, 2H), 2.59 (m, 2H), 2.43 (s, 3H), 1.67–1.50 (m, 4H), 1.43 (s, 9H); δ_C 201.1, 155.6, 141.6, 139.2, 129.6, 123.6, 76.4, 67.5, 43.8, 39.5, 28.7, 28.0, 21.0, 19.7.

3.2.3. (R)-2-p-Tolylsulfinylmethyl-3,4,5,6-tetrahydropyridine **10**

To a cold (0°C) solution of 5 g (14.0 mmol) of the preceding sulfinyl ketone in 200 ml of CH_2Cl_2, 10.3 ml (140.0 mmol) of trifluoroacetic acid were added. The mixture was stirred at room temperature for 2 h, hydrolysed with 250 ml of aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3×20 ml). The solvent was evaporated under reduced pressure. Compound **13** was obtained as an oil in 60% yield after chromatography (acetone); $[\alpha]_D$=+106.5 (*c* 1.0, chloroform); δ_H 7.55 and 7.35 (AA′BB′ system, 4H), 3.73 and 3.25 (AB system, 2H, *J*=12.0 Hz), 3.59 (m, 2H), 2.40 (s, 3H), 2.50–2.00 (m, 2H), 1.80–1.50 (m, 4H); δ_C 162.3, 140.6, 139.6, 136.4, 123.3, 66.2, 48.6, 30.3, 20.5, 18.3; HRMS: calcd for $C_{13}H_{17}NOS$ 235.1031. Found: 235.1036.

3.3. Reduction of α-sulfinyl imines with DIBAL/Lewis acid. General procedure

To a solution of 3.5 g (10 mmol, 1.4 equiv.) of Lewis acid (zinc bromide or zinc iodide; see Tables 1 and 2) in 90 ml of CH_2Cl_2, a solution of 7.95 mmol of sulfinyl imine in 70 ml of anhydrous CH_2Cl_2 was slowly added. The reaction mixture was stirred at room temperature until disappearance of the chelating agent suspension was observed. The solution was cooled at –48°C and 8.8 ml of a 1 M solution (8.8 mmol, 1.1 equiv.) of DIBAL in hexane was added. After the time recorded for each case (see Tables 1 and 2), the mixture was allowed to reach 0°C and 70 ml of a 20% aqueous solution of NaOH were added. The mixture was gently stirred for 2 h and the aqueous layer was extracted with CH_2Cl_2 (2×25 ml). The extracts were washed with a saturated aqueous NaCl solution (2×25 ml) and concentrated under reduced pressure.

3.4. (1R,(S)R)-N-Benzyl-1-methyl-2-(p-tolylsulfinyl)ethylamine **14**

Compound **14** was obtained as a white solid from **1** in 94% yield after chromatography (acetone:hexane, 3:2); mp 54–56°C; $[\alpha]_D$=+151.0 (*c* 1.0, CH_2Cl_2); δ_H 7.53–7.17 (m, 9H), 3.83 and 3.70 (AB system, 2H, *J*=13.0 Hz), 3.20 (m, 1H), 3.06 (dd, 1H, *J*=6.4 and 13.0 Hz), 2.64 (dd, 1H, *J*=6.1 and 13.0 Hz), 2.39 (s, 3H), 1.30 (d, 3H, *J*=6.3 Hz); δ_C 140.9, 140.7, 139.7, 129.5, 128.0, 127.7, 126.6, 123.6, 64.3, 50.5, 48.7, 21.0 and 20.2; HRMS calcd for $C_{17}H_{21}NOS$: 287.1343. Found: 287.1328.

3.5. (1R,(S)R)-N-Benzyl-1-n-propyl-2-(p-tolylsulfinyl)ethylamine **15**

Compound **15** was obtained as a white solid from **2** in 70% yield after chromatography (acetone:hexane, 2:5, containing 10% triethylamine); mp 112–114°C; $[\alpha]_D$=+116.4 (*c* 1.0, CH_2Cl_2); δ_H 7.51–7.22 (m, 9H), 3.74 (m, 2H), 3.09–2.96 (m, 3H), 2.73 (dd, 1H, *J*=8.0 and 15.5 Hz), 2.39 (s, 3H), 1.84 (b s, 1H), 1.65–1.55 (m, 2H), 1.43–1.32 (m, 2H), 0.89 (t, 3H, *J*=7.2 Hz); δ_C 141.3, 141.1, 140.0, 129.8, 128.3, 128.0, 126.8, 124.0, 62.7, 53.1, 50.5, 36.1, 21.3, 18.4, 13.9; IR 2980, 2960, 1590, 1490, 1450, 1130, 1080, 1030, 1010, 910 cm^{-1}; HRMS calcd for $C_{19}H_{25}NOS$: 315.1656. Found: 315.1521.

3.6. (1R,(S)R)-N-Benzyl-1-isopropyl-2-(p-tolylsulfinyl)ethylamine **16**

Compound **16** was obtained as an oil from **3** in 90% yield after chromatography (acetone:hexane, 2:5, containing 10% triethylamine); $[\alpha]_D$=+90.9 (*c* 1.1, CH_2Cl_2); δ_H 7.55–7.25 (m, 9H), 3.84 and 3.73 (AB system, 2H, *J*=13.0 Hz), 3.09–2.74 (m, 3H), 2.43 (s, 3H), 2.18–2.00 (m, 1H), 1.97 (b s, 1H), 0.92 (d, 3H, *J*=6.8 Hz), 0.85 (d, 3H, *J*=6.9 Hz); δ_C 141.5, 141.1, 140.1, 129.8, 128.3, 128.2, 126.8, 124.2, 59.6, 58.3, 50.9, 29.3, 21.3, 18.3, 16.9; IR 3300, 2950, 2325, 1433, 1273, 1100, 1040, 910 cm^{-1}.

3.7. (1R,(S)R)-N-Benzyl-1-tert-butyl-2-(p-tolylsulfinyl)ethylamine **17**

Compound **17** was obtained as an oil from **4** in 10% yield after chromatography (CH_2Cl_2:AcOEt, 3:1); $[\alpha]_D$=+80.6 (*c* 0.8, CH_2Cl_2); δ_H 7.56–7.22 (m, 9H), 3.99 and 3.81 (AB system, 2H, *J*=12.9 Hz), 3.03 (dd, 1H, *J*=4.3 and 13.4 Hz), 2.90 (dd, 1H, *J*=7.2 and 13.4 Hz), 2.55 (dd, 1H, *J*=4.3 and 7.2 Hz), 2.40 (s, 3H), 0.87 (s, 9H); δ_C 141.7, 141.1, 140.4, 129.8, 128.3, 128.2, 126.8, 124.2, 62.4, 62.1, 53.9, 35.8, 26.3, 21.3.

3.8. (1R,(S)R)-N-Benzyl-1-phenyl-2-(p-tolylsulfinyl)ethylamine **18**

Compound **18** was obtained as a white solid from **5** in 75% yield after chromatography (CH_2Cl_2:AcOEt, 4:1); mp 102–103°C; $[\alpha]_D$=+76.6 (*c* 1.0, CH_2Cl_2); δ_H 7.48–7.24 (m, 14H), 4.18 (dd, 1H, *J*=4.9 and 8.7 Hz), 3.66 and 3.50 (AB system, 2H, *J*=13.3 Hz), 3.23 (dd, 1H, *J*=8.7 and 13.1 Hz), 2.81 (d, 1H, *J*=5.0 and 13.2 Hz), 2.38 (s, 3H); δ_C 141.5, 141.3, 140.7, 139.7, 129.8, 128.6, 128.2, 128.0, 127.7, 127.0, 126.7, 123.7, 65.2, 58.6, 50.9, 21.2; IR 2990, 1595, 1487, 1450, 1080, 1030 cm^{-1}; anal. calcd for $C_{22}H_{23}NOS$: C 75.61, H 6.63, N 4.01. Found: C 75.74, H 6.73, N 4.04.

3.9. (1R,(S)R)-N-(p-Methoxyphenyl)-1-n-propyl-2-(p-tolylsulfinyl)ethylamine **19**

Compound **19** was obtained as a white solid from **6** in 95% yield after chromatography (acetone:hexane, 2:1); mp 89–90°C; $[\alpha]_D$=+160.7 (*c* 1.0, CH_2Cl_2); δ_H 7.49 and 7.29 (AA′BB′ system, 4H), 6.77 and 6.55 (AA′BB′ system, 4H), 3.75 (s, 3H), 3.73–3.66 (m, 1H), 3.13 (dd, 1H, *J*=5.2 and 13.3 Hz), 2.75 (dd, 1H, *J*=7.4 and 13.3 Hz), 2.41 (s, 3H), 1.96–1.55 (m, 2H), 1.52–1.31 (m, 2H), 0.93 (t, 3H, *J*=7.1 Hz); δ_C 151.8, 141.1, 140.5, 140.3, 129.8, 123.8, 114.6, 114.3, 62.1, 55.3, 49.3, 36.6, 21.0; IR 2990, 2420, 1540, 1240, 1100, 1060, 940 cm^{-1}; anal. calcd for $C_{19}H_{25}NO_2S$: C 68.85, H 7.60, N 4.22. Found: C 69.12, H 7.62, N 4.16.

3.10. (1R,(S)R)-N-(p-Methoxyphenyl)-1-isopropyl-2-(p-tolylsulfinyl)ethylamine **20**

Compound **20** was obtained as a white solid from **7** in 90% yield after chromatography (hexane:AcOEt, 3:2); mp 72–74°C; $[\alpha]_D$=+114.8 (*c* 1.0, CH_2Cl_2); δ_H 7.49 and 7.29 (AA′BB′ system, 4H), 6.75 and 6.51 (AA′BB′ system, 4H), 3.74 (s, 3H), 3.49 (m, 1H), 3.09 (dd, 1H, *J*=7.5 and 13.3 Hz), 2.83 (dd, 1H, *J*=5.9 and 13.3 Hz), 2.41 (s, 3H), 2.12 (m, 1H), 0.96 (d, 3H *J*=6.8 Hz), 0.90 (d, 3H, *J*=6.8 Hz); δ_C 152.0, 141.5, 140.6, 140.5, 129.8, 124.1, 114.7, 59.5, 55.5, 54.8, 30.2, 21.2 17.8, 17.7; IR 2875, 2390, 1590, 1505, 1230, 1080, 1030, 915, 875 cm^{-1}; anal. calcd for $C_{19}H_{25}NO_2S$: C 68.85, H 7.60, N 4.22. Found: C 68.96, H 7.77, N 4.31.

3.11. (1R,(S)R)-N-(p-Methoxyphenyl)-1-tert-butyl-2-(p-tolylsulfinyl)ethylamine **21**

Compound **21** was obtained as an oil from **8** in 83% yield after chromatography (hexane:AcOEt, 3:2); $[\alpha]_D$=+8.2 (*c* 2.4, CH_2Cl_2); δ_H 7.39 and 7.22 (AA′BB′ system, 4H), 6.71 and 6.49 (AA′BB′ system, 4H), 3.71 (s, 3H), 3.12 (s, 3H), 2.36 (s, 3H), 0.86 (s, 9H); δ_C 151.6, 142.0, 141.7, 140.5, 129.7, 124.7, 114.5, 114.3, 61.9, 58.3, 55.6, 36.1, 26.4, 21.2; IR 2900, 2310, 1600, 1250, 1080, 1030, 875 cm^{-1}.

3.12. (1R,(S)R)-N-(p-Methoxyphenyl)-1-phenyl-2-(p-tolylsulfinyl)ethylamine **22**

Compound **22** was obtained as a yellow solid from **9** in 70% yield after chromatography (hexane:AcOEt, 3:2); mp 147–149°C; $[\alpha]_D$=+141.0 (*c* 1.0, CH_2Cl_2); δ_H 7.54–7.20 (m, 9H), 6.66 and 6.43 (AA′BB′ system, 4H), 4.75 (dd, 1H, *J*=4.8 and 9.6 Hz), 3.65 (s, 3H), 3.27 (dd, 1H, *J*=9.7 and 13.4 Hz), 2.92 (dd, 1H, *J*=4.8 and 13.4 Hz), 2.37 (s, 3H); δ_C 152.2, 141.8, 140.5, 140.4, 129.9, 128.8, 127.6, 126.1, 123.9, 115.1, 114.5, 64.9, 56.4, 55.4, 21.3; IR 2830, 2230, 1425, 1130, 1050, 950, 850 cm^{-1}; anal. calcd for $C_{22}H_{23}NO_2S$: C 72.30, H 6.34, N 3.83. Found: C 72.06, H 6.22, N 3.74.

3.13. (2R,(S)R)-2-(p-Tolylsulfinylmethyl)piperidine **23**

Compound **23** was obtained as an oil from **10** in 65% yield after chromatography (acetone:methanol, 3:1); $[\alpha]_D$=+80.9 (*c* 0.5, CH_2Cl_2); δ_H 7.55 and 7.35 (AA′BB′ system, 4H), 3.20–2.90 (m, 4H), 2.65 (m, 1H), 2.43 (s, 3H), 1.62–1.40 (m, 6H); δ_C 141.5, 140.6, 129.9, 123.9, 64.1, 53.6, 46.5, 32.8, 25.8, 24.4, 21.2; IR 3310, 2990, 1650, 1450, 1030 cm^{-1}.

3.14. (1R,2R,(S)R) and (1R,2S,(S)R)-N-(p-Methoxyphenyl)-1-phenyl-2-(p-tolylsulfinyl)propylamine **24**

The reduction of the enamine tautomer of sulfinyl imine **11** (see Ref. 17) yielded **24** as a 1:1 mixture of both epimers, which was purified by chromatography (hexane:AcOEt, 3:2) affording separated epimers (80% yield). (1*R*,2*R*,(S)*R*)-**24** (white solid), mp 166–167°C; $[\alpha]_D$=+1.0 (*c* 1.0, CH_2Cl_2); δ_H 7.56–7.21 (m, 9H), 6.68 and 6.50 (AA′BB′ system, 4H), 4.90 (b s, 1H), 4.13 (d, 1H, *J*=9.2 Hz), 3.42 (s, 3H), 3.32 (m, 1H), 2.42 (s, 3H), 0.88 (d, 3H, *J*=6.8 Hz); δ_C 152.1, 141.8, 140.0, 139.8, 135.8, 129.5, 128.5, 127.6, 127.3, 126.0, 115.1, 114.5, 63.7, 60.2, 55.4, 21.4, 7.9; IR 3000, 2400, 1550, 1270, 1065, 970 cm^{-1}; anal. calcd for $C_{23}H_{25}NO_2S$: C 72.79, H 6.64, N 3.69. Found: C 72.55, H 6.43, N 3.44. (1*R*,2*S*,(S)*R*)-**24** (white solid), mp 177–178°C; $[\alpha]_D$=+104.0 (*c* 1.0, CH_2Cl_2); δ_H 7.53–7.19 (m, 9H), 6.68 and 6.43 (AA′BB′ system, 4H), 4.83 (d, 1H, *J*=3.9 Hz), 4.62 (b s, 1H), 3.69 (s, 3H), 2.86 (dq, 1H, *J*=3.9 and 7.1 Hz), 2.40 (s, 3H), 1.08 (d, 3H, *J*=7.1 Hz); δ_C 151.5, 140.7, 139.8, 138.0, 129.1, 128.0, 126.7, 125.9, 123.6, 64.8, 59.7, 54.8, 20.6, 3.5; IR 2950, 2400, 1510, 1225, 1115, 1045, 920 cm^{-1}; anal. calcd for $C_{23}H_{25}NO_2S$: C 72.79, H 6.64, N 3.69. Found: C 72.39, H 6.57, N 3.57.

3.15. (1R,2R,(S)R)-N-(p-Methoxyphenyl)-1-methyl-2-(p-tolylsulfinyl)butylamine **25**

Compound **25** was obtained as a white solid from **12** in 82% yield after chromatography (CH_2Cl_2:AcOEt, 3:1) and further crystallisation (acetone:ether); mp 105–106°C; $[\alpha]_D$=–58.4 (*c* 1.0, CH_2Cl_2); δ_H 7.57 and 7.45 (AA′BB′ system, 4H), 6.64 and 6.21 (AA′BB′ system, 4H), 3.80 (m, 1H), 3.73 (s, 3H), 3.37 (b s, 1H), 2.60 (m, 1H), 2.46 (s, 3H), 1.90–1.54 (m, 2H), 1.31 (d, 3H, *J*=6.6 Hz), 0.94 (t, 3H, *J*=7.5 Hz); δ_C 151.8, 141.2, 139.8, 138.6, 129.5, 124.9, 114.5, 114.3, 67.0, 55.4, 47.5, 21.1, 17.5, 16.3, 12.7; IR 2800, 2220, 1425, 1120, 1000, 950, 840 cm^{-1}; anal. calcd for $C_{19}H_{25}NO_2S$: C 68.85, H 7.60, N 4.22. Found: C 68.77, H 7.54, N 4.12

3.16. (1R,2S,(S)R)-N-(p-Methoxyphenyl)-1-methyl-2-(p-tolylsulfinyl)butylamine **26**

Compound **26** was obtained as a white solid from **13** in 82% yield after chromatography (CH_2Cl_2:AcOEt, 3:1) and further crystallisation (acetone:ether); mp 133–134°C; $[\alpha]_D$=−13.8 (*c* 1.0, CH_2Cl_2); δ_H 7.20 and 7.15 (AA′BB′ system, 4H), 6.83 and 6.50 (AA′BB′ system, 4H), 3.88 (m, 1H), 3.77 (s, 3H), 2.76 (m, 1H), 2.35 (s, 3H), 1.82–1.54 (m, 2H), 1.45 (d, 3H, *J*=6.6 Hz), 0.88 (t, 3H, *J*=7.5 Hz); δ_C 152.4, 140.3, 140.1, 140.0, 129.5, 123.8, 115.2, 115.0, 114.6, 69.8, 55.6, 49.8, 21.1, 16.9, 14.8, 11.9; IR 3350, 2990, 1620, 1520, 1470, 1320, 1270, 1250, 1140, 1035, 810 cm^{-1}; anal. calcd for $C_{19}H_{25}NO_2S$: C 68.85, H 7.60, N 4.22. Found: C 68.23, H 7.67, N 4.29.

3.17. Desulfurisation of aminosulfoxides

This was carried out with Raney nickel following the previously described procedure.[28] (*R*)-1-Methyl-*N*-(*p*-methoxyphenyl)butylamine **27** was obtained from a 1:1 mixture of **25**+**26** as an oil in 79% yield,

after chromatography (CH_2Cl_2); $[\alpha]_D$=–19.0 (*c* 1.0, CH_2Cl_2); δ_H 6.75 and 6.54 (AA′BB′ system, 4H), 3.74 (s, 3H), 3.38 (m, 1H), 1.62–1.32 (m, 4H), 1.28 (b s, 1H), 1.15 (d, 3H, *J*=6.6 Hz), 0.92 (t, 3H, *J*=6.7 Hz). Enantiomer (*R*)-**27** was obtained from **19** as an oil in 90% yield after chromatography (CH_2Cl_2); $[\alpha]_D$=+19.4 (*c* 1.0, CH_2Cl_2).

Acknowledgements

We thank Dirección General de Investigación Científica y Técnica (DGICYT, Grant PB95-210 and PB96-35) for financial support.

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