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Synthesis and enantioselective rearrangement of *meso*-aziridino cyclohexene oxides

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Abstract

Stereoselective routes to *N*-Ph_2PO-protected *cis* and *trans meso*-aziridino cyclohexene oxides have been developed. Enantioselective rearrangement of the *cis* epoxide with chiral bases gave the allylic alcohol in a maximum of 47% ee whilst that of the *trans* epoxide proceeded with enantioselectivity of up to 68% ee. Both these results demonstrate for the first time that chiral bases which smoothly rearrange epoxides to allylic alcohols do not react with *N*-Ph_2PO-protected aziridines.

Keywords: aziridines; epoxides; rearrangement; allylic alcohols.

The rearrangement of *meso*-epoxides to enantiomerically enriched allylic alcohols using chiral lithium amide bases is well-known.[1,2] In contrast, lithium amide bases have never been used to convert aziridines into allylic amines[3] although such an enantioselective rearrangement can be carried out using vitamin B_{12}.[4] As part of our continuing programme of research into the rearrangement of *meso* epoxides using chiral bases,[5–7] we decided to synthesise and rearrange aziridino cyclohexene oxides such as *cis*- and *trans*-**2**. In addition, this would allow us to probe whether it was possible to rearrange an aziridine to an allylic amine using chiral bases. Alternatively, if the aziridine was inert to the reaction conditions as we suspected[8] then the allylic alcohols **3** and **4** thus obtained would be highly functionalised building blocks for use in synthesis. Herein, we describe the stereoselective synthesis (from **1**) of each of epoxides *cis*- and *trans*-**2** and their subsequent enantioselective rearrangement to allylic alcohols **3** and **4**, respectively, (Scheme 1).

The diphenylphosphinoyl *N*-protecting group, originally introduced by Ramage[9] and made popular recently by Sweeney,[10] was chosen as it enabled the epoxidation reactions to proceed uneventfully in a stereodivergent manner under different conditions and it rendered the aziridine inert under the lithium amide base conditions (vide infra). In contrast, the epoxidation reactions failed when carbamates or amides were used as the *N*-protecting group and the rearrangement reactions proceeded with significant decomposition of starting aziridino epoxide when a *N*-tosyl protecting group was employed.

Aziridino alkene **1** was prepared following the procedure of Paquette et al.:[11] we obtained a 40% yield of **1** over three steps from 1,4-cyclohexadiene (Scheme 2). Next, the alkene in **1** was epoxidised under

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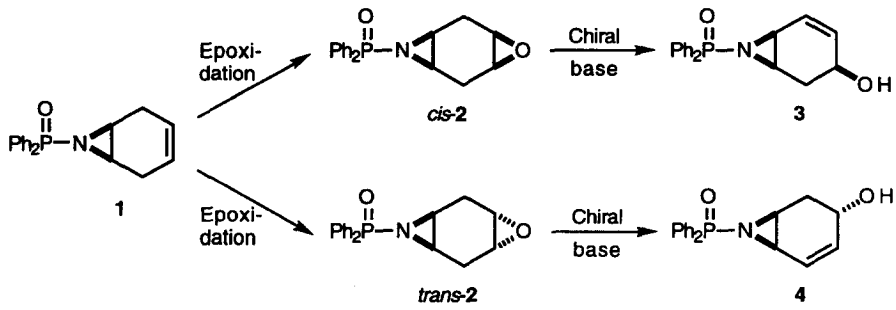
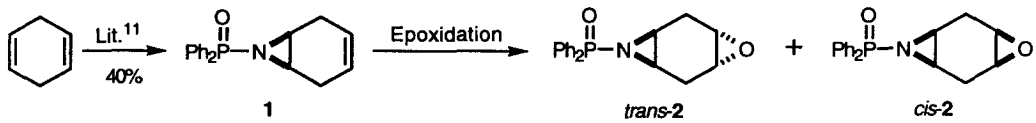


Scheme 1.

different conditions and the stereoselectivity assessed from the ^{1}H NMR spectrum of the crude reaction mixtures. The results obtained using *m*-CPBA in dichloromethane and methyl(trifluoromethyl)dioxirane (generated in situ using the procedure of Yang et al.[12]) are shown below and the relative stereochemistry was assigned by an independent and unambiguous synthesis of epoxide *trans*-**2** (vide infra).

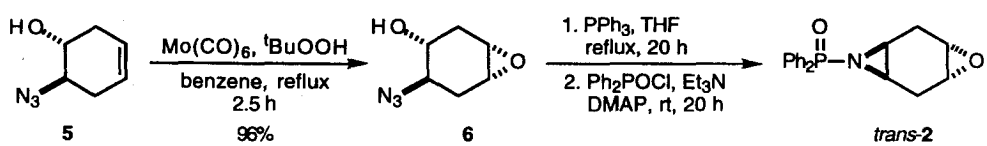


Epoxidation conditions	*trans* : *cis*	Yield of *trans*-**2** (%)	Yield of *cis*-**2** (%)
m-CPBA, $NaHCO_3$ CH_2Cl_2, rt, 14 h	10 : 90	9	81
Oxone®, trifluoroacetone, Na_2EDTA, $NaHCO_3$, MeCN-water, 0 °C, 1.5 h	64 : 36	56	31

Scheme 2.

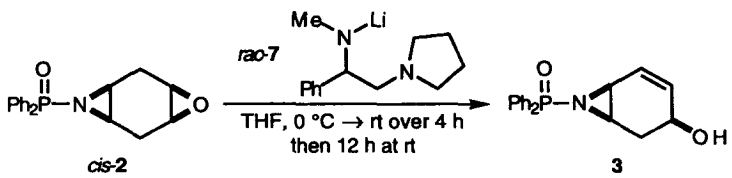
Epoxidation of aziridino alkene **1** with *m*-CPBA in dichloromethane generated a 90:10 mixture of *cis*- and *trans*-**2** from which we were able to isolate an 81% yield of pure *cis*-**2** after column chromatography. In contrast, epoxidation using an in situ generated dioxirane gave a *trans* selective reaction (64:36 mixture of *trans*- and *cis*-**2**; 56% isolated yield of epoxide *trans*-**2**). To rationalise the observed stereoselectivity, we suggest that the diphenylphosphinoyl group hydrogen bonds to *m*-CPBA leading to *cis* selectivity whereas hydrogen bonding is not possible with the dioxirane.[13,14] In this case, steric effects dominate and *trans* selectivity is observed. A similar trend is observed with the *N*-tosyl aziridino alkene[13] and some structurally similar cyclopropane-substituted cyclohexenes show similar *trans* selectivity upon epoxidation.[15]

As shown in Scheme 3, we have also prepared epoxide *trans*-**2** from known[16] epoxide **6** (prepared via a transition metal *cis*-directed epoxidation of azido alcohol **5**[17]). Thus, Staudinger reaction[18] of the azido alcohol in **6** followed by *N*-protection afforded epoxide *trans*-**2** which was identical by ^{1}H and ^{13}C NMR spectroscopy to the minor product obtained from *m*-CPBA epoxidation of alkene **1**.



Scheme 3.

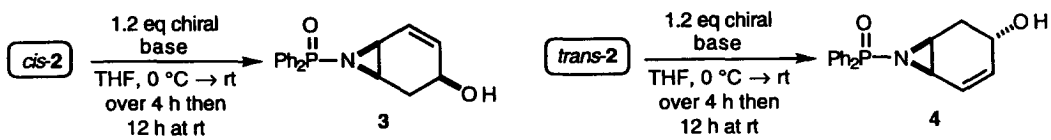
With stereoselective routes to each of aziridino epoxides *cis*- and *trans*-**2** in hand, we were now ready to study their lithium amide-mediated rearrangement to allylic alcohols. Since it was easier to prepare larger quantities of epoxide *cis*-**2**, initial rearrangement reactions were carried out on this substrate (Scheme 4). The reaction was optimised by reacting epoxide *cis*-**2** with different amounts (1.0–2.0 molar equivalents) of racemic lithium amide base **7** under our standard conditions.[5–7] The highest yield of allylic alcohol *rac*-**3**[19] (62%) was obtained with 1.2 equivalents of the lithium amide base and quenching the reaction with aqueous ammonium chloride.[20] Lower yields were obtained with more or less base: if 1.0 equivalent of lithium amide was used, the reaction did not go to completion (34% starting material was isolated) and if 2.0 equivalents (our generally preferred conditions[7]) were used, we presume that decomposition of the aziridine (via α-lithiation) by the excess base occurs. Use of 1.2 equivalents of lithium amide **7** (the optimised conditions) with epoxide *trans*-**2** generated allylic alcohol *rac*-**4** in 72% yield. Clearly, *N*-diphenylphosphinoyl protected aziridines do not rearrange to any significant extent (if at all) under treatment with lithium amide bases at room temperature.



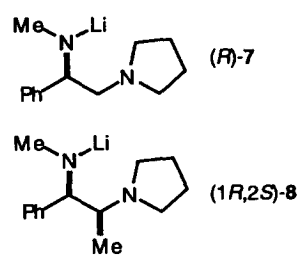
Equiv of *rac*-7	Yield of 3 (%)
1.0	46
1.2	62
1.5	32
2.0	42

Scheme 4.

The rearrangement of epoxides *cis*- and *trans*-**2** using chiral bases (*R*)-**7** and (1*R*,2*S*)-**8** have also been studied and the results are shown in Scheme 5. In this way, allylic alcohol **3** of 47% ee and allylic alcohol **4** of 68% ee were obtained. The enantiomeric excess of **3** was determined by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol[21] whilst that of **4** was measured by making diastereomeric Mosher's esters.[22] The preparation of the Mosher's esters from **4** has also allowed us to assign the absolute stereochemistry to **3** and **4** as that shown below.[23,24] Epoxide *trans*-**2** rearranged with higher enantioselectivity than *cis*-**2** and, although a better enantioselectivity was obtained using our new chiral base (1*R*,2*S*)-**8**[7] with epoxide *trans*-**2**, the opposite trend was observed with epoxide *cis*-**2**.



SM	Chiral Base	Prod	Yield (%)	ee (%)
cis-2	(*R*)-7	3	55	47
cis-2	(1*R*,2*S*)-8	3	60	25
trans-2	(*R*)-7	4	62	58
trans-2	(1*R*,2*S*)-8	4	82	68



Scheme 5.

In conclusion, stereoselective routes to each of the aziridino epoxides *cis*- and *trans*-**2** and conditions for their enantioselective rearrangement to allylic alcohols **3** (47% ee) and **4** (68% ee), respectively, have

been developed. The present research indicates that epoxides rearrange faster than aziridines using chiral lithium amides and that aziridines are compatible with chiral bases at room temperature.

Acknowledgements

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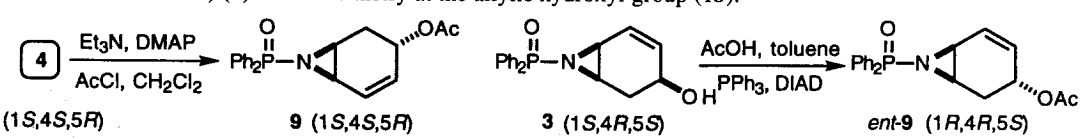

(1*S*,4*S*,5*R*) **9** (1*S*,4*S*,5*R*) **3** (1*S*,4*R*,5*S*) *ent*-**9** (1*R*,4*R*,5*S*)