COVER FEATURE

Dr Peter O'Brien*

Recipient of one of the 1999 RSC Meldola medals

Career

Peter O'Brien was born in South Manchester in 1970 and went on to study Natural Sciences at the University of Cambridge. He graduated in 1992 and remained in Cambridge carrying out a PhD on *enantio- and diastereoselective reactions with phosphine oxides* under the supervision of Dr Stuart Warren. After the award of his PhD in 1995, he moved to The University of York as a Royal Commission for the Exhibition of 1851 Research Fellow.

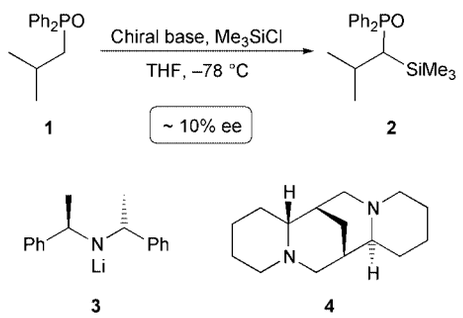
In March 1996, just a few months into the fellowship and carrying on the tradition of Warren group members embarking on an academic career, O'Brien was appointed as a lecturer in organic chemistry at The University of York. In 1999, he was awarded one of the Royal Society of Chemistry's Meldola medals and prizes and in 2000, he received a GlaxoWellcome award for innovative organic chemistry.

Research

Chirality is all around us—in the macroscopic world (see the Whirpool spiral galaxy on the front cover) and at the molecular level. My research motivation is to develop new methods for the synthesis of single enantiomers of chiral molecules.

The beginnings of the ongoing research in my group, affectionately known in York as the "POB group", can be found in a 1996 *Synlett* paper I published with Stuart Warren on some aspects of my PhD work.[1] In that communication, among other things, we describe our unsuccessful attempts at using chiral bases to transform prochiral phosphine oxide **1** into silyl phosphine oxide **2**. Two chiral base systems were explored: chiral lithium amide bases such as **3** and alkyllithiums complexed by the chiral diamine sparteine **4** and both systems gave essentially no enantioselectivity (Scheme 1).

* Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: paob1@york.ac.uk

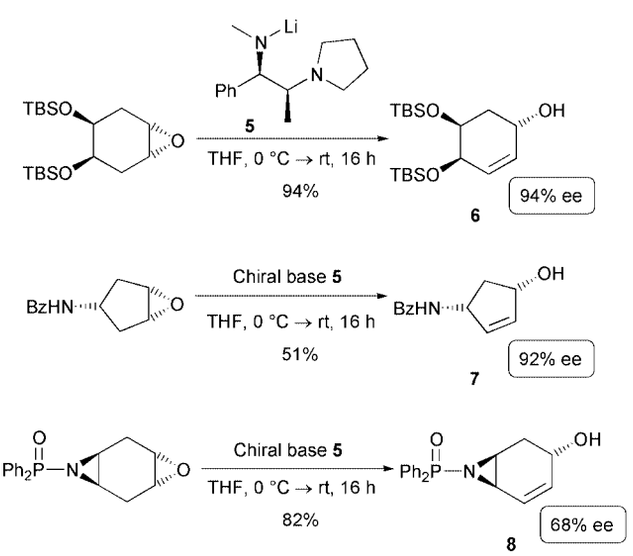


Scheme 1 Attempted asymmetric functionalisation of a prochiral phosphine oxide.

On reflection, although my attempts at carrying out the reaction shown in Scheme 1 with chiral bases were hopeless, this research fostered my interest in chiral base chemistry. Currently, my research group is involved in studying different aspects of the two fundamentally different types of chiral base reagents exemplified by lithium amide **3** and alkyllithium–sparteine **4**.

Enantioselective epoxide rearrangement reactions

The first ever example of the use of chiral lithium amide bases was the rearrangement of an epoxide to an allylic alcohol, reported in 1980. I felt that the scope of this process could be extended by carrying out the rearrangement on more highly functionalised *meso*-epoxides—in that way, more elaborate chiral allylic alcohols for use in synthesis could be generated. Some of our highlights, all of which we reported for the first time, are shown in Scheme 2.



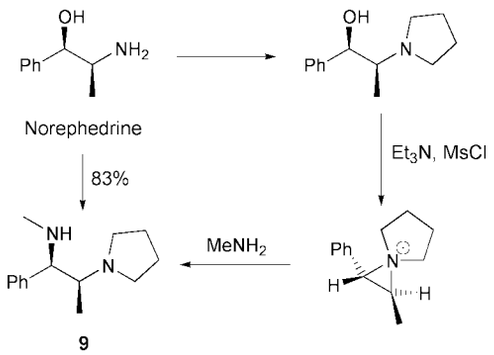
Scheme 2 Enantioselective epoxide rearrangement reactions.

Using the novel chiral base **5**, derived from norephedrine in an easy two-step synthesis (*vide infra*), chiral allylic alcohols **6**–**8** have been prepared in good to high enantiomeric excess.[2–4] Allylic alcohol **6** has been used to prepare conduritol F and amino alcohol **7** is a useful precursor to carbocyclic nucleoside

DOI: 10.1039/b007422p

analogues. The successful synthesis of aziridino allylic alcohol **8** demonstrated that aziridines do not rearrange under these conditions.

Crucial to the synthetic usefulness of our chiral base methodology was the availability of chiral diamines. Thus one of the first things we did was to develop a simple, one-pot synthesis of chiral diamines[5] which led to these diamines now being commercially available. In addition, this methodology was subsequently applied to the preparation of diamine **9**,[2] the precursor to chiral base **5** (Scheme 3).



Scheme 3 Simple synthesis of chiral diamines *via* aziridinium ions.

The preparation of diamine **9** starts from norephedrine, commercially available in both enantiomeric forms. Dialkylation with 1,4-dibromobutane followed, without any purification, by mesylation led to the formation of an aziridinium ion which reacted regiospecifically at the benzylic position to afford diamine **9**. This two-step synthesis proceeded in 83% yield on a multi-gram scale.

Starting out with the simple idea of extending the scope of the epoxide rearrangement chemistry, the research in my group has also evolved into a number of new and interesting areas. For example, we have looked at stereoselective epoxidation reactions,[6] aziridinium ion chemistry,[5] asymmetric aminohydroxylation[7] and target synthesis.[8]

In search of the enantiomer of sparteine

Sparteine **4** is a naturally occurring chiral diamine that is particularly good at chelating to lithium and has found widespread use as a chiral ligand in asymmetric synthesis. However, only one enantiomer of sparteine is commercially available and this is a significant limitation. Three years ago, I initiated a programme of research aimed at synthesising sparteine-like diamines that would function as the enantiomer of sparteine. I have tried to capture the rationale of our design of sparteine-like diamine **10** in Fig. 1.

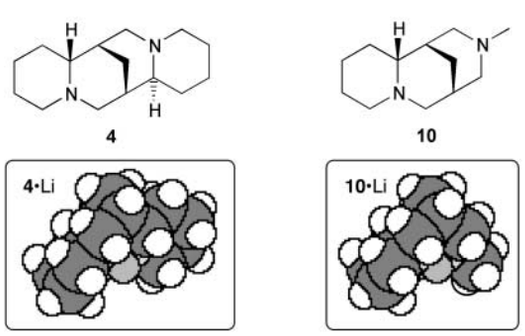
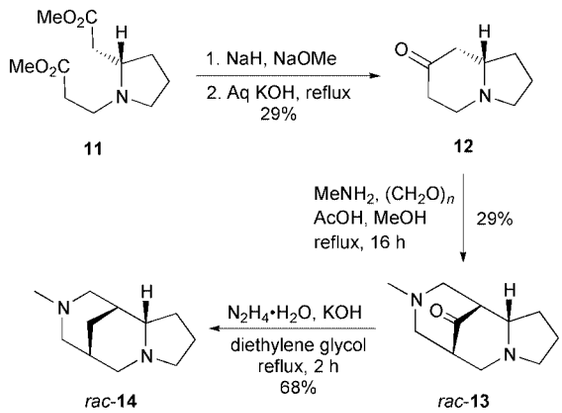


Fig. 1 Designing a sparteine-like diamine.

Space-filling models of sparteine **4** and diamine **10** complexed to lithium are shown in Fig. 1. The similarity of the chiral environment around the lithium in these two complexes is strikingly similar. Thus, we speculated that one of the rings of sparteine is superfluous and that diamines like **10** would function as sparteine surrogates and be easier to synthesise. Most importantly of all, if we could prepare the enantiomers of diamines like **10** then we could address the limitation of sparteine. Our first approach to the synthesis of the enantiomer of a diamine like **10** is shown in Scheme 4.



Scheme 4 Synthesis of *ent*-sparteine analogue **14**.

To prepare diamine **14**, a five-ring relative of the enantiomer of diamine **10**, (*S*)-proline was converted into diester **11**. Then, a Dieckmann condensation gave ketone **12** in high enantiomeric excess. However, when we carried out a double Mannich reaction to give tricyclic ketone **13**, complete racemisation was observed under the acidic conditions used. Retro-Michael or retro-Mannich reactions can be invoked to explain this racemisation. We did complete the synthesis of diamine **14** albeit in racemic form using a Wolff–Kishner reduction as the last step.[9]

We have also investigated two routes to sparteine-like diamines that avoid the use of the troublesome double Mannich reaction.[10] However, it has not proved possible to render either of these syntheses asymmetric. Other ways of preparing enantiomerically pure diamines like **10** and **14** are currently being looked at and our endeavours at solving the racemisation problem will form the basis of future research papers.

Acknowledgements

All of the above described research has been carried out by talented and dedicated researchers whose names appear in the list of references. I thank them for all their efforts.

References

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