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A new norephedrine-derived chiral base for epoxide rearrangement reactions

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Abstract

The conversion of (1*R*,2*S*)-norephedrine into a novel chiral diamine (83% yield, simple two step synthesis) and its use as a chiral base in two epoxide rearrangement reactions is reported. Rearrangement of a 4,5-disubstituted cyclohexene oxide and of a 4-aminosubstituted cyclopentene oxide generated allylic alcohols of >90% ee. These results represent the highest levels of enantioselectivity reported to date for such substrates. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: diamines; epoxides; rearrangement; allylic alcohols.

For some time now, we[1,2] have been exploring the use of lithiated diamine (*R*)-**1**, introduced by Singh,[3] as a chiral base[4] for the enantioselective rearrangement of epoxides to allylic alcohols (Scheme 1). Diamine **1** is an attractive chiral reagent as it is easy to prepare and each enantiomer is available.[5–7] Sometimes, however, epoxide rearrangement using (*R*)-**1** proceeds with only modest enantioselectivity (e.g. cyclohexene oxide→cyclohexen-1-ol of 77% ee[3]). Because of this, Asami[8,9] and Andersson[10] have introduced structurally more complex diamines (e.g. **2** and **3**) for epoxide rearrangement reactions. Although these diamines can be used in sub-stoichiometric amounts (20 mol% typically) and produce allylic alcohols of >90% ee, the syntheses of the diamines are somewhat lengthy. In this paper we report that diamine (1*R*,2*S*)-**6**, readily prepared in just two simple steps from (1*R*,2*S*)-norephedrine, effects epoxide rearrangements with equally high enantioselectivity.

Diamine **6** was selected because of its structural similarity to Singh's diamine **1** and we imagined that it could be prepared from norephedrine (which is available in either enantiomeric form) via our dialkylation route.[5,6] Thus, treatment of (1*R*,2*S*)-norephedrine with 1,4-dibromobutane, tetra-*n*-butylammonium iodide and sodium carbonate in refluxing THF for 48 h gave known[11] amino alcohol **4** which was used directly in the next step. Mesylation of crude **4** (in THF) followed by reaction with aqueous methylamine generated the novel diamine (1*R*,2*S*)-**6** {$[\alpha]_D$ −22.6 (*c* 1.0 in $CHCl_3$)}[12] in 83% yield from (1*R*,2*S*)-norephedrine (Scheme 1). Diamine (1*R*,2*S*)-**6** was obtained as a single

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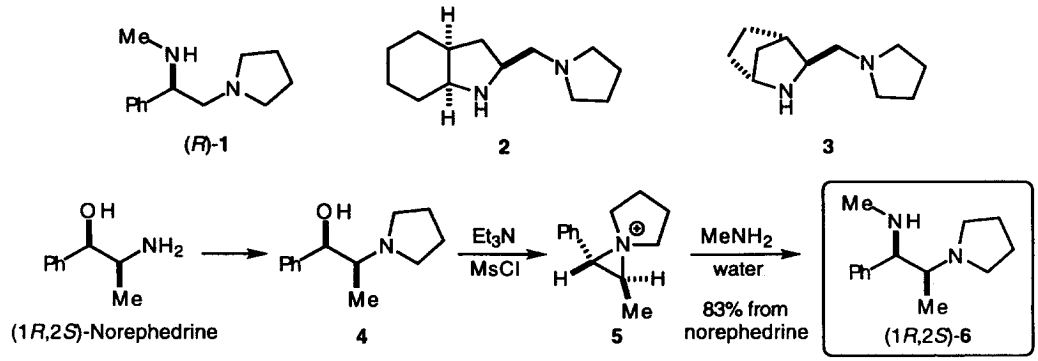
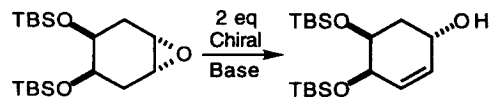


Scheme 1.

diastereoisomer and regioisomer via preferential opening of the aziridinium ion **5** at the benzylic position. This is consistent with our previous work[5,6] and with Dieter's work[13] on the preparation of diamines from ephedrine derivatives.

To compare diamine (1*R*,2*S*)-**6** with Singh's diamine (*R*)-**1**, we have investigated two[14] representative examples: rearrangement of *meso*-epoxides *trans*-**7** and *cis*-**9** (*R*=benzamide and trifluoroacetamide) under our standard conditions.[1,2] The results (Schemes 2 and 3) indicate that the new chiral diamine (1*R*,2*S*)-**6** outperforms Singh's diamine (*R*)-**1** in terms of enantioselectivity. Using the new chiral base, rearrangement of epoxide *trans*-**7** generated (1*S*,4*R*,5*S*)-**8** of 94% ee, a compound which we are currently using to synthesise conduritols and related derivatives. Furthermore, we have also used the new chiral base to prepare (1*S*,4*R*)-**10** of 88–92% ee, compounds which are useful for the synthesis of carbocyclic nucleoside analogues.[2]



trans-7 (1*S*,4*R*,5*S*)-8

Chiral Base†	Yield (%)	ee (%)
(*R*)-1, BuLi	71	76
(1*R*,2*S*)-6, BuLi	94	94

† *Reaction conditions:* Chiral base, THF, 0 °C → rt over 4 hours then12 hours at rt

Scheme 2.

Using diamine (1*R*,2*S*)-**4**, which can be easily synthesised (in each enantiomeric form) from commercially available norephedrine, we can prepare synthetically useful allylic alcohols such as (1*S*,4*R*,5*S*)-**6** and (1*S*,4*R*)-**8** in >90% ee. These results represent the highest levels of enantioselectivity reported to date for such substrates and it is likely that the new chiral base will have many other applications in asymmetric synthesis.

Acknowledgements

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cis-**9** (1*S*,4*R*)-**10**

Chiral Base†	R	Yield (%)	ee (%)
(*R*)-**1**, BuLi	COPh	73	60
(1*R*,2*S*)-**6**, BuLi	COPh	51	92
(*R*)-**1**, BuLi	$COCF_3$	52	46
(1*R*,2*S*)-**6**, BuLi	$COCF_3$	73	88

Scheme 3. † Reaction conditions: chiral base, THF, 0°C→rt over 4 hours then 12 hours at rt

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