

Remote Stereocontrol Transmitted Through Helicity**

Craig P. Johnston and Martin D. Smith*

conformation · helicity · remote stereocontrol ·
asymmetric induction · foldamer

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^[1] or via binding to an external chiral influence (Figure 1).^[2] The former system has become a practical method for the transmission of stereochemical information to remote locations distant from any stereogenic centres.^[3,4,5]

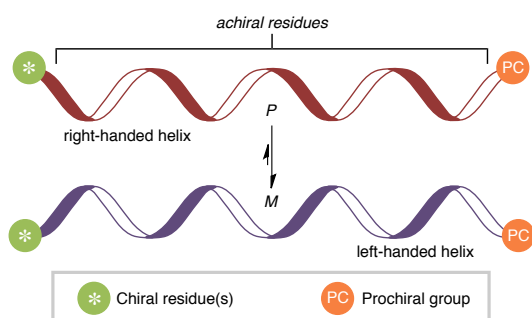
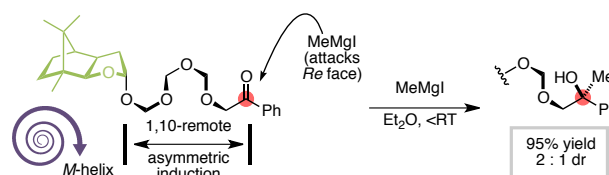


Figure 1.

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 anomeric effect.^[6] A bias for a particular screw-sense was induced by tethering the

paraformaldehyde chain to a chiral non-racemic bornane 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.



Scheme 1.

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.^[7] 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.^[8] Chains of achiral amino acids such as Aib and Ac₆c form an equal mixture of 3_{10} 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.^[1] 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.^[9] 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.

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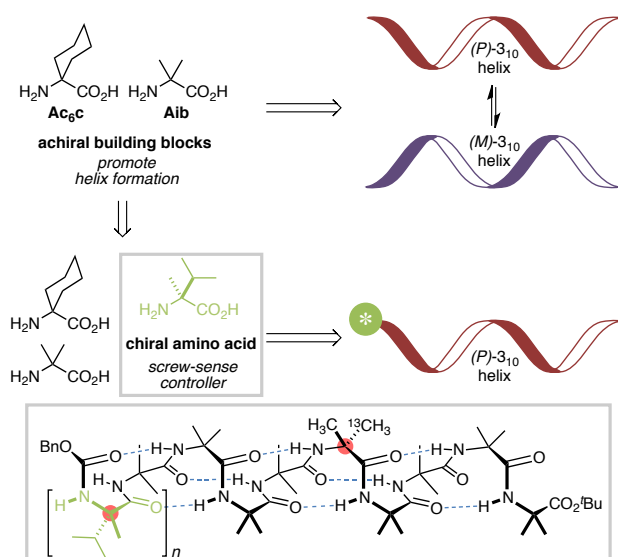
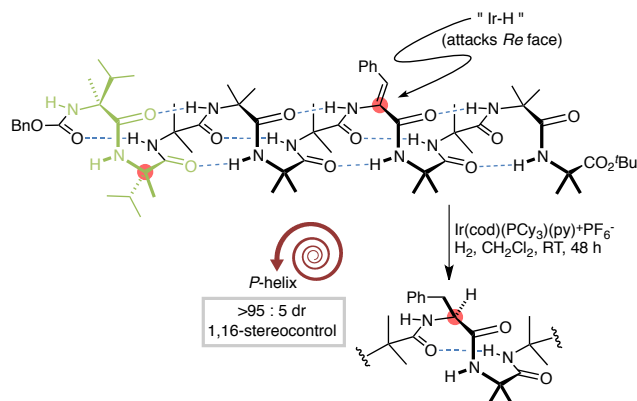


Figure 2.

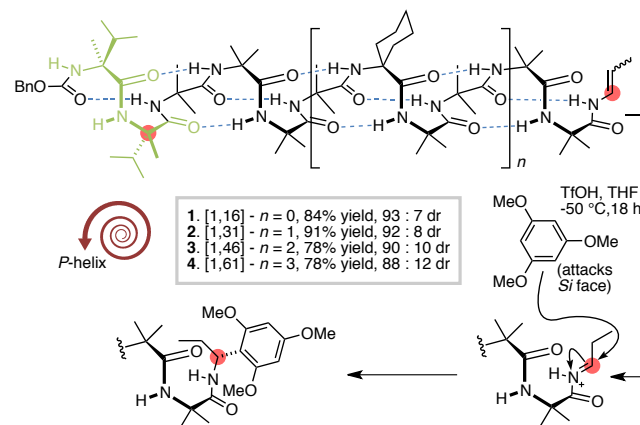
Following quantitative determination of the screw-sense preference of model oligomers, Clayden et al. probed the ability of such helices to transmit stereochemical information to a remote reaction site. Initially, a new oligomer was synthesized that embedded a *Z*-didehydrophenylalanine residue within the structure (Scheme 2). Reduction of the styrenyl olefin with Crabtree's catalyst and H_2 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 conformational control. Nonetheless, remarkably effective 1,16-remote asymmetric induction was achieved and the competence of helicity as a stereochemical transmitter demonstrated.



Scheme 2.

Subsequently, Clayden et al. examined the stereoselective modification of terminal functional groups distant from the chiral residue, which would require end-to-end communication within the helical foldamer. Following a review of potential reactions, trapping of an *N*-acyliminium ion located at the *C*-terminus of an oligomer by an electron-rich arene was selected for its reliable stereoselectivity. This was accomplished through isomerization of

an enamide with triflic acid to generate the reactive species *in situ*, which is intercepted by 1,3,5-trimethoxybenzene. Initially, an oligomer **1**, containing Aib as the repeating unit was evaluated and yielded the expected product in 84% yield as 93 : 7 mixture of diastereomers (Scheme 3). The major diastereomer was determined to occur through attack of the *Si* face of the *N*-acyliminium ion by synthesis of authentic standards using materials with known absolute configuration. Iterative extension of this general structure through insertion of achiral helical fragments (to yield **2-4** respectively) moved the reactive group further from the nearest site of asymmetric induction. A marginal decay in stereocontrol was observed after each iteration but remained substantial even with communication through nineteen achiral residues. The authors negated the possibility of intermolecular interactions dictating the stereochemical outcome by demonstrating that a racemic product is generated when the source of chiral induction and the enamide group are located in separate substrates. The reaction involving the longest oligomer **4** constitutes 1,61-remote asymmetric induction and necessitates the transmission of stereochemical information across a distance of around 4 nm.



Scheme 3.

This represents a significant enhancement over the previous record for remote stereocontrol^[10] 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.^[11]

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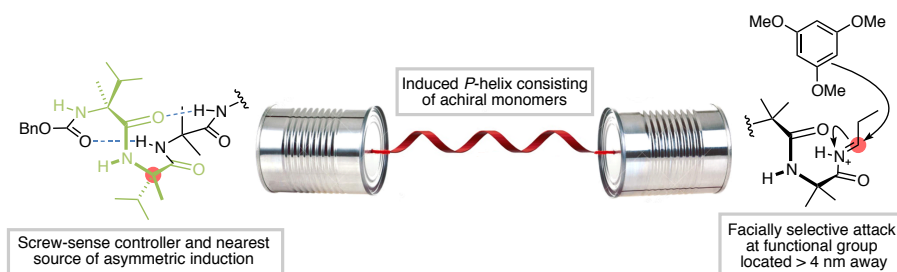
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Near...far...wherever you are! Two chiral residues at the N-terminus of a helical foldamer are sufficient to induce a significant helical screw-sense preference. The capacity of this helix to transmit stereochemical information is exemplified through conducting highly stereoselective transformations over nanometre distances.