Reaction at a Distance

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Foldamer-mediated remote stereocontrol: >1,60 asymmetric induction

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Abstract:
An N-terminal L-α-methylvaline dimer induces complete conformational control over the screw-sense of an otherwise achiral helical peptide foldamer formed from the achiral quaternary amino acids Aib and Ac_6c. The persistent right-handed screw-sense preference of the helix enables remote reactive sites to fall under the influence of the terminal chiral residues, and permits diastereoselective reactions such as alkene hydrogenation or iminium ion addition to take place with 1,16-, 1,31-, 1,46- and even 1,61 asymmetric induction. Stereochemical information may be communicated in this way over distances of up to 4 nm.

In a typical stereoselective reaction, existing stereochemistry governs the formation of a new stereogenic centre by controlling the direction of attack of a reagent or a catalyst at a reactive site.. Close spatial contact between the controlling centre and the reaction site is typically required, and 1,2- or 1,3-asymmetric induction (where the two sites are separated by one or two bonds) can routinely be expected to give high levels of stereoselectivity.[1] Asymmetric induction over longer distances ('remote asymmetric induction' usually refers to 1,4-asymmetric induction and beyond) is possible,[2] but only if the flexibility of the molecule is limited, usually by the (sometimes temporary) formation of a cyclic structure.[3] Asymmetric induction can be achieved over more than 20 bonds[4] in non-cyclic molecules by using semi-rigid structures in which relayed interactions between a series of polarized groups allow a controlling stereogenic centre to influence the local environment of a remote reactive site.[5]

Here we present a way to achieve asymmetric induction over much greater distances by using molecules that have inherent helicity, or foldamers.[6,7] The conformational properties of foldamers as structural analogues of biomolecules have been investigated widely,[7-9] but their ability to control reactivity remains largely unexplored.[10] By linking an appropriate controller and a reactive site through a molecular fragment strongly disposed to adopt a helical structure, we show that it becomes possible for the controlling centre to govern the environment at a remote reactive site located several nanometers away.

The helical foldameric parts of our molecules were made from oligomers of aminoisobutyric acid (Aib, **1**) and aminocyclohexylcarboxylic acid (Ac_6c, **2**) (Figure 1a). Peptide-like oligomers of these achiral quaternary amino acids typically adopt well-defined 3_{10} helical structures in solution[11] but because the individual amino acids each possess a plane of symmetry, their oligomers exist as a rapidly interconverting[12,13] equal mixture of left- and right-handed helices. A bias towards a single screw sense[14] was induced by ligating to the N-terminus of these oligomers one or more residues of the chiral quaternary amino acid L-α-methylvaline (αMv, **3**). The structure of L-α-methylvaline is compatible with the 3_{10} helical structure of Aib oligomers,[15] and we reasoned that incorporating a sufficient number of chiral quaternary L-amino acid residues would maximize the chances of inducing a high degree of preference for the right-handed[16] screw sense in the helical chain. Two oligomers were synthesized, **4** and **5**, containing one and two αMv residues respectively (Figure 1b). Circular dichroism spectra of **4** and **5** in MeOH, and titration of **5** in THF with DMSO, were consistent with the adoption of a characteristic 3_{10} helical structure in these solvents (see Supporting Information).

Before carrying out the remotely selective reactions, we quantified the screw-sense preference induced in the helical chains of the oligomers **4** and **5** by incorporating at the fifth Aib residue of the chain a ^{13}C label asymmetrically into its two methyl groups.[17] The anisochronicity of the two ^{13}C labelled Me groups in the ^{13}C NMR spectra in MeOH and in THF of both **4** and **5** confirmed that the population of left- and right-handed helical conformers is unequal,[13] and the location of the majority of the label in the same (upfield) member of the pair of anisochronous signals, in conjunction with the CD spectra in MeOH, indicates that both **4** and **5** prefer a right-handed preferred screw sense.[16] Analysis of the spectra acquired at a range of temperatures (Figure 1c, 1d and Supporting Information) showed that while the oligomer **5** displayed good conformational selectivity for the right-handed screw sense in MeOH, in THF—and especially at low temperature—the preference for a single, right-handed, screw sense becomes almost quantitative. At –50 °C, for example, we calculate that the ^{13}C-labelled residue of **5** finds itself in a right-handed helical environment more than 98% of the time. Data for both **4** and **5**, in MeOH and in THF at +40 °C and at –50 °C, are shown in Table 1. Two chiral residues are evidently necessary to induce this almost complete screw-sense preference: studies of related compounds containing three chiral residues (see Supporting Information) showed that the third offered no improvement in the degree of conformational control.

Support for the conclusion that an N-terminal L-αMv dimer provides close to quantitative screw-sense control was provided by conformational analysis of two related compounds, **6a** $Cbz(\alpha Mv)_2Aib_4GlyNH_2$ and **6b** $Ac(\alpha Mv)_2Aib_4GlyNH_2$ (Figure 1e). The X-ray crystal structure of **6a** shows a well-formed right-handed

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

3_{10} helix, and density functional theory calculations on **6b** indicate that the lowest energy left-handed helical conformation is more than 10 kJ mol^{-1} higher in energy than the lowest energy right-handed helical conformation.

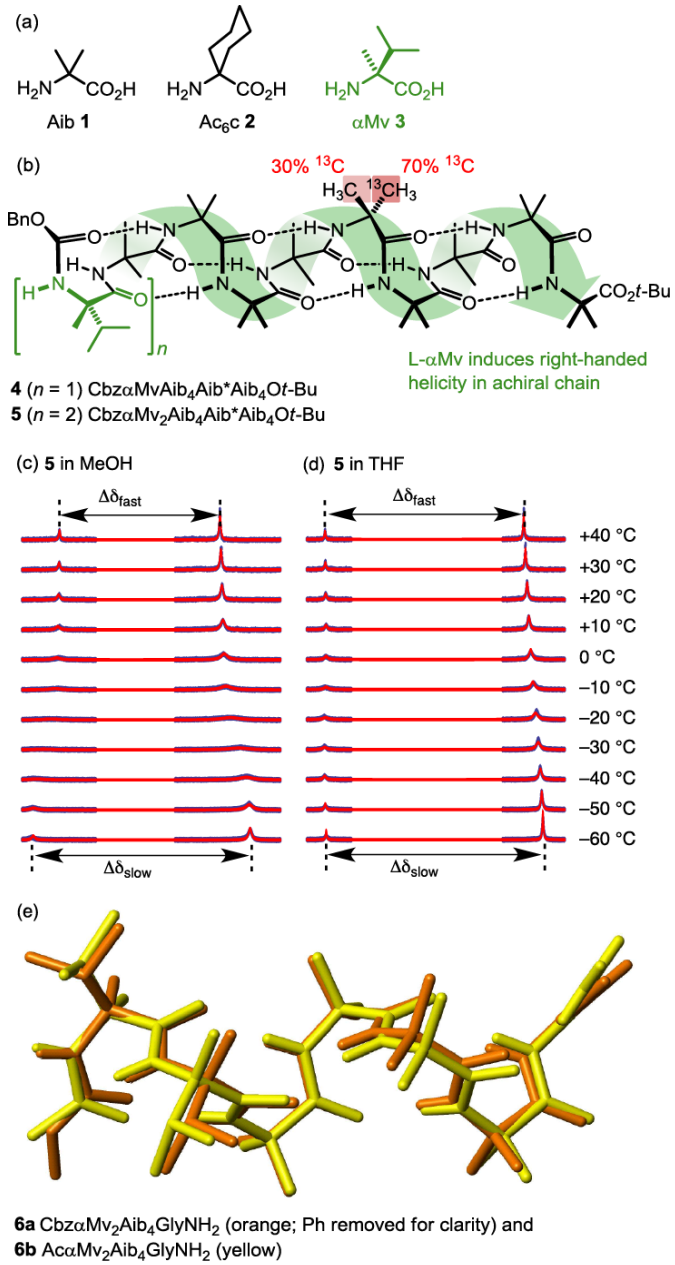
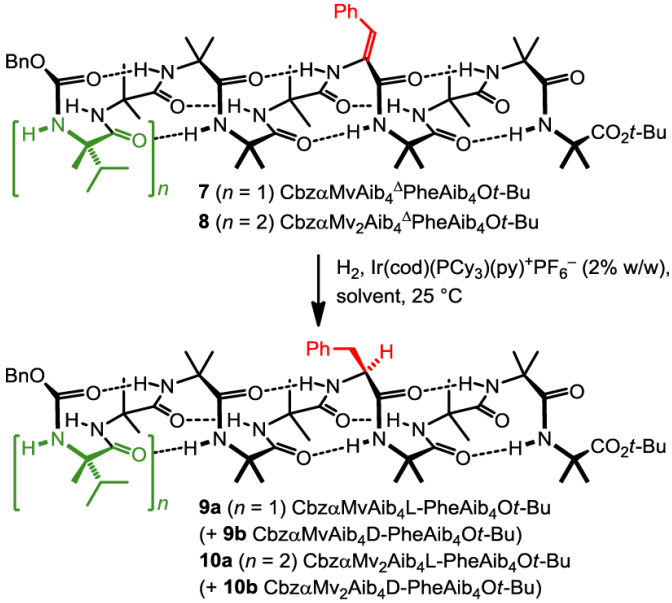


Figure 1. **Control of screw sense in foldamers built from achiral monomers** (a) Achiral and chiral monomers **1-3**; (b) Induction of helicity in ^{13}C-labelled oligomers **4** and **5**; (c) Stacked plots of the ^{13}C NMR spectrum of **5** in methanol, indicating a strong preference for right-handed helical screw sense which rises to almost quantitative control (d) in THF. Blue points are experimental data; red lines are best-fit line shapes (see Supporting Information). The ratio of $\Delta\delta_{fast}/\Delta\delta_{slow}$ gives an estimate of the 'helical excess' at the ^{13}C label at temperatures above coalescence; full line shape analysis (see ref 13 and supporting information) allows calculation of the helical excess at all temperatures (Table 1); (e) X-ray crystal structure of **6a** (orange; Ph removed for clarity) and calculated lowest energy conformation of **6b** (yellow).

compound	solvent	T (°C)	K[a]	h.e.[b] (%)	P:M[c]
4	MeOH	+40		50	75:25
4	MeOH	–50	4.9		83:17
5	MeOH	+40		64	83:17
5	MeOH	–50	9.5		91:9
5	THF	+40		92[d]	96:4
5	THF	–50	60		98.5:1.5

Table 1. Conformational preferences in **4** and **5** derived by analysis of their ^{13}C NMR spectra. [a]Equilibrium constant *K* for interconversion of P and M conformers at –50 °C, calculated by line shape analysis of the variation of the ^{13}C NMR spectrum with temperature; [b]The value $\Delta\delta_{fast}/\Delta\delta_{slow}$ (see Figure 1c, 1d) interpreted as 'helical excess' (i.e. [P]–[M] / [P]+[M]) [13]; [c]Calculated ratio of P and M conformers derived from either K or h.e. [d]Value is identical on two-fold dilution.



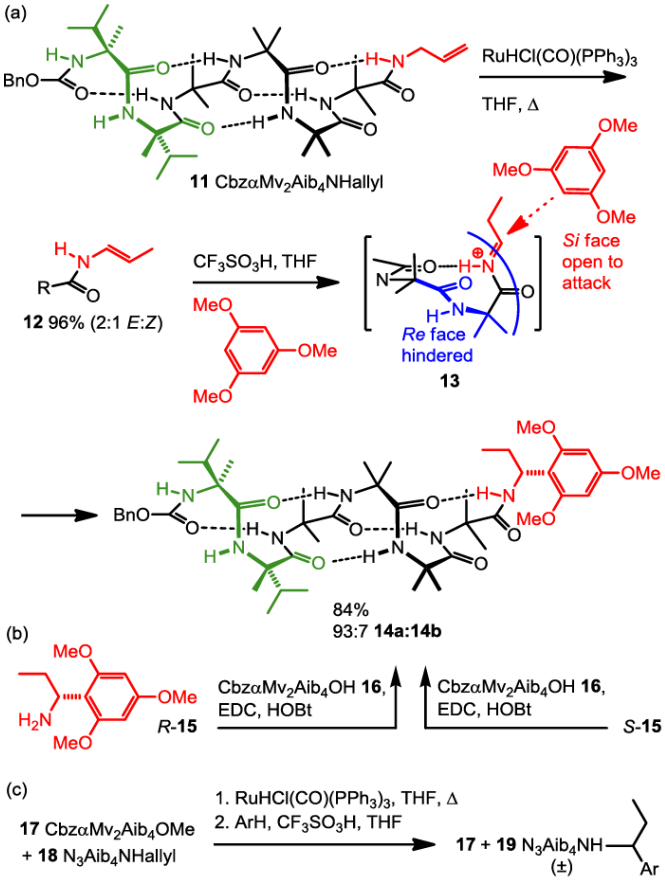
starting material	*n* =	solvent	products, ratio
7	1	EtOH	**9a:9b**, 79:21
7	1	CH_2Cl_2	**9a:9b**, 88:12
8	2	EtOH	**10a:10b**, 89:11
8	2	CH_2Cl_2	**10a:10b**, >95:5

Scheme 1. Asymmetric induction of an L-Phe residue by hydrogenation of a didehydrophenylalanine residue embedded in an induced right-handed helix.

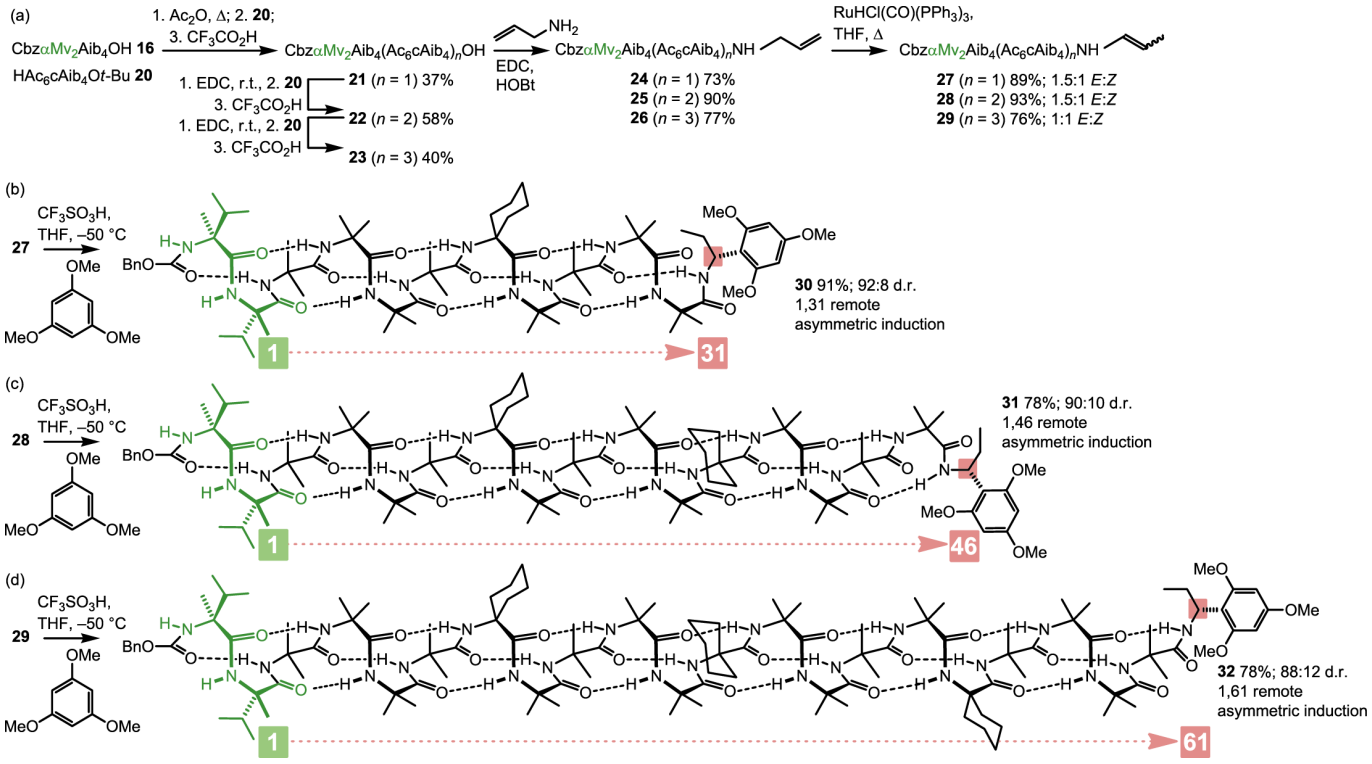
Our next challenge was to utilise the helical screw-sense preference to induce, at a distance, the formation of a new stereogenic centre.[18] To demonstrate the possibility of an asymmetric reaction induced solely by the screw sense of a helix, we made oligomers **7** and **8** in which the ^{13}C labelled Aib probe of **4** and **5** was replaced by a reactive, but still achiral, *Z*-didehydrophenylalanine (ΔPhe) residue (Scheme 1).[14c,19] This unsaturated residue was converted to phenylalanine by chemoselective hydrogenation in the presence of Crabtree's catalyst,[19] Ir(cod)(PCy$_3$)(py)$^+$PF$_6^-$, in ethanol or in dichloromethane. Two diastereoisomeric products were formed in each case, and the synthesis of authentic samples of **10a** and **10b** from L- and D-Phe showed that the major compound was the L-Phe containing oligomer. The ratios of **9a:9b** and of **10a:10b** are shown in Scheme 1. Selectivities were higher in the reactions of **8** than of **7**, and were

higher in a dichloromethane than in ethanol. Hydrogenation of **8** in dichloromethane gave >95:5 selectivity for the formation of **10a**, which arises from attack of hydrogen on the *Re*-face of the double bond of **7** (the back face as shown in Scheme 1). Given the remoteness of the nearest stereogenic centre, we propose that this selectivity arises purely from the preferred screw sense of the helical foldamer structure in which the reactive site is embedded. Lower selectivities with hydroxylic solvents and with a single controlling chiral residue presumably result from the lower levels of screw-sense control attained in these cases (see Table 1).

Next, we sought reactions of terminal prochiral groups that would allow asymmetric induction to be relayed from one end of a foldamer chain to the other. A survey of the reactions of C-terminal reactive C=C, C=O and C=N groups revealed that trapping of a C-terminal *N*-acyliminium ion by a nucleophilic arene takes place with excellent diastereoselectivity. *N*-Allyl amide **11** was isomerised with a Ru catalyst to the enamide **12** (Scheme 2).[21] Protonation of **12** (which is an inconsequential mixture of geometrical isomers) by trifluoromethanesulfonic acid in THF at –50 °C in the presence of 1,3,5-trimethoxybenzene gave acyliminium ion **13** which was trapped *in situ* by the arene to yield a pair of diastereoisomeric amides **14a** and **14b** in a ratio of 93:7. Authentic samples of **14a** and **14b** were made by coupling samples of amine *R*-**15** and *S*-**15** of known absolute configuration[22] with the hexamer **16**. This allowed us to deduce that the arene attacks the rear face of the iminium ion **13**, the face that is more exposed in the proposed hydrogen-bonded structure shown in Scheme 2. To confirm that the observed diastereoselectivity is indeed the result of an intramolecular relay mediated by the screw sense of the helical foldamer, a control experiment was carried out in which the chiral inducer is in a separate molecule from the reactive enamide residue. Thus chiral oligomer **17** and achiral *N*-allyl amide **18** gave, after isomerization and trapping, oligomer **19** in racemic form, ruling out mechanisms of asymmetric induction involving intermolecular interaction between the reactive iminium ion and the chiral portion of the oligomer.



Scheme 2. (a) Diastereoselective acyliminium addition by end-to-end asymmetric induction though a helical oligomer; (b) Identification of the diastereoisomers by synthesis from authentic samples of **15**; (c) Control experiment: racemic product results when the controller and the reactive site are in different molecules.



Scheme 3. Remote asymmetric induction through achiral helices. (a) Synthesis of the three oligomers **21-23** and their conversion to the enamides **27-29**. (b) 1,31 Asymmetric induction through nine achiral residues to yield **30**. (c) 1,46 Asymmetric induction through fourteen achiral residues to yield **31**. (d) 1,61 Asymmetric induction through nineteen achiral residues to yield **32**.

With this evidence that the remote asymmetric reactions at the terminus of a helical foldamer may be mediated solely by the foldamer's screw sense, we proceeded to lengthen the chain by successive homologation of **16** with achiral helical fragments **20** comprising Ac_6cAib_4 pentamers, as shown in Scheme 3a. A series of carboxylic acids **21-23** were coupled with allylamine to make the amides **24-26**, and then isomerized to their enamide isomers **27-29**. The enamides **27** and **28** were treated with trifluoromethanesulfonic acid in the presence of 1,3,5-trimethoxybenzene to give amide products **30** and **31** as mixtures of diastereoisomers (Scheme 3b, c). Authentic samples of both diastereoisomeric products were synthesized from **21** or **22** and the enantiomers of **15**, and comparison by ^{1}H NMR (800 MHz, d_8-THF) of these compounds with the product mixtures **30** and **31** by ^{1}H NMR showed that selectivities remained >5:1 in these reactions, even as the remote relationship between the controlling centre and the newly formed asymmetric centre was extended from 1,16 in **14** to 1,31 in **30** to 1,46 in **31**.

Finally, under the same conditions, enamide **29** yielded two diastereoisomers of the product **32** in a ratio of 88:12 (Scheme 3d). This reaction displays 1,61 asymmetric induction, a value almost three times the greatest 'through-bond' distance previously reported,[4] representing the communication of stereochemical information over a distance of about 4 nm,[23] through more than six induced right-handed turns of the helical structure.

To summarise, we have shown that the screw sense of a molecular helix, induced under thermodynamic control, can act as the mechanism by which information may be transmitted over long distances (over 60 bonds) on the molecular scale. By inducing complete preference for right-handed helicity in a chain having no inherent screw-sense preference of its own, an appropriate controller enables distant reactive sites to fall under its influence, resulting in a reaction displaying 1,61 asymmetric induction. Such remote control of chemical reactivity is characteristic of allosteric enzymes and receptors, and conceptually similar designs could be used to make artificial analogues of such biological signal transduction mechanisms.

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Remote Stereocontrol

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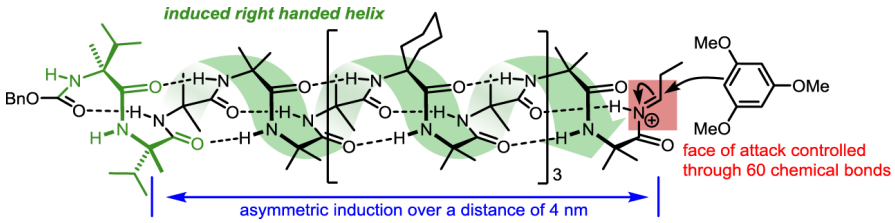

Reaction at a distance. By inducing a quantitative, persistent preference for right-handed helicity, chirality at one end of an otherwise achiral helical molecule is able to control the stereoselectivity of reactions at sites located up to 60 bonds away, shattering previous records for remote stereochemical control.