Dilithiated Aminoalcohols as Homochiral Bases

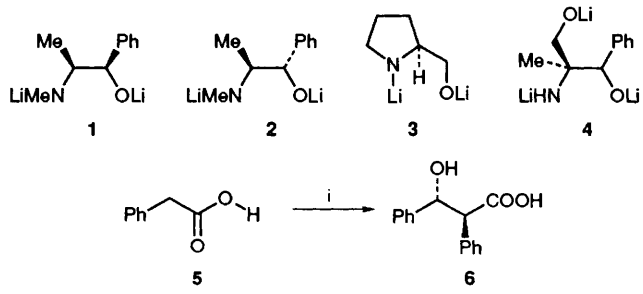
David Milne and Patrick J. Murphy*

Department of Chemistry, University of Wales, Bangor, Gwynedd, UK LL57 2UW

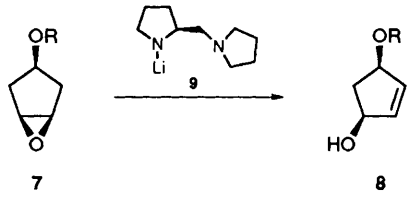
The dilithium salts of (+)- or (−)-norephidrine effect the enantioselective and enantiodivergent deprotonation of *meso*-epoxide **17** in higher enantiomeric excess than previously reported.

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.[1] A recent report detailing the use of homochiral alcoholates derived from *N*-methylephidrine and pseudoephedrine for enantioselective dehydrohalogenation[2] 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 °C, then PhCHO, 15 min



Scheme 2 R = Bu^tMe_2Si or tetrahydropyran-2-yl

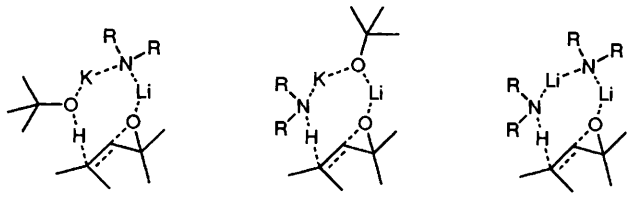
that create a highly ordered species at the point of deprotonation or create an aggregated intermediate which undergoes further enantioselective reactions. These bases suffer a severe disadvantage in that they are complex structures which require several synthetic steps, often giving low overall yield.[1,3]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

Mulzer[4] 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.[1]

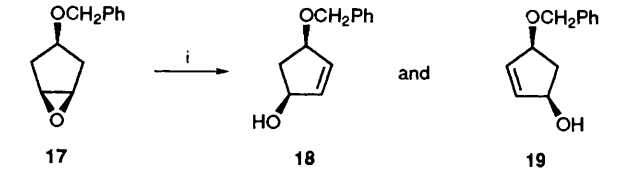
One problem that has been studied by several groups[1,3] is the conversion of *meso*-epoxides to homochiral allylic alcohols; for example, the rearrangement of the protected oxycyclopentane oxides **7** to allylic alcohols **8** using proline-derived bases such as **9** gave reproducible and reliable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

Schlosser[5] 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[2,3] 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** (R = Bu^tMe_2Si or $PhCH_2O$) proceeds to completion over 3–5 h whilst warming from −70 to −20 °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 °C, 16 h

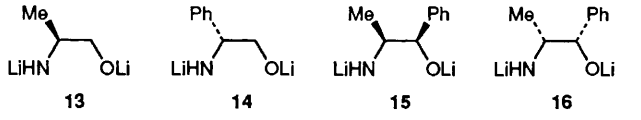


Table 1

Entry	Base	Solvent[a]	Yield (%)	Ratio[b] 18:19	E.e. (%)[b]
1	**13**	THF	40	50:50	0
2	**14**	THF	60	50:50	0
3	**15**	THF	91	07:93	86
4	**15**	C_6H_6–THF[c]	98	10:90	80
5	**16**	THF	92	90:10	80
6	**16**	C_6H_6–THF[c]	96	87:13	74
7	**1**	THF	51	43:57	14
8	**2**	THF	96	61:39	22

[a] Method: The aminoalcohols (1.5 mmol) were dissolved in the appropriate solvent (4 ml) and treated with 2 equiv. of n-butyllithium (0 °C). The mixture was cooled (−78 °C), **17** (0.5 mmol) in tetrahydrofuran (THF) (1 ml) was added and the mixture warmed slowly to 0 °C over 16 h. [b] Determined using the method outlined in ref. 3*a*. [c] 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**† 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.[5] 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.[3] Use of benzene as co-solvent‡ increased the temperature required for the reaction, owing to solubility

† Prepared (95% yield) by treatment of the corresponding epoxyalcohol[3] with sodium hydride in tetrahydrofuran at 0 °C followed by the addition of benzyl bromide.

‡ Benzene was shown to be the most effective solvent in some of the previous work.[2]

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;[4] 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 considerble value in synthesis.

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References

1 P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1.
2 J. Vadecard, J. C. Plaquevent, L. Duhamel and P. Duhamel, *J. Chem. Soc., Chem. Commun.*, 1993, **116**.
3 (*a*) S. K. Hendrie and J. Leonard, *Tetrahedron*, 1987, **43**, 3289; (*b*) M. Asami, *Tetrahedron Lett.*, 1985, **26**, 5803.
4 J. Mulzer, P. D. Lasalle, A. Chucholowski, U. Blaschek, G. Bruntrup, I. Jibril and G. Huttner, *Tetrahedron*, 1984, **40**, 2211.
5 A. Mordidi, E. Ben Rayana, C. Margot and M. Schlosser, *Tetrahedron*, 1990, **46**, 2401.