Asymmetric Synthesis of Dipeptidomimetics and Phosphine-Boranes – Routes Involving Stereoselective Olefination, Epoxidation, and Lipase-Catalysed Reactions

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Abstract

This thesis deals with the development and application of methods for the stereoselective synthesis of (*E*)-alkene dipeptidomimetics and phosphine-boranes involving phosphorus ylide-based olefination and lipase-catalysed reactions. Stereoselective epoxidation of alkenes with peracid reagents is also investigated.

Efficient synthesis of dipeptidomimetics containing the (*E*)-alkene amide bond replacement requires control of the stereochemistry of both side chain centres as well as of the double bond. A convergent synthesis of (*E*)-alkene dipeptidomimetics relying on a Wittig reaction to couple two chiral fragments was devised. Both enantiomers of an α-chiral propionaldehyde was prepared in good yields and enantiomeric purity from a 1,3-propanediol derivative by lipase-catalysed kinetic resolution or desymmetrisation. It was joined with an amino acid-like phosphonium salt in an unusually *E*-selective Wittig reaction to afford Pheψ[(*E*)-CH=CH]Phe isosteres.

Another amide bond surrogate considered in this thesis is the epoxy moiety. Observations of peracid dependent diastereoselectivity in substrate directed epoxidation of (*E*)-alkene dipeptide isosteres have been made in previous work, and the current study investigates the origin of these phenomena. *m*-CPBA and trifluoroperacetic acid were found to have different hydrogen bonding preferences, which may explain why they epoxidise some Pheψ[(*E*)-CH=CH]Phe derivatives containing two directing groups with opposing stereoselectivity. The Schlosser modification of the Wittig reaction was found useful in the synthesis of nitrogen free phenylalanyl-phenylalanine (*E*)-alkene dipeptide isosteres which were used to probe peracid stereoselectivity.

New methodology for the enantioselective synthesis of *P*-chirogenic phosphine-boranes is presented in this thesis, which may be a valuable addition to the limited number of preparative routes to such compounds. Lipase-catalysed desymmetrisation of a prochiral phosphine-borane 1,3-propanediol analogue was found to be highly enantioselective, and high yielding. Both enantiomers of *P*-chirogenic monoacetate derivatives were obtained independently, and a preliminary study of the synthetic versatility of the products indicate that they can be used for the synthesis of a wide range of interesting *P*-chirogenic compounds.

Keywords: (*E*)-alkene dipeptidomimetic, amide bond surrogate, amino acid analogue, Wittig reaction, olefination, chiral aldehyde, lipase-catalysed reaction, kinetic resolution, desymmetrisation, peracid, epoxidation, functional group coordination, Schlosser modification, *P*-chirogenic phosphine-borane, stereoselective synthesis

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