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Diastereoselective alkylation of α-amino-substituted benzyllithiums

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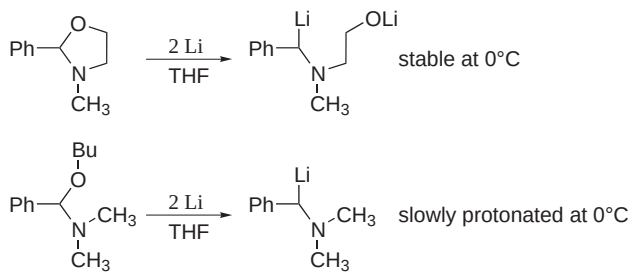
Abstract—Reductive lithiation of a distereoisomeric mixture of bicyclic oxazolidines followed by reaction with alkyl halides afforded aminoalcohols in a highly *syn*-selective fashion. Reductive lithiation occurs with racemization at the benzylic carbon atom; the observed diastereoselectivities are rationalized in terms of a pair of rapidly equilibrating diastereoisomeric organolithium intermediates, one of which reacts preferentially under appropriate reaction conditions.

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.[1–5] Investigations on the carbolithiation of cinnamyl alcohol and derivatives have shown that appropriately positioned substituents are sometimes able to coordinate to the organometallic center, fixing its configuration and allowing a diastereoselective alkylation.[6–9]

Whilst investigating the generation of α-amino-substituted benzyllithiums by reductive lithiation of cyclic and open chain α-*N*,*N*-dialkylamino-substituted benzyl alkyl ethers, we observed that a dilithium derivative generated from 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 substrate (Scheme 1).[10]



Scheme 1. Reductive lithiation of α-*N*,*N*-dialkyl-substituted benzyl alkyl ethers.

We ascribed this finding to intramolecular coordination of the carbanionic moiety with the alkoxy group,[11] and wish to report that reductive lithiation of a distereoisomeric mixture of a bicyclic 2-phenyl-1,3-oxazolidine **1**, followed by alkylation, allows the highly diastereoselective synthesis of *N*-(α-alkyl-substituted)benzyl-2-hydroxymethylpiperidines **5**–**7** (Scheme 2).

Results and discussion

Oxazolidine **1** was obtained in 83% yield as a 92:8 mixture of diastereoisomers according to a known procedure;[12] ^{1}H NMR nOe difference spectra allowed us to ascribe the *syn* configuration to the prevailing diastereoisomer. Reaction of oxazolidine **1** with Li powder (5 equiv.) in the presence of a catalytic amount of naphthalene (10 mol%) in THF at −20°C for 4 h quantitatively afforded, after aqueous work up, the corresponding aminoalcohol **3** (Table 1, entry 1).

Quenching the reaction mixture with electrophiles different from H_2O resulted in the formation of diastereoisomeric aminoalcohols **4a**/**4b**–**7a**/**7b**. Quantitative formation of intermediate dilithium derivative(s) **2** was evidenced as quenching the reaction mixture with D_2O: aminoalcohols **4a**/**4b** were obtained in a 52:48 diastereoisomeric ratio (Table 1, entry 2); quenching the reaction mixture with *t*-BuOD or with 2,6-

Keywords: carbanions; diastereoselectivity; lithium and compounds; reduction.

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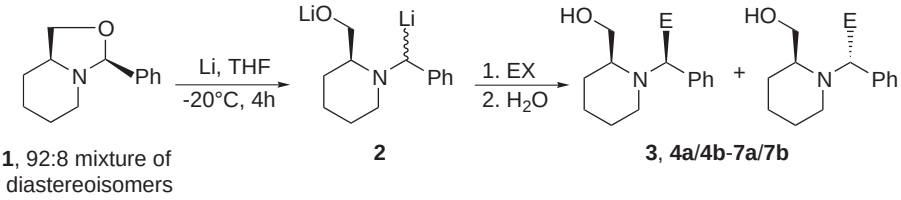


1, 92:8 mixture of diastereoisomers — **2** — **3**, **4a/4b**-**7a/7b**

Scheme 2. Reductive lithiation of oxazolidine **1**.

Table 1. Reductive lithiation and reaction with electrophiles of oxazolidine **1**

Entry	EX	T (°C)[a]	Product, E =	Yield (%)[b]	Diastereoisomeric ratio, **a**/**b**[c]
1	H_2O	−20	**3**, H	>95	–
2	D_2O	−20	**4a**/**4b**, D	>95	52:48[d]
3	*t*-BuOD	−20	**4a**/**4b**, D	>95	55:45[d]
4	2,6-$(CH_3)_3CC_6H_3OD$	−20	**4a**/**4b**, D	>95	56:44[d]
5	D_2O	−80	**4a**/**4b**, D	>95	55:45[d]
6	$PhCH_2Cl$	−20	**5a**/**5b**, $PhCH_2$	74[e]	93:7
7	$C_6H_{13}Br$	−20	**6a**/**6b**, C_6H_{13}	50[e]	>95:<5
8	C_4H_9I	−20	**7a**/**7b**, C_4H_9	57[e]	>95:<5
9	C_4H_9Br	−20	**7a**/**7b**, C_4H_9	56	>95:<5
10	C_4H_9Cl	−20	**7a**/**7b**, C_4H_9	<5[f]	63:37
11	C_4H_9Cl	0	**7a**/**7b**, C_4H_9	23[g]	67:33

[a] All reactions run at −20°C for 4 h; the electrophile was added at the temperature reported and the mixture stirred for 15 min before aqueous work-up. For a general procedure see Ref. 10
[b] As determined by ^1H NMR spectroscopy, unless otherwise indicated.
[c] As determined by GC-MS, unless otherwise indicated.
[d] As determined by ^1H NMR spectroscopy.
[e] Isolated yield.
[f] >90% of **3** was also detected.
[g] 72% of **3** was also detected.

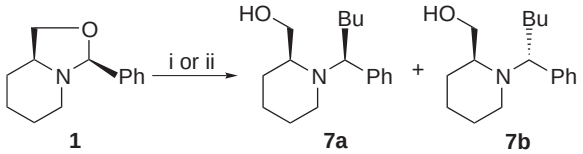
$(CH_3)_3CC_6H_3OD$, or lowering the reaction temperature to −80°C prior to quenching, did not affect this result (Table 1, entries 3–5).

At variance with the above results, reductive cleavage followed by reaction with $PhCH_2Cl$, $C_6H_{13}Br$, C_4H_9I or C_4H_9Br afforded aminoalcohols **5a**/**5b**, **6a**/**6b** and **7a**/**7b**, respectively, in satisfactory yields and good diastereoselectivities (Table 1, entries 6–9). However, low yields of aminoalcohols **7a**/**7b**, and low diastereoselectivities were observed quenching the reaction mixture with C_4H_9Cl (Table 1, entries 10 and 11).

To determine the relative stereochemistry of the reductive alkylation products, aminoalcohols **7a**/**7b** were synthesized by reacting oxazolidine **1** with C_4H_9MgBr; indeed, reaction of Grignard reagents with *N*-substituted-2-aryl-1,3-oxazolidines is reported to occur with an overall prevailing inversion of configuration at the electrophilic carbon.[13–16] Under the new conditions, aminoalcohols **7a**/**7b** were obtained in 32% yield; the diastereoselectivity of this reaction (30:70, as determined by GC-MS) is opposite to that obtained in the reductive alkylation procedure (Scheme 3). We therefore ascribe the *anti* configuration to aminoalcohol **7b** and the *syn* configuration to aminoalcohol **7a**, as well as to aminoalcohols **5a** and **6a**.

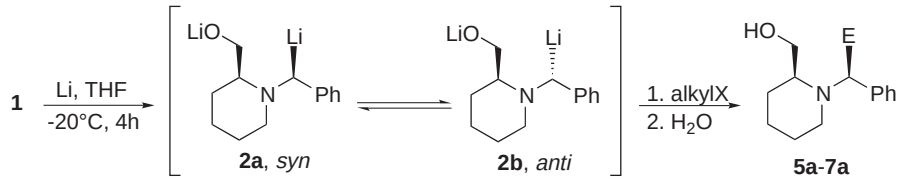
The results obtained could be rationalized assuming that reductive lithiation of oxazolidine **1** affords an essentially planar organolithium intermediate, which reacts stereoselectively with alkylating reagents and non stereoselectively with deuterating agents. This hypothesis appears to us relatively unlikely, due to the results obtained in the synthesis of aminoalcohols **7a**/**7b**, where C_4H_9I and C_4H_9Br afford higher diastereoselectivities than the less reactive C_4H_9Cl.

We can alternatively assume that reductive lithiation of oxazolidine **1** occurs with racemization at the benzylic carbon atom, giving rise to a pair of rapidly interconverting diastereoisomeric organolithium intermediates **2a**/**2b**, one of which reacts preferentially and in a stereodefined way (either under retention or inversion of configuration) under appropriate reaction conditions (Scheme 4).[1,2]



1 — **7a** — **7b**

Scheme 3. Syntheses of diastereoisomeric alcohols **7a**/**7b**: i: 1. Li, THF, −20°C; 2. BuBr, then H_2O: **7a**/**7b** = >95:<5; ii: BuMgBr, THF, −20°C, then H_2O: **7a**/**7b** = 30:70.



Scheme 4. Epimerization and kinetic resolution of **2a**/**2b**.

Racemization is supported not only by the results of deuteration experiments, but also by the reaction mechanism commonly accepted for the reductive cleavage of benzylic carbon–oxygen bonds, which occurs via intermediate configurationally labile benzylic radicals.[17]

We propose that deuteriation of the rapidly equilibrating intermediates requires an activation energy lower than (or comparable to) the activation energy of their epimerization, whilst a relatively high activation energy can be hypothesized for the alkylation step. This assumption is supported by the low reactivity of the organolithium(s) toward C_4H_9Cl, which eventually renders a less stereospecific alkylation step. Indeed, it has been reported that activation barriers for retentive and inverse electrophilic attack at benzyllithiums should not differ very much.[18]

In summary, we have shown an additional useful feature of the reductive lithiation of 2-aryl-substituted oxygen heterocycles, i.e. the possibility to turn into intramolecular coordination and, as a consequence, into a highly diastereoselective reaction, the contemporary generation of a carbanionic and an oxyanionic center by a reductive cleavage procedure. Further work is in progress to extend the scope of this methodology.

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