Diastereoselective electrophilic substitution of α-amino-substituted benzylic organometallics

Ugo Azzena

Dipartimento di Chimica, Università di Sassari, via Vienna 2, 07100 Sassari, Italy.
E-mail: ugo@ssmain.uniss.it

Received (in Cambridge, UK) 22nd October 2001, Accepted 27th November 2001
First published as an Advance Article on the web 9th January 2002

Reductive metallation of a diastereoisomeric bicyclic 2-phenyloxazolidine derived from 2-hydroxymethylpiperidine occurs with racemization at the benzylic carbon atom. Reaction of intermediate organometallics with alkyl halides affords substituted amino alcohols in a highly *syn*-selective fashion. Observed diastereoselectivities are rationalized in terms of rapidly equilibrating epimeric intermediate organometallics, one of which reacts preferentially under appropriate reaction conditions. Deuteration of the same intermediates usually leads to deuterated amino alcohols with low diasteroselectivities, unless lithium is employed as the reducing agent and the resulting mixture is allowed to equilibrate before deuteration.

Introduction

Reductive cleavage of arylmethyl alkyl ethers by electron transfer from alkali metals in ethereal solvents results in the regioselective cleavage of the arylmethyl carbon–oxygen bond, with generation of arylmethyl organometallics.[1] Application of this procedure to the reductive metallation of aromatic acetals or α-*N*,*N*-dialkylamino-substituted benzyl alkyl ethers allows the generation of, respectively, α-oxygen-[2] and α-amino-substituted[3] arylmethyl organometallics. Furthermore, this procedure is well suited to generate oxy- or amino-functionalized arylmethyl organometallics *via* reductive metallation of suitable α-aryl-substituted heterocycles.[3–6] Interestingly, a dilithium derivative generated by reductive metallation of an oxazolidine, *i.e.*, an organolithium bearing an oxyanionic group, was more stable under the reaction conditions than a similar monolithium derivative generated from an open-chain amino ether.[3]

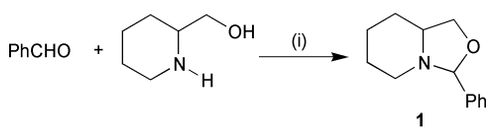
The configurational stability of chiral α-substituted arylmethyl organometallic reagents and their ability to react with electrophiles in a stereodefined manner is a topic of current interest in organic chemistry.[7–12] Investigations on the carbolithiation of cinnamyl alcohol and derivatives have shown that appropriately positioned substituents are sometimes able to coordinate the organometallic centre, fixing its configuration and allowing a diastereoselective alkylation.[13–16]

I wish now to report that reductive metallation of the diastereoisomeric bicyclic 2-phenyloxazolidine **1** followed by reaction with alkyl halides allows the highly diastereoselective synthesis of *N*-(α-alkylbenzyl)-2-(hydroxymethyl)piperidines, *via* intermediate formation of α-amino-substituted organometallic derivatives bearing a potentially coordinative oxyanionic group. A preliminary report has already appeared.[17]

Results

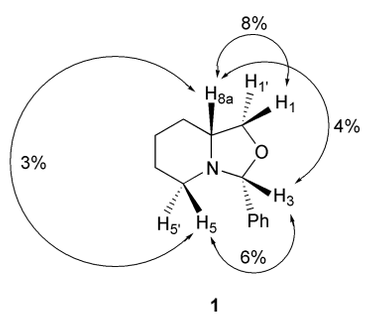
Starting materials

The oxazolidine **1** was synthesized in 83% isolated yield as a 92 : 8 mixture of diastereoisomers by the acid-catalyzed reaction of benzaldehyde with *rac*-2-(hydroxymethyl)piperidine, according to a known procedure (Scheme 1).[18] Selective ^{1}H–^{1}H decoupling experiments allowed assignment of the ^{1}H resonances and a *syn*-relationship between H3 and H8a was assigned according to ^{1}H NMR NOE difference spectra; in particular, presaturation of the H3 resonance resulted in enhancement (4%) of the signal for the H8a proton and *vice-versa* (Fig. 1).



1

Scheme 1 Synthesis of 3-phenylhexahydrooxazolo[3,4-*a*]pyridine **1**. *Reagents, conditions and yield*: (i) CH_3COOH, C_6H_6, reflux, 4 h (83%, 92 : 8 mixture of diastereoisomers).



1

Fig. 1 Stereochemistry of the major stereoisomer of the oxazolidine **1**, as determined by ^{1}H NMR NOE difference spectra. Besides geminal correlations, H1 shows correlations with H8a; H3 shows NOE correlations with H5 and H8a; H8a shows NOE correlations with H1, H3 and H5.

Reductive metallation reactions of 1

The reduction of **1** was carried out under Ar with Li or K metal in the presence of a catalytic amount of naphthalene in tetrahydrofuran (THF) (Scheme 2, Table 1). The results of D_2O; *t*-BuOD- and 2,6-[$(CH_3)_3C]_2C_6H_3$OD-quenching experiments, carried out to check the formation of carbanionic intermediates, as well as their behaviour as a function of reaction time, temperature and concentration, are reported in Table 1.

Reaction of the oxazolidine **1** with Li metal (5 equiv.) in the presence of a catalytic amount of naphthalene (10 mol%) in THF at −20 °C for 4 h furnished a deep red heterogeneous reaction mixture which, upon aqueous work-up, afforded amino alcohol **3** in quantitative yield (Table 1, entry 1).

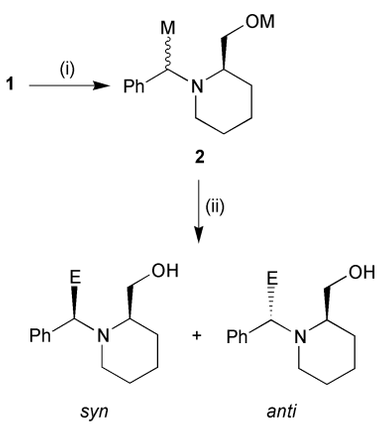
 DOI: 10.1039/b109633h

This journal is © The Royal Society of Chemistry 2002

Table 1 Reductive metallation of oxazolidines **1**

Entry	Metal	Time (t/h)	EX	Temp. (θ/°C)[a]	Product E	Yield (%)[b]	Diastereoisomeric ratio **4a** : **4b**[b]
1	Li	4	H_2O	−20	**3**, H	>95	
2	Li	4	D_2O	−20	**4a/4b**, D	>95	52 : 48
3	Li	4	t-BuOD	−20	**4a/4b**, D	>95	55 : 45
4	Li	4	ArOD[c]	−20	**4a/4b**, D	>95	56 : 44
5	Li	4	D_2O	−80[d]	**4a/4b**, D	>95	55 : 45
6	Li	4	t-BuOD	−80[d]	**4a/4b**, D	>95	56 : 44
7	Li	6	D_2O	−20	**4a/4b**, D	>95	76 : 24
8	Li	8	D_2O	−20	**4a/4b**, D	>95	94 : 6
9	Li	22	D_2O	−20	**4a/4b**, D	>95	94 : 6
10	Li	22	ArOD	−20	**4a/4b**, D	>95	84 : 16
11	Li	8	D_2O	−20	**4a/4b**, D	>95	61 : 39[e]
12	Li	15	D_2O	−20	**4a/4b**, D	>95	61 : 39[e]
13	K	1	H_2O	−20	**3**, H	>95	
14	K	1	D_2O	−20	**4a/4b**, D	83	74 : 26
15	K	4	D_2O	−20	**4a/4b**, D	81	75 : 25
16	K	24	D_2O	−20	**4a/4b**, D	51	75 : 25

[a] All reactions run in the presence of 5 equiv. of the metal and 10 mol% of naphthalene; starting concentration of **1** is 0.05 M, unless otherwise indicated. [b] As determined by ^{1}H NMR spectroscopy. [c] ArOD = 2,6-$[(CH_3)_3C]_2C_6H_3OD$. [d] Reductive metallation performed at −20 °C, D_2O added at −80 °C. [e] Starting concentration of **1** is 0.01 M.



3, **4a/4b**-**7a/7b**

Scheme 2 Reductive metallation and reaction with electrophiles of the oxazolidine **1**. *Reagents and conditions*: (i) Li or K, naphthalene (10 mol%), THF; (ii) EX, then water.

Quantitative formation of intermediate organometallic(s) was evidenced after quenching of the reductive lithiation mixture with D_2O. Under these conditions, amino alcohols **4a** and **4b** were obtained in a 52 : 48 ratio (Table 1, entry 2); quenching the reaction mixture with t-BuOD or with 2,6-$[(CH_3)_3C]_2C_6H_3OD$, or lowering the temperature to −80 °C prior to quenching, did not affect this result (Table 1, entries 3–6).

However, when the reaction mixture was stirred for 6–22 h at −20 °C before quenching with D_2O, the ratio between the diastereoisomers rose to 94 : 6 (Table 1, entries 7–9); a similar result was obtained upon quenching of the reaction mixture with 2,6-$[(CH_3)_3C]_2C_6H_3OD$ after 22 h at −20 °C (Table 1, entry 10).

The above-described dramatic effect of reaction time on the diastereoisomeric ratio of recovered amino alcohols **4a** and **4b** was observed in reactions run with a starting 0.05 M concentration of the oxazolidine **1**. Lowering the starting concentration of the oxazolidine **1** to 0.01 M led to a completely different result. Indeed, under the new conditions, quenching of the reaction mixture with D_2O afforded amino alcohols **4a** and **4b** in a 61 : 39 diastereoisomeric ratio, independent of the reaction time (Table 1, entries 11 and 12).

Reductive cleavage of the oxazolidine **1** can be obtained also by the action of K metal (5 equiv.) in the presence of a catalytic amount of naphthalene (10 mol%) in THF (Table 1, entry 13). Quenching of the reaction mixture with D_2O showed intermediate formation of organometallic reagent(s) and afforded amino alcohols **4a** and **4b** in a 74 : 26 diastereoisomeric ratio; although the intermediate organopotassium reagent slowly decays, the diastereoisomeric ratio of recovered amino alcohols is practically time independent (Table 1, entries 14–16).

Reductive metallation and alkylation of 1

The reactivity of the intermediate organometallic reagent(s) obtained as described in the above paragraph towards alkyl halides was investigated (Scheme 2, Table 2). Reductive lithiation followed by reaction with $PhCH_2Cl$, n-$C_6H_{13}Br$, n-C_4H_9I or n-C_4H_9Br afforded amino alcohols **5a** and **5b**, **6a** and **6b** and **7a** and **7b**, respectively, with yields ranging from 75 to 45% and good diastereoselectivities (Table 2, entries 1–6). Furthermore, the diastereoisomeric ratio of recovered amino alcohols **5a** and **5b** and **7a** and **7b** is time independent (Table 2, entry 1 *vs.* entry 2 and entry 4 *vs.* entry 5).

A comparable result was obtained in the K-mediated reductive cleavage of **1** followed by quenching with n-C_4H_9Br (Table 2, entry 7).

In contrast to the above reported results, low yields and low diastereoselectivites were observed upon quenching of the mixture of reductive lithiation of the oxazolidine **1** with n-C_4H_9Cl (Table 2, entries 8 and 9).

Relative stereochemistry of amino alcohol 4a

To determine the stereochemistry of the reductive metallation reaction followed by deuteration of intermediate organometallic(s), amino alcohols **3** and **4a** were cyclized to the corresponding 1,2,3,4-tetrahydroisoquinolines, in order to assess the relative orientation of protons at stereocentres by means of NOE correlations.

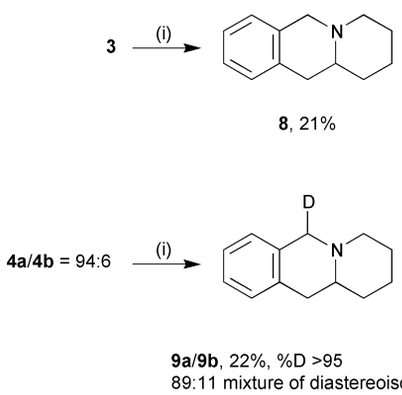
According to a procedure developed by Mendelson *et al.*,[19,20] the tetrahydroisoquinoline **8** was obtained in 21% isolated yield by reaction of amino alcohol **3** in fused $AlCl_3$ and NH_4Cl. Application of the same procedure to a 94 : 6 mixture of deuterated amino alcohols **4a** and **4b** (%D > 95) led to isolation of the corresponding deuterated tetrahydroisoqunolines **9a** and **9b** (%D > 95) as an 89 : 11 mixture of diastereoisomers in 22% isolated yield (Scheme 3).

Although a minor variation of the diastereoisomeric ratio was evidenced, it was confidently assumed that a comparison between the relative stereochemistry of starting material and

Table 2 Reductive alkylation of oxazolidines **1**

Entry	Metal	Time (*t*/h)	EX	Temp. (θ/°C)[a]	Product E	Yield (%)[b]	Diastereoisomeric ratio **a** : **b**[c]
1	Li	4	$PhCH_2Cl$	−20	**5a/5b**, $PhCH_2$	74[d]	93 : 7
2	Li	8	$PhCH_2Cl$	−20	**5a/5b**, $PhCH_2$	75	92 : 8
3	Li	4	*n*-$C_6H_{13}Br$	−20	**6a/6b**, *n*-C_6H_{13}	50[d]	>95 : <5
4	Li	4	*n*-C_4H_9I	−20	**7a/7b**, *n*-C_4H_9	57[d]	>95 : <5
5	Li	8	*n*-C_4H_9I	−20	**7a/7b**, *n*-C_4H_9	45	94 : 6
6	Li	4	*n*-C_4H_9Br	−20	**7a/7b**, *n*-C_4H_9	56	>95 : <5
7	K	4	*n*-C_4H_9Br	−20	**7a/7b**, *n*-C_4H_9	63	>95 : <5
8	Li	4	*n*-C_4H_9Cl	−20	**7a/7b**, *n*-C_4H_9	<5	63 : 27
9	Li	4	*n*-C_4H_9Cl	0[e]	**7a/7b**, *n*-C_4H_9	23	67 : 23

[a] All reactions run in the presence of 5 equiv. of the metal; starting concentration of **1** is 0.05 M. [b] As determined by ^{1}H NMR spectroscopy, unless otherwise indicated. [c] As determined by GC–MS; compounds **5**–**7a** showed higher retention times than diastereoisomers **5**–**7b**. [d] Isolated yield. [e] Reductive metallation performed at −20 °C, *n*-C_4H_9Cl added at 0 °C.



Scheme 3 Synthesis of isoquinolines **8** and **9**: *Reagents and conditions*: (i) $AlCl_3$–NH_4Cl, 180 °C, 15 h.

reaction product is reliable: indeed, no loss of deuterium at the benzylic position was observed, and a comparable result was reported in the cyclization of a similar benzylaminoethanol selectively deuterated at the carbon atom in the α-position to the hydroxy group.[20]

A comparison of the ^{1}H NMR spectra of isoquinolines **8** and **9** allowed us to assign the configuration of the major stereoisomer of the deuterated product and, therefore, to assign the relative stereochemistry to the major diastereoisomer of amino alcohols **4a** and **4b**.

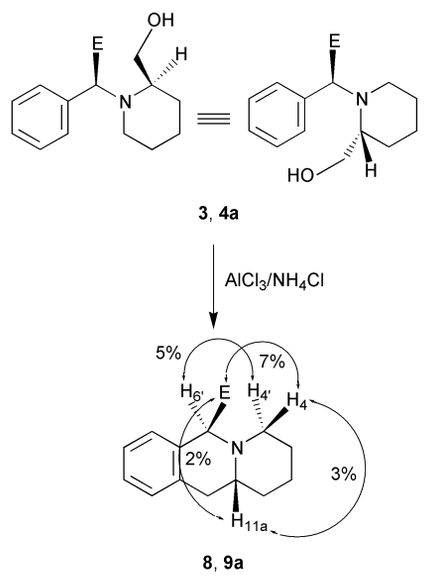
Selective ^{1}H–^{1}H decoupling experiments as well as ^{1}H–^{13}C COSY experiments allowed assignment of the ^{1}H resonances of the isoquinoline **8**, and a *syn*-relationship between H6 and H11a was assigned according to ^{1}H NMR NOE difference spectra. In particular, presaturation of the H6 resonance in the oxazolidine **8** resulted in enhancement (2%) of the signal for the H11a proton.

The ^{1}H NMR spectrum of the deuterated isoquinolines **9a** and **9b** showed two α-aminobenzylic protons in a 89 : 11 ratio corresponding, respectively, to the H6′ and H6 resonances of the isoquinoline **8** (see Experimental section). This finding is indicative of a *syn* relationship between the α-aminobenzylic deuterium and H11a in the major stereoisomer, *i.e.*, the isoquinoline **9a**. Accordingly, the *anti* configuration can be ascribed to the deuterated isoquinoline **9a**, and the *syn* configuration to the deuterated amino alcohol **4a** (Scheme 4).

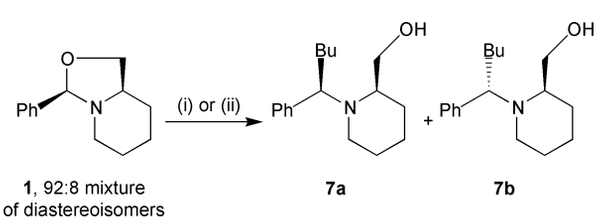
Relative stereochemistry of amino alcohols 5–7

To determine the relative stereochemistry of the reductive alkylation products, amino alcohols **7a** and **7b** were synthesized by reaction of the oxazolidine **1** with *n*-C_4H_9MgBr (Scheme 5).

Under these conditions, amino alcohols **7a** and **7b** were obtained as a 30 : 70 diastereoisomeric mixture (as determined by GC–MS) in 32% isolated yield. According to the literature, reaction of Grignard reagents with *N*-substituted-2-aryl-



Scheme 4 Cyclization of amino alcohols **3a** (E = H) and *syn*-**4a** (E = D) and stereochemistry of the isoquinoline **8** (E = H6) and **9a** (E = D), as determined by ^{1}H NMR NOE difference spectra: besides geminal correlations, H6 shows NOE correlations with H4 and H11a; H6′ shows NOE correlations with H4′; H4 shows correlatons with H6 and H11a.



Scheme 5 Syntheses of diastereoisomeric alcohols **7a** and **7b**. *Reagents and conditions*: (i) Li or K, THF, −20 °C; then BuBr: **7a** : **7b** = >95 : <5; (iii) BuMgBr, THF, 0 °C: **7a** : **7b** = 30 : 70.

oxazolidines should occur with an overall prevailing inversion of configuration at the electrophilic carbon[21–25] thus leading, in the present example, to the preferential formation of the *anti* amino alcohol. Accordingly, the *anti* configuration can be ascribed to amino alcohol **7b**, and the *syn* configuration to amino alcohol **7a**, as well as to amino alcohols **5a** and **6a**.

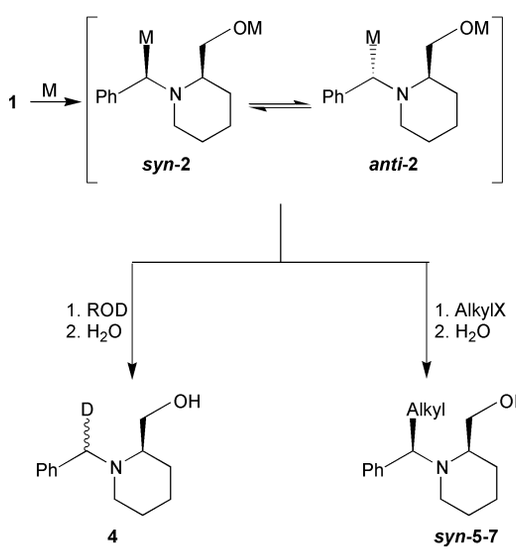
Discussion

This paper describes the generation of organometallic derivatives which behave in a markedly different way with different electrophiles. Indeed, reaction of both lithium and potassium intermediates with deuterating reagents usually led, with one notable exception discussed below, to the formation of

deuterated amino alcohols **4** with low diastereoselectivities (Table 1, entries 2–7, 11, 12 and 14–16) whilst, in contrast, reaction of the same intermediates with alkyl halides usually led to amino alcohols **5**–**7** with good to very good diastereoselectivities (Table 2, entries 1–7).

It is accordingly proposed that reductive metallation of the oxazolidine **1** occurs with racemization, giving rise to a pair of rapidly interconverting diastereoisomeric intermediates, *syn*-**2** and *anti*-**2**. Racemization at the benzylic carbon atom is supported not only by the above-mentioned deuteration experiments, but also by the reaction mechanism usually considered for the reductive metallation of benzyl alkyl ethers, which occurs *via* intermediate formation of configurationally labile benzylic radicals.[1,†]

Observed diastereoselectivities can be rationalized by assuming that the configuration at the benzylic carbon of organometallic intermediates is fixed by coordination of the carbanionic mojety to the alkoxy group.[13–16] One of the intramolecularly coordinated organometals reacts preferentially and stereoselectively with carbon electrophiles (either with retention or inversion of configuration),[‡] *i.e.*, the behaviour of the intermediate organometallics with alkyl halides can be rationalized by assuming that the activation energy of the electrophilic reaction is higher than the activation energy of their epimerization.[9,13] It is particularly interesting to note that potassium as a counter-ion is, in the present example, as effective as lithium for such coordination. On the other hand, deuteration of the equilibrating reaction mixture requires an activation energy lower than (or comparable to) the activation energy of epimerization.[9,13] This hypothesis is represented in Scheme 6, where a specific coordination between the alkoxy



Scheme 6 Epimerization and reaction with electrophiles of *syn*-**2** and *anti*-**2**; M = Li or K; AlkylX = $PhCH_2Cl$, *n*-$C_6H_{13}Br$, *n*-C_4H_9I or *n*-C_4H_9Br; R = D, $(CH_3)_3C$ or 2,6-$[(CH_3)_3C]_2C_6H_3$.

and the carbanionic mojety is not shown. Indeed, fixation of configuration at the benzylic carbon could involve chelation of benzylic metal by oxygen or interaction of alkoxide metal with the benzylic carbon,[16] and it has been recently pointed out that the actual nature of such a coordination depends on several parameters like, *inter alia*, solvation and formation of aggregates.[14]

Interestingly, equilibration of intermediates **2** (M = Li) before deuteration afforded amino alcohols **4a** and **4b** with high diastereoselectivity (Table 1, entries 7–10). Such behaviour could be, in principle, an indication of thermodynamic resolution of the intermediates. Alternatively, owing to the heterogeneity of the reaction mixture, I suggest dynamic resolution through preferential crystallization of one diastereoisomeric intermediate.[28] Indeed, under the above-reported reaction conditions (initial concentration of the oxazolidine **1** = 0.05 M), resolution could result from a selective dissolution/epimerization/selective crystallization process.

The completely different result obtained upon performing the reductive cleavage reaction at higher dilution (initial concentration of the oxazolidine **1** = 0.01 M, Table 1, entries 11 and 12), *i.e.*, no variation of the diastereoisomeric ratio of amino alcohols **4a** and **4b** with time, supports this hypothesis. Although always in the presence of an heterogeneous reaction mixture, dilution could well affect the solubility of intermediates and the selectivity of a dissolution/crystallization process, whilst it should not affect thermodynamic resolution to such an extent.

The finding that resolution of the intermediates did not affect the result of alkylation reactions (Table 2, entry 1 *vs.* entry 2, and entry 4 *vs.* entry 5) can be accordingly rationalized. As mentioned above, I suggest that the activation energy of alkylation reactions is higher than the activation energy of interconversion of the epimeric intermediate organometallics. According to the Curtin–Hammett principle, the product composition of a similar reaction is solely dependent on the difference in energies of the transition states; as a consequence, whatever the relative amount of the most reactive intermediate in the reaction mixture after equilibration, it should drive the reaction to an unchanging diastereoisomeric composition of reaction products.

Whatever the reason of the resolution process, it strongly supports the hypothesis concerning the formation of interconverting diastereoisomeric organometallic intermediates and rules out a possible alternative explanation of the above-reported results, *i.e.*, formation of essentially planar organometallic intermediates which react stereoselectively with alkyl halides, and non-stereoselectively with deuterating agents.

The last hypothesis appears unlikely also in view of the results obtained in the synthesis of amino alcohols **7a** and **7b** by alkylation of intermediates **2** (M = Li), where *n*-C_4H_9I and *n*-C_4H_9Br afforded higher diastereoselectivities than did the less reactive *n*-C_4H_9Cl (Table 2, entries 4–6, 8 and 9). Apparently, the low reactivity of *n*-C_4H_9Cl rendered the alkylation step less stereospecific, *i.e.*, one (or both) intermediates **2** (M = Li) reacted comparatively well with this electrophile under retention or inversion of configuration at the organometallic centre. This hypothesis is in agreement with the statement that activation barriers for retentive and inverse electrophilic attack at organometallic derivatives should not differ very much.[13,29]

In summary, the results reported in the present investigation show that reductive metallation of the diastereoisomeric oxazolidine **1** is a practical approach to a highly *syn*-selective synthesis of *N*-(α-substituted benzyl)-2-(hydroxymethyl)piperidines, illustrate an interesting example of resolution of diastereoisomeric organometallics, and add additional evidence to the hypothesis that coordination with an appropriately positioned substituent enhances the configurational stability of organometallic centres.

Experimental

General remarks

Boiling points are uncorrected; the air-bath temperature on bulb-to-bulb distillations is given as the boiling point. Starting materials were of the highest commercial quality and were used without further purification. D_2O was 99.8% isotopic purity. THF was distilled from Na–K alloy under N_2 immediately prior

† Examples of configurationally stable $Cr(CO)_3$-complexed benzylic radicals were recently reported.[26]

‡ Reaction of benzyllithium derivatives with different electrophiles can occur either with retention or with inversion of configuration.[27]

to use. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz, in $CDCl_3$ (unless otherwise indicated) with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra of the crude mixtures and comparing the integration of the signal corresponding to the proton in the arylmethyl position with that of known signals. Mass spectra were recorded on a quadrupole mass spectrometer operating at 70 eV, interfaced with a gas chromatograph equipped with a DBS 30-m capillary column (i.d. 0.25 mm). IR spectra were recorded on thin films. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Grignard reactions were performed according to a general procedure described in ref. 25. Petroleum ether refers to the fraction with distillation range 35–60 °C. TLC analyses were performed on aluminium plates precoated with silica gel 60 F254, developed with the solvent systems reported for flash chromatography purifications, and visualized by UV light.

Preparation of starting materials

Oxazolidine derivative **1** was obtained in 83% isolated yield according to a procedure described in ref. 18 and purified by vacuum distillation; diastereoisomeric ratio was calculated by monitoring ^{1}H NMR spectra and comparing integrations of clearly separated singlet resonances of H3 protons. The oxazolidine **1** was characterized as follows:

3-Phenylhexahydrooxazolo[3,4-*a*]pyridine 1. Oil; bp 117–120 °C/1 mmHg (lit.,[18] 134–136/8 Torr); δ_H (*syn* stereoisomer, CD_3OD) (Hs at C6, C7 and C8 superimpose between δ 1.28 and 1.90), 1.49 (4H, m), 1.84 (2H, m), 2.04 (1H, td, J = 11.0, 3.3 Hz, H5), 2.51 (1H, m, H8a), 2.71 (1H, m, H5′), 3.67 (1H, dd, J = 9.9, 6.6 Hz, H1′), 4.07 (1H, t, J = 6.6 Hz, H1), 4.57 (1H, s, H3), 7.34 (3H, m, ArH), 7.44 (2H, m, ArH); δ_C (*syn* stereoisomer, CD_3OD) 24.5, 25.7, 27.7, 48.3, 64.2, 72.1, 98.1, 129.2, 129.2, 130.2, 139.9; (*anti* stereoisomer, CD_3OD) 23.2, 24.2, 26.1, 47.5, 57.5, 70.9, 95.7, 128.1, 129.1, 129.5 139.9.

Reductive cleavage of the oxazolidine 1 and reaction with electrophiles—general procedure

Li metal (5–10 equiv. of a 30% wt. dispersion in mineral oil) was placed under Ar in a 100 ml two-necked flask equipped with reflux condenser and magnetic stirrer, washed with THF (3 × 10 ml), and suspended in THF (30 ml). Alternatively, K dispersion was prepared in a similar apparatus by vigorous stirring of the freshly cut metal (5 equiv.) in THF (30 ml) at reflux temperature for 10 min; the unstirred metal suspension was then allowed to cool to rt. A catalytic amount of naphthalene (10 mol%) was added to the suspension of the metal, and the mixture was stirred until a dark green colour appeared. The mixture was chilled to the reported temperature (Tables) and a solution of the substrate (5 mmol) in THF (2 ml) was added dropwise. After stirring of this mixture for the reported time (Tables), a solution of the appropriate electrophile (1.1 equiv.) in THF (5 ml) was slowly added to the dark red heterogeneous reaction mixture. After stirring for 15–60 min, the mixture was quenched by slow dropwise addition of water (10 ml, **CAUTION:**), the cold bath was removed, and the resulting mixture was extracted with Et_2O (3 × 20 ml). The organic phase was washed with brine (10 ml), dried (K_2CO_3), and evaporated.

D_2O quenching was performed by dropwise addition of 1 ml (0.055 mol) of the electrophile dissolved in THF (5 ml) during 2 min. After stirring of this mixture for 15 min, water (10 ml, **CAUTION:**) was slowly added dropwise to quench unchanged Li metal, the cold bath was removed, and the mixture worked up as described above.

Crude products were purified by flash chromatography (AcOEt–petroleum ether–Et_3N); compound **3**[30] is already known. Other products were characterized as follows. Amino alcohols **5b** and **6b** were not separated from the corresponding major stereoisomer; their relative amount was determined by GC–MS, and they were characterized by means of their repective MS fragmentation pattern, closely related to the fragmentation pattern of the corresponding major stereoisomer. Yields are reported in the Tables.

***N*-(α-Deuterio benzyl)-2-(hydroxymethyl)piperidine (*syn*-4a : *anti*-4b = 94 : 6).** Oil; purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 3 : 7 : 1), R_f = 0.34; bp 120–125 °C/1 mmHg; ν_{max} 3410 cm^{-1}; δ_H 1.35 (2H, m, CH_2), 1.63 (4H, m, 2 × CH_2), 2.14 (1H, m, CHN), 2.46 (1H, m, CHN), 2.58 (1H, br s, OH), 2.86 (1H, m, CHN), 3.29 (0.94H, br s, CHD, **4a**), 3.51 (1H, dd, J = 10.8, 3.9 Hz, CHO), 3.87 (1H, dd, J = 10.8, 4.2 Hz, CHO), 4.03 (0.06H, br s, CHD, **4b**), 7.28 (5H, m, ArH); δ_C 23.4, 24.1, 27.3, 50.7, 57.3 (t, J = 21.0 Hz), 60.8, 62.2, 127.0, 128.3, 128.8, 138.9 (Found: C, 75.9; H + D, 10.0; N, 6.5. $C_{13}H_{18}DNO$ requires C, 75.7; H + D, 9.8; N, 6.8%).

***syn*-*N*-(1′,2′-Diphenylethyl)-2-(hydroxymethyl)piperidine 5a.** Oil; purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 4 : 6 : 1), R_f = 0.43; bp 200–205 °C/1 mmHg; ν_{max} 3400 cm^{-1}; δ_H 1.49 (6H, m, 3 × CH_2), 2.50 (1H, br s, OH), 2.82 (3H, m, 3 × CHN), 2.95 (1H, dd, J = 13.5, 10.2 Hz, PhC*H*), 3.31 (1H, dd, J = 13.5, 4.2 Hz, PhC*H*), 3.60 (1H, dd, J = 10.5, 5.1 Hz, CHO), 3.69 (1H, dd, J = 10.5, 6.6 Hz, CHO), 4.33 (1H, dd, J = 10.2, 4.2 Hz, PhC*H*N), 6.96 (2H, m, ArH), 7.15 (8H, m, ArH); δ_C 22.0, 22.7, 24.8, 36.5, 43.2, 55.8, 60.8, 64.4, 125.8, 127.0, 128.0, 128.0, 128.8, 129.2, 139.4, 141.7; *m*/*z* 264 (M^+ − 31), 204 (M^+ − 91, 100%), 181 (M^+ − 114) (Found: C, 81.2; H, 8.8; N, 4.6. $C_{20}H_{25}NO$ requires C, 81.3; H, 8.6; N, 4.7%).

***syn*-*N*-(1′-Phenylheptyl)-2-(hydroxymethyl)piperidine 6a.** Oil purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 2 : 8 : 1), R_f = 0.44; bp 146–148 °C/1 mmHg; ν_{max} 3378 cm^{-1}; δ_H 0.84 (3H, t, J = 7.0 Hz, CH_3), 1.02 (2H, m, CH_2), 1.24 (8H, m, 4 × CH_2), 1.65 (6H, m, 3 × CH_2), 2.47 (1H, br s, OH), 2.73 (3H, m, 3 × CHN), 3.48 (1H, dd, J = 10.5, 5.1 Hz, CHO), 3.65 (1H, dd, J = 10.5, 7.1 Hz, CHO), 3.96 (1H, dd, J = 10.4, 3.7 Hz, PhC*H*N), 7.28 (5H, m, ArH); δ_C 14.0, 21.9, 22.4, 22.6, 24.3, 26.7, 29.5, 29.9, 31.7, 42.6, 55.3, 60.3, 62.7, 126.9, 128.2, 128.5, 142.7; *m*/*z* 258 (M^+ − 31), 204 (M^+ − 85), 91 (M^+ − 198, 100%) (Found: C, 78.5; H, 11.0; N, 4.6. $C_{19}H_{31}NO$ requires C, 78.8; H, 10.8; N, 4.8%).

***syn*-*N*-(1-Phenylpentyl)-2-(hydroxymethyl)piperidine 7a.** Oil; purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 3 : 7 : 1), R_f = 0.49; bp 125–130 °C/1 mmHg; ν_{max} 3420 cm^{-1}; δ_H 0.83 (3H, t, J = 7.2 Hz, CH_3), 1.04 (2H, m, CH_2), 1.29 (4H, m, 2 × CH_2), 1.67 (6H, m, 3 × CH_2), 2.74 (3H, m, 3 × CHN), 2.95 (1H, br s), 3.49 (1H, dd, J = 10.2, 5.1 Hz, CHO), 3.65 (1H, dd, J = 10.2, 7.2 Hz, CHO), 3.96 (1H, dd, J = 10.2, 3.9 Hz, PhC*H*N), 7.28 (5H, m); δ_C 14.0, 21.9, 22.4, 22.9, 24.3, 29.0, 29.7, 42.6, 55.3, 60.4, 62.7, 126.9, 128.2, 128.6, 142.7; *m*/*z* 230 (M^+ − 31), 204 (M^+ − 57), 91 (M^+ − 170, 100%) (Found: C, 77.9; H, 10.6; N, 5.2. $C_{17}H_{27}NO$ requires C, 78.1; H, 10.4; N, 5.4%).

***anti*-*N*-(1-Phenylpentyl)-2-(hydroxymethyl)piperidine 7b.** Oil; purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 3 : 7 : 1), R_f = 0.51; bp 125–130 °C/1 mmHg; ν_{max} 3420 cm^{-1}; δ_H 0.85 (3H, t, J = 6.9 Hz, CH_3), 1.21 (6H, m, 3 × CH_2), 1.51 (4H, m, 2 × CH_2), 1.74 (3H, m), 2.11 (1H, m, CHN), 2.57 (1H, m, CHN), 2.93 (1H, m, CHN), 3.50 (1H, dd, J = 10.5, 3.9 Hz, CHO), 3.99 (1H, t, J = 6.6 Hz, PhC*H*N), 4.01 (1H, dd, J = 10.5, 4.5 Hz, CHO), 7.28 (5H, m, ArH); δ_C 13.9, 22.8, 22.9, 24.2, 27.4, 29.0, 32.9, 43.7, 56.0, 61.6, 61.7, 127.0, 127.9, 128.9, 139.3; *m*/*z* 230 (M^+ − 31), 204 (M^+ − 57), 91 (M^+ − 170, 100%) (Found: C, 77.9; H, 10.6; N, 5.2. $C_{17}H_{27}NO$ requires C, 78.1; H, 10.4; N, 5.4%).

Synthesis of 1,2,3,4-tetrahydroisoquinolines 8 and 9

Tetrahydroisoquinolines **8** and **9** were synthesized according to a modification of a procedure described in ref. 19. The starting amino alcohol (2.5 mmol) was dissolved in decalin (1 ml) in a 25 ml flask equipped with reflux condenser and magnetic stirrer under dry Ar. To this solution were added NH_4Cl (0.10 g, 1.83 mmol) and $AlCl_3$ (0.64 g, 4.8 mmol), and the resulting mixture was vigorously stirred at 185 °C. Two portions of $AlCl_3$ (0.32 g, 2.4 mmol, and 0.64 g, 4.8 mmol) were added after 40 and 70 min, respectively, and the mixture was stirred at 185 °C for another 15 h. After chilling of the mixture to 100 °C, PhCl was added (4 ml) and the mixture was stirred at 185 °C for a few minutes before chilling to 0 °C and quenching with ice-cold 1 M HCl (10 ml). The organic phase was washed with ice-cold 1 M HCl (2 × 20 ml). The collected aqueous phases were extracted with Et_2O (3 × 10 ml), then basified with solid NaOH. The basic mixture was extracted with Et_2O (3 × 20 ml), and these extracts were dried K_2CO_3, filtered, and evaporated. Reaction products were characterized as follows.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline 8. From amino alcohol **3** (0.51 g, 2.5 mmol). The product was obtained as an oil (99 mg, 0.53 mmol, 21%), which solidified upon storage and was purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 8 : 2 : 1), R_f = 0.53; bp 125 °C/1 mmHg (lit.,[31] 160 °C/15 Torr); δ_H (Hs at C1, C2 and C3 superimpose between δ 1.28 and 1.96) 1.37 (2H, m), 1.77 (4H, m), 2.12 (1H, m, H4), 2.27 (1H, m, H11a), 2.75 (2H, m, 2H at C11), 3.08 (1H, m, H4′), 3.39 (1H, d, J = 15.3 Hz, H6), 3.83 (1H, d, J = 15.3 Hz, H6′), 7.12 (4H, m, ArH); δ_C (C1, C2 and C3 resonate between δ_C 24.2 and 33.6) 24.2 (t), 25.8 (t), 33.6 (t), 36.7 (t, C11), 56.1 (t, C4), 58.3 (d, C11a), 58.3 (t, C6), 125.5 (d, aromatic), 125.9 (d, aromatic), 126.1 (d, aromatic), 128.0 (d, aromatic), 133.9 (s, aromatic), 134.2 (s, aromatic).

1,3,4,6,11,11a-Hexahydro-6-deuterio-2*H*-pyrido[1,2-*b*]-isoquinoline (*anti*-9a : *syn*-9b = 89 : 11). From a mixture of amino alcohols **4a** and **4b** (94 : 6 mixture; 0.52 g, 2.5 mmol) The product was obtained as an oil (0.1 g, 0.55 mmol, 22%), which solidified upon storage and was purified by flash chromatography (AcOEt–petroleum ether–Et_3N = 8 : 2 : 1), R_f = 0.53; bp 125 °C/1 mmHg; δ_H (Hs at C1, C2 and C3 superimpose between δ 1.28 and 1.96) 1.37 (2H, m), 1.77 (4H, m), 2.12 (1H, m, H4), 2.27 (1H, m, H11a), 2.75 (2H, m, 2H at C11), 3.08 (1H, m, H4′), 3.35 (0.11H, br s, **9b**, H6), 3.80 (0.89H, br s, **9a**, H6′), 7.12 (4H, m, ArH); δ_C (C1, C2 and C3 resonate between δ_C 24.2 and 33.6) 24.2 (t), 25.9 (t), 33.6 (t), 36.7 (t, C11), 56.1 (t, C4), 57.9 (t, J = 19.5 Hz, C6), 58.3 (d, C11a), 125.5 (d, aromatic), 125.9 (d, aromatic), 126.1 (d, aromatic), 128.0 (s, aromatic), 134.0 (s, aromatic), 134.2 (s, aromatic); *m*/*z* 188 ($M^{\bullet+}$), 187 ($M^+ - 1$, 100%), 105 ($M^+ - 82$) (Found: C, 82.8; H + D, 9.9; N, 7.3. $C_{13}H_{16}DN$ requires C, 82.9; H + D, 9.7; N, 7.4%).

Acknowledgements

Financial support from Università di Sassari (ex 60% funds) and Regione Autonoma della Sardegna is gratefully acknowledged.

References

1 U. Azzena, *Trends Org. Chem.*, 1997, **6**, 55.
2 U. Azzena, G. Melloni, L. Pisano and B. Sechi, *Tetrahedron Lett.*, 1994, **35**, 6759.
3 U. Azzena, L. Pilo and E. Piras, *Tetrahedron*, 2000, **56**, 3775.
4 U. Azzena, S. Demartis and G. Melloni, *J. Org. Chem.*, 1996, **61**, 4913.
5 U. Azzena and L. Pilo, *Synthesis*, 1999, 664.
6 U. Azzena, S. Demartis, L. Pilo and E. Piras, *Tetrahedron*, 2000, **56**, 8375.
7 O. Stratmann, B. Kaiser, R. Fröhlich, O. Meyer and D. Hoppe, *Chem. Eur. J.*, 2001, **7**, 423.
8 D. Hoppe and T. Hense, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2282.
9 P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552.
10 H. Ahlbrecht, J. Harbach, R. W. Hoffmann and T. Ruhland, *Liebigs Ann.*, 1995, 211.
11 R. W. Hoffmann, T. Rühl, F. Chemla and T. Zahneisen, *Liebigs Ann. Chem.*, 1992, 719.
12 R. W. Hoffmann, T. Rühl and J. Harbach, *Liebigs Ann. Chem.*, 1992, 725.
13 C. Mück-Lichtenfeld and H. Ahlbrecht, *Tetrahedron*, 1999, **55**, 2609.
14 C. Mück-Lichtenfeld and H. Ahlbrecht, *Tetrahedron*, 1996, **52**, 10025.
15 S. Klein, I. Marek and J.-F. Normant, *J. Org. Chem.*, 1994, **59**, 2925.
16 T. Kato, S. Marumoto, T. Sato and I. Kuwajima, *Synlett*, 1990, 671.
17 U. Azzena, L. Pilo and E. Piras, *Tetrahedron Lett.*, 2001, **42**, 129.
18 S. Kasuga and T. Taguchi, *Chem. Pharm. Bull.*, 1965, **13**, 233.
19 W. L. Mendelson, A. J. Villani, L. A. Petka and C. B. Spainhour, Jr., *J. Labelled Compd. Radiopharm.*, 1984, **21**, 961.
20 W. L. Mendelson, C. B. Spainhour, Jr., S. S. Jones, B. L. Lam and K. L. Wert, *Tetrahedron Lett.*, 1980, **21**, 1393.
21 H. Takahashi, Y. Chida, K. Higashiyama and H. Onishi, *Chem. Pharm. Bull.*, 1985, **33**, 4662.
22 H. Takahashi, B. C. Hsieh and K. Higashiyama, *Chem. Pharm. Bull.*, 1990, **38**, 2429.
23 M. Yamato, K. Hashigaki, S. Ishikawa and N. Qais, *Tetrahedron Lett.*, 1988, **29**, 6949.
24 L. Neelakantan, *J. Org. Chem.*, 1971, **36**, 2256 see also G. Just, P. Potvin, P. Uggowitzer and P. Bird, *J. Org. Chem.*, 1983, **48**, 2923.
25 M.-J. Wu and L. N. Pridgen, *J. Org. Chem.*, 1991, **56**, 1340 and references therein.
26 H.-G. Schmalz, C. B. de Koning, D. Bernicke, S. Siegel and A. Pfletschinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 1620.
27 D. Hoppe, A. Carstens and T. Krämer, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1424 see also refs. 8, 9 and 13.
28 For related examples, see M. Marsch, K. Harms, O. Zschange, D. Hoppe and G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 321; M. Schlosser and D. Limat, *J. Am. Chem. Soc.*, 1995, **117**, 12342.
29 E. D. Jemmins, J. Chandrasekhar and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1979, **101**, 527.
30 B. Weber, J. Schwerdtfeger, R. Fröhlich, A. Göhrt and D. Hoppe, *Synthesis*, 1999, 1915.
31 v. J. Braun and W. Pinkernelle, *Ber. Dtsch. Chem. Ges.*, 1931, **64**, 1871.