Dr Stephen Marsden *

Recipient of the Meldola Medal and Award

COVER FEATURE
PERKIN 1

Career

Steve Marsden was born in 1969 in Bury, Greater Manchester. He received his first degree from Imperial College in 1990, and remained there to study for his PhD under the guidance of Professor Steven Ley, FRS. His postgraduate work concerned synthetic approaches to the important immunosuppressive agent rapamycin. Following the award of his PhD in 1993, he spent a year as an SERC (now EPSRC) NATO post-doctoral fellow, working with Professor Samuel Danishefsky at Columbia University, New York. His research here focused on the development of a novel and efficient approach to the hexahydropyrroloindole alkaloids amauromine and 5-*N*-acetylardeemin. He was also introduced to carbohydrate chemistry and completed the synthesis of the Lewis X antigenic determinant in glycal form. In 1994, he returned to Imperial College to take up a lectureship in organic chemistry. He was the recipient of a Glaxo Wellcome Award for Innovative Organic Chemistry in 1996.

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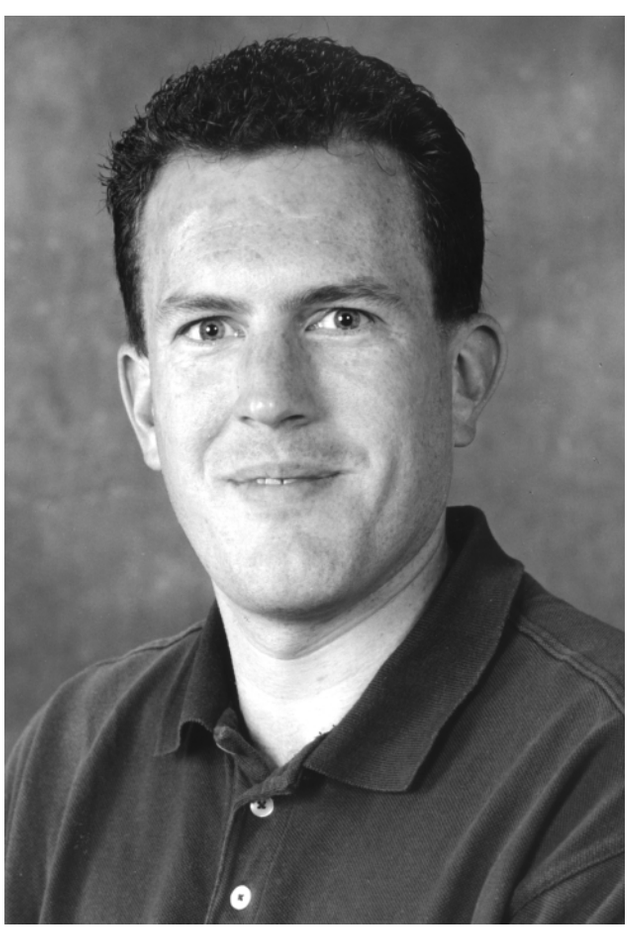
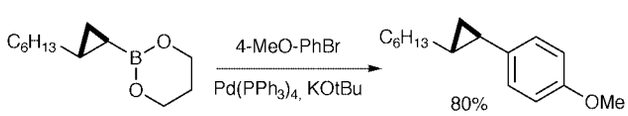


Research

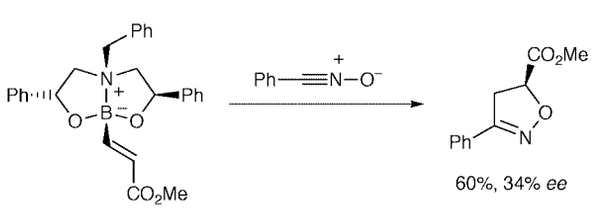
Research in our group is chiefly concerned with the development of methods for the control of relative and absolute stereochemistry, with particular relevance to structural motifs found in biologically active molecules. In the course of solving such problems, we have frequently relied upon main group chemistries, and in particular those of boron and silicon.

An early synthetic goal was a general method for the stereocontrolled *convergent* synthesis of cyclopropanes. Most asymmetric approaches to cyclopropane synthesis rely upon the elaboration of a stereochemically defined olefin with a suitable carbenoid or equivalent, and are limited structurally by the requirements for directing functionality on the olefin, or stabilising functionality on the carbenic partner. We noted that some success had been observed in the asymmetric cyclopropanation of vinyl boronate esters derived from tartramides, and realised that the boron might act as a handle for the formation of a new C–C bond through Suzuki reactions with aryl and alkenyl halides. Although alkyl boronates are particularly reluctant to participate in Suzuki reactions, we were hopeful that the unique hybridisation of cyclopropanes would endow them with sufficient 'alkene-like' reactivity to function as workable nucleophiles in these reactions, and indeed this is the case (Scheme 1).[1]



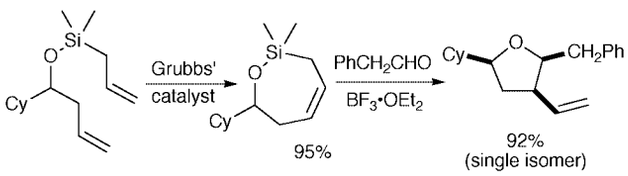
Scheme 1

The ease of attachment of heteroatom ligands to boronates, coupled with the synthetic versatility of the C–B bond encouraged us that chiral vinyl boronates would prove useful intermediates in asymmetric synthesis. Previous workers in the area had observed only limited stereocontrol in cycloaddition reactions using chiral diols as ligands, the problem presumably being that the planar geometry at boron ensures that there is a large distance between the site of reaction (the olefin) and the asymmetric centres in the ligand. By employing as ligands diols bearing a Lewis basic nitrogen atom, we sought to change the hybridisation at boron from sp^2 to sp^3, and in so doing bring the site of reaction closer to the chiral auxiliary. These dioxazaborocines have proven useful in asymmetric dipolar cycloadditions (Scheme 2)[2] and organometallic addition reactions, and the readily available ligands are simple to recover.



Scheme 2

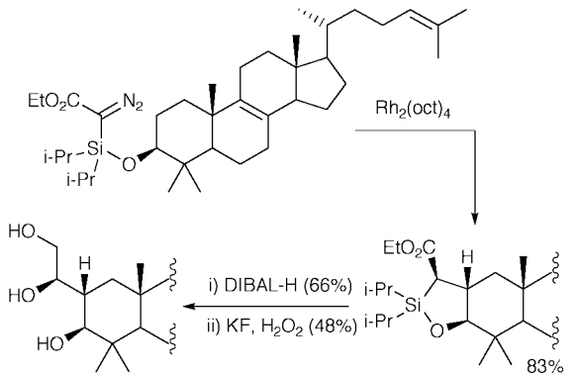
Organosilicon chemistry is now a mainstay of synthetic organic chemistry. We have sought to develop practical new methods for the elaboration of functionalised organosilicon compounds. One important development was the synthesis of functionalised allylsilanes by the ring closing metathesis of allyl silyl ethers of unsaturated alcohols.[3] Many of the existing methods for allylsilane synthesis involve strongly basic and/or nucleophilic conditions, and hence the development of such a mild and functional group tolerant method is of considerable utility. The resulting cyclic allylsiloxanes are useful nucleophiles, and undergo condensation with acetals or aldehydes under Lewis acid catalysis to form trisubstituted tetrahydrofurans with a high degree of stereocontrol (Scheme 3).



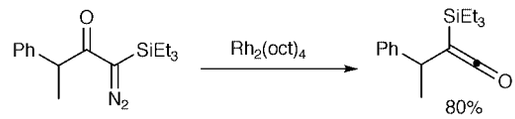
Scheme 3

Silylated diazocarbonyl compounds have been known since the 1960's, but have received surprisingly little attention from organic chemists. We have investigated the interaction of these species with dirhodium tetracarboxylate catalysts, and have harnessed the C–H insertion chemistry of the resulting carbenoids to form silylated γ-lactones[4] and oxasilacyclopentanes (Scheme 4).[5] In the latter examples, the silicon not only acts as a tether to link the substrate undergoing insertion to commercially available diazoacetates, but also forms a masked hydroxy group which can be liberated by Fleming–Tamao oxidation. This leads to a useful stereocontrolled elaboration of alcohols to 1,2,4-triols by the formal insertion of an hydroxycarbene equivalent to the carbon backbone.

Silyl diazoketones do not undergo such reactions; rather, we have found that they instead suffer a rapid and efficient rearrangement to give stable, isolable silyl ketenes (Scheme 5).[6] This is not only a general and practical synthesis of these useful intermediates, but is also a rare example of a rhodium mediated Wolff rearrangement. We are currently investigating the applications of all aspects of silyl diazocarbonyl chemistry to the development of new linking technologies for solid phase organic synthesis.



Scheme 4



Scheme 5

Current research in the group is not only building on our findings in the above areas, but is also encompassing the chemistry of α-silyl anions, asymmetric organophosphorus chemistry, tin free methods for radical generation and the application of these methods to target synthesis. We also have a longstanding collaboration with Professor Bill Griffith of this department concerning the development of clean oxidation processes,[7,8] and the synthesis of hybrid metal-organic polymers.

References

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