Remote Stereocontrol Transmitted Through Helicity**

Craig P. Johnston and Martin D. Smith

Highlight

Remote stereocontrol

Helicity is observed in both natural and synthetic materials. For example, DNA adopts a double P-helix conformation by virtue of the absolute configuration of its individual monomers; this is the same handedness as a α-helix generated from chains of l-amino acids. This shows that materials constructed from chiral non-racemic building blocks can populate a helix with a single screw-sense preference. However, an assembly of achiral components will generate a conformationally racemic mixture of left (M)- and right (P)-handed helices. This ratio of conformers can be biased by the incorporation of a single stereogenic centre into the chain or via binding to an external chiral influence (Figure 1). The former system has become a practical method for the transmission of stereochemical information to remote locations distant from any stereogenic centres.

This suggests that the stereochemical environment at an entity distant to the chiral inducer can be influenced through the persistent screw-sense bias of a helix. This approach was first delineated by Noe et al. who utilized polyoxymethylene chains that adopt helical conformations in solution as a result of the anomic effect. A bias for a particular screw-sense was induced by tethering the paraformaldehyde chain to a chiral non-racemic borane lactol, leading to the Re face of a ketone group being preferentially attacked with a Grignard reagent (2 : 1 diastereomeric ratio of products, Scheme 1). The level of stereoselectivity was demonstrated to be dependent on the chain length, but up to 1,10-remote stereoinduction through the polyoxymethylene M-helix was observed. An analogous system that replaced the non-terminal oxygen atoms with methylene groups exhibited poor levels of remote asymmetric induction, highlighting the vital role of the helix as a stereochemical transmitter. Despite the modest levels of diastereoselectivity, this provided the first example of remote asymmetric induction over a significant distance through conformational bias of a helical structure.

Recently, Clayden et al. have applied helical foldamers generated from unnatural amino acids as part of a strategy to control asymmetric induction over unprecedented distances. Typically, close proximity is a prerequisite for high levels of stereocontrol but the formation of (temporary) rigid structures through ring formation or global conformation control can overcome this limitation. Chains of achiral amino acids such as Aib and AcC form an equal mixture of 3 helical conformers that rapidly interconvert at room temperature. However, the introduction of a helicity ‘controller’ (a single N-terminal chiral amino acid is sufficient) promotes an almost absolute helical screw-sense preference. When l-α-methylvaline residues were situated at the N-terminus of an Aib oligomer, a P-helix was formed preferentially. Quantification of the helical ratio was achieved by incorporating a 13C labelled Aib amino acid into the middle of the chain. It was determined that incorporation of two chiral residues was optimal for inducing high levels of screw-sense preference with a third offering no significant improvement (Figure 2). At low temperatures (~ 50 °C) the peptide oligomer with two chiral l-α-methylvaline residues adopts a right-handed helical conformation with near perfect P-selectivity.

[**] We thank the European Research Council (grant agreement no. 259056 to MDS), and EPSRC and Pfizer for an industrial CASE award (to CPJ).

Dr C. P. Johnston and Dr M. D. Smith
Chemistry Research Laboratory
University of Oxford
12 Mansfield Road, Oxford, OX1 3TA
E-mail: martin.smith@chem.ox.ac.uk
Homepage: http://msmith.chem.ox.ac.uk

---

**Scheme 1.**

**Figure 1.**

DOI: 10.1002/anie.200((will be filled in by the editorial staff))
Following quantitative determination of the screw-sense preference of model oligomers, Clayden et al. probed the ability of such helices to transmit stereochemical information to a remote reaction site. Initially, a new oligomer was synthesized that embedded a Z-didehydrophenylalanine residue within the structure (Scheme 2). Reduction of the styrenyl olefin with Crabtree’s catalyst and H₂ in dichloromethane provided the hydrogenated product in >95 : 5 dr. Authentic samples of the products were synthesized from D- and L-phenylalanine, which confirmed that the major diastereomer resulted from reduction on the Re face of the alkene (from the back as drawn). Lower diastereoselectivities were observed in ethanol or with an oligomer containing a solitary chiral monomer, which were consistent with a reduction in global conformation control. Nonetheless, remarkably effective 1,6-remote asymmetric induction was achieved and the competence of helicity as a stereochemical transmitter demonstrated.

This represents a significant enhancement over the previous record for remote stereocontrol and showcases the remarkable potential of helical materials to communicate stereochemical information over long distances. Future research in this area may seek to develop catalytic variants where, for example, a prochiral entity binds and reacts at a foldamer terminus before disengaging to facilitate turnover. This would herald the development of artificial receptors that can relay information across lipid bilayers providing mimics of G-protein coupled receptors.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))
Near...far...wherever you are! Two chiral residues at the N-terminus of a helical foldamer are sufficient to induce a significant helical screw-sense preference. The capacity of this helix to transmit stereochemical information is exemplified through conducting highly stereoselective transformations over nanometre distances.