

## Dilithiated Aminoalcohols as Homochiral Bases

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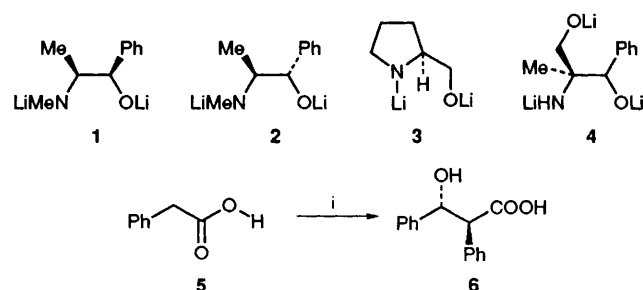
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The dilithium salts of (+)- or (–)-norephedrine effect the enantioselective and enantiodivergent deprotonation of *meso*-epoxide **17** in higher enantiomeric excess than previously reported.

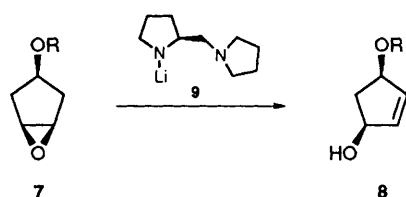
The reaction of a prochiral starting material with a homochiral lithium amide base has been used to generate chiral lithium enolate complexes which are useful for stereoselective alkylations, carboxylations and aldol condensations; they have also been applied to enantioselective structural rearrangements.<sup>1</sup>

A recent report detailing the use of homochiral alcoholates derived from *N*-methylephedrine and pseudoephedrine for enantioselective dehydrohalogenation<sup>2</sup> has prompted us to present our findings on a similar theme.

Some of the most successful chiral bases to date are those



**Scheme 1** Reagents and conditions: i) base (2 mol. equiv.), hexamethylphosphoric triamide, tetrahydrofuran,  $-110^{\circ}\text{C}$ , then  $\text{PhCHO}$ , 15 min



**Scheme 2**  $\text{R} = \text{Bu}^t\text{Me}_2\text{Si}$  or tetrahydropyran-2-yl

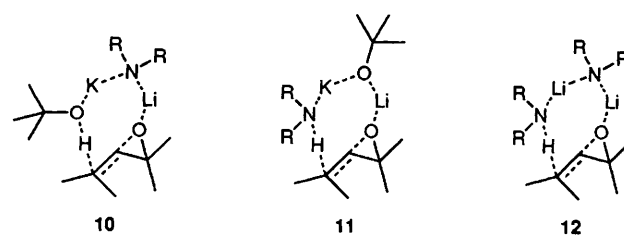
that create a highly ordered species at the point of deprotonation or create an aggregated intermediate which undergoes further enantioselective reactions. These bases suffer a severe disadvantage in that they are complex structures which require several synthetic steps, often giving low overall yield.<sup>1,3</sup> This fact, tied to the additional problem that stems from the ease of recyclability, can diminish the applicability of the methodology.

Mulzer<sup>4</sup> used di- and tri-lithiated aminoalcohols **1–4** to effect the aldol-type transformation of **5** to **6** (Scheme 1). The lowest enantiomeric excesses (e.e.s) were obtained using bases **1–3** (58, 31 and 31% e.e. respectively) and the best were obtained using base **4** (85% e.e.). The induction found in the process was explained in terms of association of the base to the enolate mediated by amido or alkoxide function, the increase in efficiency for base **4** being in some way due to the additional OLi anchor, which enhances the rigidity of the intermediate complex. Similar rationales have been suggested for many such systems.<sup>1</sup>

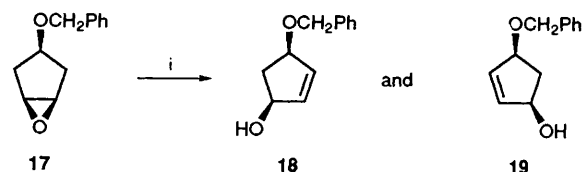
One problem that has been studied by several groups<sup>1,3</sup> is the conversion of *meso*-epoxides to homochiral allylic alcohols; for example, the rearrangement of the protected oxycyclopentane oxides **7** to allylic alcohols **8** using proline-derived bases such as **9** gave reproducible and reliable e.e.s of up to 76%<sup>3</sup> (Scheme 2).

Schlosser<sup>5</sup> reported that the rates of reaction for deprotonations of this type were considerably accelerated by the use of lithium amide bases in conjunction with potassium *tert*-butoxide (LIDAKOR reagent); indeed reactions that normally required forcing conditions (*i.e.* at reflux in tetrahydrofuran) were easily attained at sub-zero temperatures. He suggested that the potassium *tert*-butoxide was involved in the formation of a transition state of the type **10** or **11** and the reaction was accelerated *via* a push-pull mechanism. Moreover it has been observed<sup>2,3</sup> that such transformations are also best effected when a threefold excess of lithium amide base is employed [in our hands the transformation of **7** into **8** ( $\text{R} = \text{Bu}^t\text{Me}_2\text{Si}$  or  $\text{PhCH}_2\text{O}$ ) proceeds to completion over 3–5 h whilst warming from  $-70$  to  $-20^{\circ}\text{C}$  in the presence of 3 mol equiv. of lithium diisopropylamide (LDA)]. These observations suggest the intermediate **12** which incorporates 2 equiv. of lithium amide base and also that the product forms an aggregated structure in solution which consumes 1 equiv. of the lithium amide base (Scheme 3).

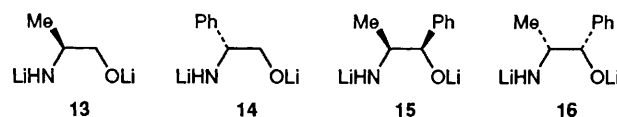
We thus reasoned that an ideal system for this reaction would have a self-contained alkoxide moiety and have



**Scheme 3**



**Scheme 4** Reagents and conditions: i) base (2 mol. equiv.),  $-78$  to  $0^{\circ}\text{C}$ , 16 h



**Table 1**

Entry	Base	Solvent <sup>a</sup>	Yield (%)	Ratio <sup>b</sup> <b>18:19</b>	E.e. (%) <sup>b</sup>
1	<b>13</b>	THF	40	50:50	0
2	<b>14</b>	THF	60	50:50	0
3	<b>15</b>	THF	91	07:93	86
4	<b>15</b>	$\text{C}_6\text{H}_6$ -THF <sup>c</sup>	98	10:90	80
5	<b>16</b>	THF	92	90:10	80
6	<b>16</b>	$\text{C}_6\text{H}_6$ -THF <sup>c</sup>	96	87:13	74
7	<b>1</b>	THF	51	43:57	14
8	<b>2</b>	THF	96	61:39	22

<sup>a</sup> Method: The aminoalcohols (1.5 mmol) were dissolved in the appropriate solvent (4 ml) and treated with 2 equiv. of *n*-butyllithium ( $0^{\circ}\text{C}$ ). The mixture was cooled ( $-78^{\circ}\text{C}$ ), **17** (0.5 mmol) in tetrahydrofuran (THF) (1 ml) was added and the mixture warmed slowly to  $0^{\circ}\text{C}$  over 16 h. <sup>b</sup> Determined using the method outlined in ref. 3a. <sup>c</sup> 3:1 (v/v).

attempted enantioselective deprotonations using dilithiated commercially available aminoalcohols **1**, **2** and **13–16**. These bases were applied to the enantioselective deprotonation of the *cis*-benzyloxycyclopentane oxide **17**<sup>†</sup> giving rise to the allylic alcohols **18** and **19** (Scheme 4, Table 1).

The simple aminoalcohols were unsuitable bases (entries 1 and 2) as they gave no asymmetric induction in the product, but there was an acceleration in reaction rate in line with the observations of Schlosser.<sup>5</sup> However treatment of **17** with the dilithiated salt of (1*R*,2*S*)-norephedrine **15** (entry 3) or (1*S*,2*R*)-norephedrine **16** (entry 5) resulted in the enantioselective and enantiodivergent transformation of **17** into **18** or **19** respectively. These two bases show greater than 90:10 selectivity for the deprotonation and effect the transformation in higher yields and at much lower temperatures than previously reported.<sup>3</sup> Use of benzene as co-solvent<sup>‡</sup> increased the temperature required for the reaction, owing to solubility

<sup>†</sup> Prepared (95% yield) by treatment of the corresponding epoxy-alcohol<sup>3</sup> with sodium hydride in tetrahydrofuran at  $0^{\circ}\text{C}$  followed by the addition of benzyl bromide.

<sup>‡</sup> Benzene was shown to be the most effective solvent in some of the previous work.<sup>2</sup>

problems; this had a marginal effect on the observed e.e. of the product (entries 4 and 6). The use of (1*R*,2*S*)-ephedrine **1** or (1*S*,2*S*)-pseudoephedrine **2** led to a drastic drop in e.e. for both bases (14 and 22% e.e. respectively). This effect was also apparent in the report by Mulzer;<sup>4</sup> in that the methyl substituent on the amide of bases **1–3** may be a hindrance to the formation of a stable and rigid intermediate complex, which in turn will result in diminished selectivity.

These results seem to suggest that it is the stereochemistry at C-1 in the aminoalcohols that has most effect on the stereochemical outcome of the reaction [*i.e.* 1*R* base stereochemistry leads to the 4*S* product **19** (entries 3, 4 and 7) and the 1*S* base stereochemistry leads to the 4*R* product **18** (entries 5, 6 and 8)]. This is also implied by the lack of any asymmetric induction observed using simple aminoalcohols (entries 1 and 2).

Whatever the mechanism involved in this process may be, these results are the best reported for a transformation of this type to date. This along with the commercial availability of the

bases, and their ease of use and re-isolation, suggests that these bases will be of considerable value in synthesis.

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