Dr Jonathan Clayden *

Recipient of one of the RSC Meldola medals

1 PERKIN

Career

Jonathan Clayden was born in Kampala, Uganda in 1968 and grew up on the east coast of England. After gaining a degree in Natural Sciences at the University of Cambridge, he remained in Cambridge to conduct research on enantioselective synthesis using phosphine oxides under the supervision of Dr Stuart Warren. In 1993 he received his PhD and moved to the École Normale Supérieure in Paris as a Royal Society Western European Research Fellow, where he joined the research group of Professor Marc Julia.

In September 1994 he moved to his current post as a Lecturer in Organic Chemistry at the University of Manchester, where he began a research programme investigating rotational restriction as a means of controlling stereochemistry. In 1998 he won one of the Royal Society of Chemistry's Meldola Medals, awarded to a British chemist under the age of 30 for original published work, and also in 1998 a Glaxo-Wellcome Award for Innovative Organic Chemistry. His research interests include stereoselective and asymmetric synthesis, using rotational restriction to control stereochemistry, design and synthesis of atropisomeric ligands for asymmetric catalysis, and the stereochemistry and reactions of amide-stabilised organolithiums.

Research

Our work with rotational restriction [1] began right at the start of my time in Manchester. At that stage, there were a number of reports of resolvable axially chiral aromatic amides of the general type **1**, but no reports of their application to synthetic and stereochemical problems.[2] Our first aim was to discover whether the steric bias offered by the perpendicular amide system shown in **2** would be sufficient to influence the direction of attack of reagents approaching the aromatic ring. This turned out to be the case—we have now found several classes of nucleophiles that attack ring substituents to create new stereogenic centres

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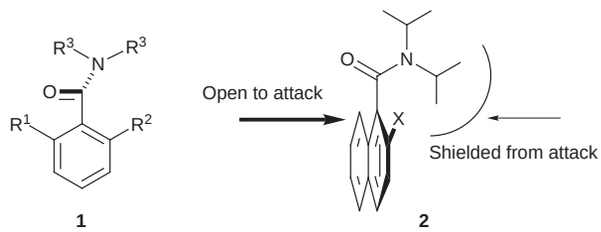
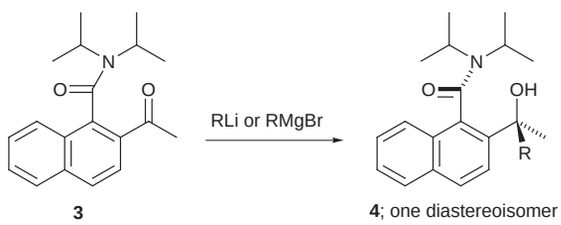


1 **2**

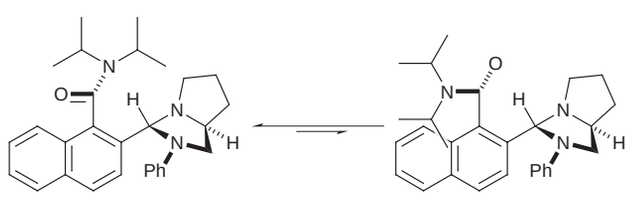
with excellent levels of stereocontrol: the conversion of **3** to **4** is just one example (Scheme 1).[3] We also found that deprotonation of alkyl groups attached to the ring was highly stereoselective,[4] and gives configurationally stable organolithiums that react stereospecifically with electrophiles.[5]



3 **4**; one diastereoisomer

Scheme 1

This work showed us that the amide system could do the sort of thing we knew was already possible with other highly sterically biased systems containing stereogenic centres, rather than axes, and in that sense was not fundamentally conceptually novel. But out of it came an approach to stereocontrol which does not have a counterpart in the use of stereogenic centres. We found that certain compounds containing a stereogenic centre *ortho* to the amide system adopted preferentially one of the two possible diastereoisomeric conformations about the Ar–CO bond. In some cases—for example, the atropisomeric diastereoisomers **5a** and **5b**—this preference was so strong that the less thermodynamically stable atropisomer was very hard to isolate, and the equilibrium ratio of **5a**:**5b** was of the order of 95:5. Fig. 1 shows the X-ray crystal structure of **5a**.



5a **5b**

This has important consequences, because it means that the stereogenic centre has a remarkably powerful influence on the preferred conformation of the amide, providing the opportunity for a means of controlling conformation using adjacent stereogenic centres as "auxiliaries". We reasoned that if this is true of naphthamides, it ought to be true of benzamides too. NMR confirmed that we were right: the conformers of benzamides interconvert too fast to be atropisomers, but slowly enough to be detectable in the NMR spectrum. The NMR spectrum of **6** shows one main set of peaks for the *syn*-conformer shown, with a smaller set accounting for about 13% of the total, which we assign to the *anti*-conformer.

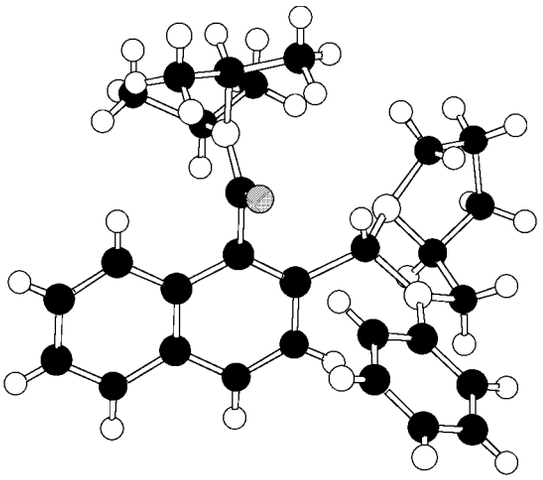
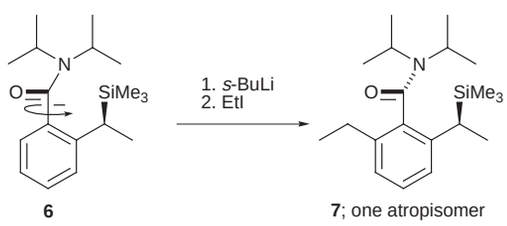


Fig. 1

To be of any value to us, these conformers need trapping as atropisomers. This can be done using Snieckus' lithiation chemistry,[6] and allows us to turn a conformational preference into a diastereoselective reaction. Ethylation of the ortholithiated **6** gives essentially a single diastereoisomeric atropisomer of **7** (Scheme 2).



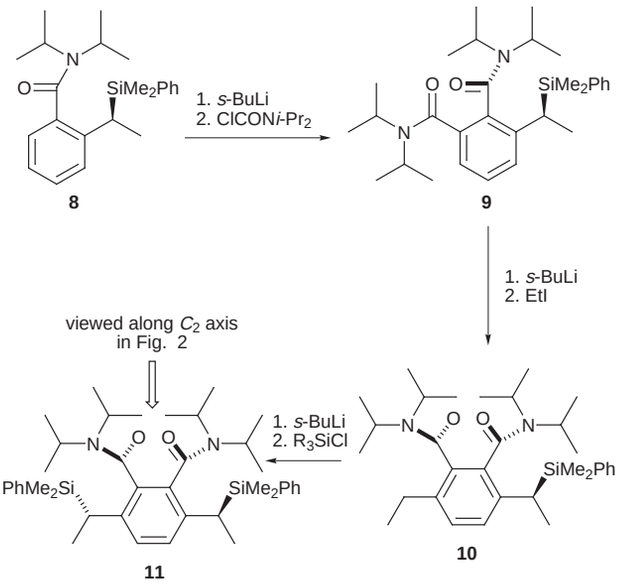
Scheme 2

This is stereochemical information transfer from stereogenic centre to stereogenic axis: since we know that we can use the axis to control new stereogenic centres, we have a means of using rotational restriction to relay stereochemical information across a molecule. Our greatest success to date in this developing area has been to make a compound **11** carrying *para* related stereogenic centres by a series of lithiation reactions. Stereochemistry is passed from the centre in the starting material **8** to one of the axes of **9**, which has a knock-on effect on a second axis (the two amides place their NR_2 groups as far apart as possible) when **10** is formed as a single atropisomer (Scheme 3). Finally, this second axis controls the second stereogenic centre of **11**: the crystal structure (Fig. 2 and front cover) beautifully shows the C_2-axis of symmetry.[7] Stereochemical information is transferred "mechanically" around the ring, and currently we are aiming to extend this type of stereocontrol further around rings, across fused polycycles, and even in flexible acyclic systems.

Such "clockwork" in amides (see front cover) is quite general. We have recently found evidence that even in quite ordinary tertiary aromatic amides bond rotations are concerted. Racemisation of **12**, for example, occurs almost solely by a one-step process involving a concerted rotation about the Ar–CO and N–CO bonds.[8] Our current targets include application of rotationally restricted relay groups to the synthesis of some biologically active compounds, along with the development of new enantiomerically pure ligands for catalytic asymmetric synthesis.

Cover picture

The cover picture shows the X-ray crystal structure of **11** along with the *Ecclesiastical Computer* of Jean Baptiste-Sosime



Scheme 3

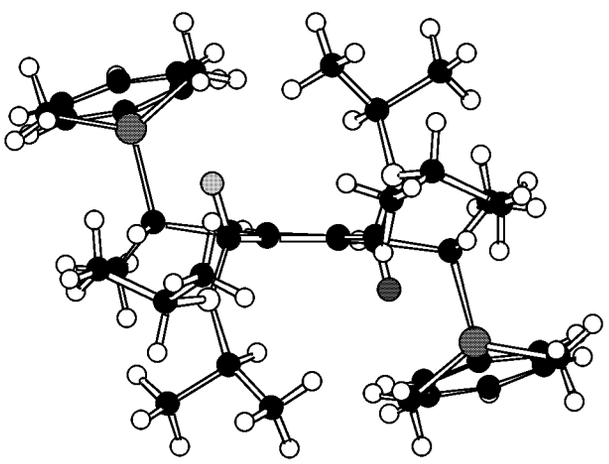
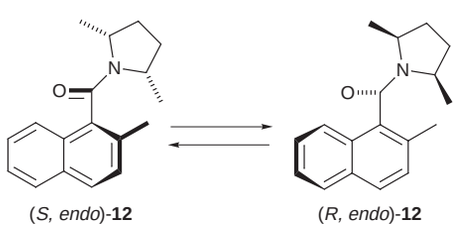


Fig. 2



Schwilgué's 1788 clock in Strasbourg Cathedral. Schwilgué's clockwork masterpiece calculates, among other things, the date of Easter each year. It will take into account the fact that 2000 is a leap year while 1900 was not, and has a mechanism due to operate in the years 5182 and 8782 to ensure the necessary omission of a leap year every 3600 years after the introduction of the Gregorian calendar.

References

1 For a more detailed account, see J. Clayden, *Synlett*, 1998, 810.
2 J. Clayden, *Angew. Chem., Int. Ed. Engl.*, 1997, **35**, 949.
3 J. Clayden, N. Westlund and F. X. Wilson, *Tetrahedron Lett.*, 1996, **37**, 5577.
4 J. Clayden and J. H. Pink, *Tetrahedron Lett.*, 1997, **38**, 2561.
5 J. Clayden and J. H. Pink, *Tetrahedron Lett.*, 1997, **38**, 2565.
6 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
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