Stereochemical relays: communication *via* conformation

Jonathan Clayden* and Neoclis Vassiliou

Received 29th March 2006, Accepted 25th May 2006
First published as an Advance Article on the web 15th June 2006
DOI: 10.1039/b604548k

Stereochemistry is information, and stereoselective reactions are the means by which that information may be communicated within and between molecules. The control of remote stereogenic centres can be achieved by stereochemical relay, and the use of thermodynamic control over conformational preference is turning out to be a very powerful method for long-range transmission of stereochemical information.

Introduction

Stereoselective synthesis, which aims to control relative and absolute configuration at new stereogenic centres, has been a remarkable success story.[1] The award, in 2001, of a Nobel Prize to three of the founding thinkers in the area of asymmetric catalysis[2] confirmed as one of the great achievements of late 20th century chemistry the science of stereoselectivity. Stereochemistry is information – binary information – and stereochemical control, mediated by stereoselective reactions, can be seen as a chemical means of information transfer – of communication of information. The reliability of the communication depends on a handful of interrelated factors, but it is clear that stereocontrol is best when proximity and rigidity are features of the reaction sites and molecules involved: it has long been a stereochemical tenet that flexible acyclic molecules provide generally poor substrates for stereoselective reactions.

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK. E-mail: clayden@man.ac.uk

Jonathan Clayden is professor of Organic Chemistry at the University of Manchester, where he has been a member of staff since 1994. His research interests encompass various areas of synthesis and stereochemistry, particularly where conformational control is important. He is co-author (with Nick Greeves, Stuart Warren and Peter Wothers) of the textbook "Organic Chemistry", published by OUP in 2001, and his book "Organolithiums: Selectivity for Synthesis" was published by Pergamon in 2002. He has received the Royal Society of Chemistry's Meldola (1997) and Corday Morgan (2003) medals, along with the GlaxoSmithKline Prize for Innovative Organic Chemistry (1998), the AstraZeneca Prize (2001), the Pfizer Prize (2001) and the Novartis Young European Investigator Award (2004).

Jonathan Clayden

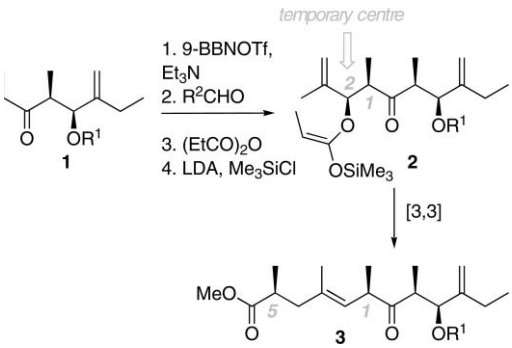
The need for stereoselective reactions to take place close to the stereocontrolling influence in general limits the distance through which stereocontrol can take place to some four or five bond lengths. The communication of stereochemistry over greater distances than this is generally described as *remote stereocontrol*, or *remote asymmetric induction*.[3] Stereocontrol apparently reaching over distances of up to 12 or 13 bond lengths has been achieved by using a metal ion to grab a remote reaction site and bring it into temporary proximity with a stereocontrolling influence.[4] But stereocontrol at a reaction site truly distant in space generally requires specific structural features to allow stereochemical information to be relayed – "unrelayed" 1,5-stereocontrol with a selectivity of 90 : 10 has been described as "remarkable".[5]

Stereochemical relays may take the form of temporary stereogenic centres, which bridge the gap between the two reaction sites. For example, Paterson's intermediate **3** *en route* to ebelactone[6] contains a 1,5-relationship between an isolated stereogenic centre and its nearest neighbour. After first setting up a proximal 1,2-relationship in **2** using a stereoselective aldol reaction of **1**, a stereospecific Ireland–Claisen [3,3]-sigmatropic rearrangement expands the 1,2-relationship to a 1,5-relationship (Scheme 1).

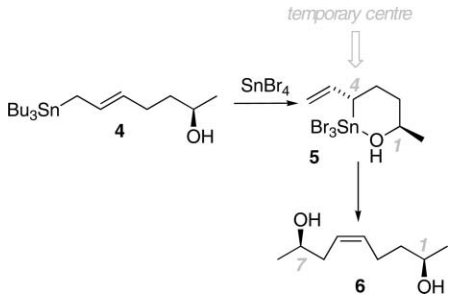
The "temporary" stereogenic centre need not be present in an isolable synthetic intermediate, but instead might be formed transiently at some point along the overall reaction pathway. Thomas[7] has achieved up to 1,7-stereocontrol in alkenes such as **6** using this strategy: the tin-bearing centre in the intermediate **5** is under the control of the hydroxyl group by virtue of tin–oxygen coordination within a six-membered ring (Scheme 2).

Scheme 3 shows both strategies combined: the strategy of Scheme 2 controls the 1,7-relationship in **7** which is extended, by the strategy of Scheme 1, to a 1,9-relationship in **8**.[7]

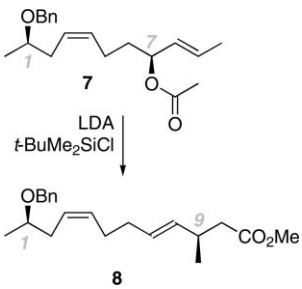
This journal is © The Royal Society of Chemistry 2006



Scheme 1 Stereospecific rearrangement as a means of relaying stereochemistry.

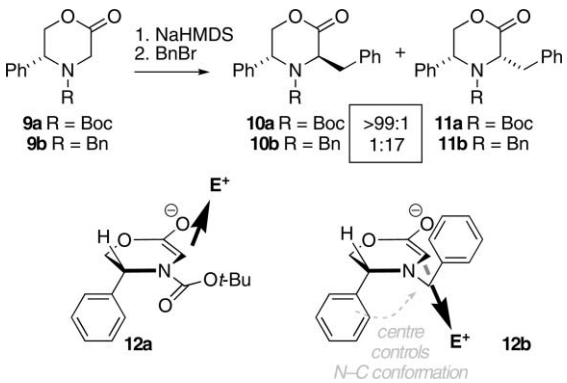


Scheme 2 Relaying stereochemistry through a transient stereogenic centre.



Scheme 3 Extending a remote stereochemical relationship.

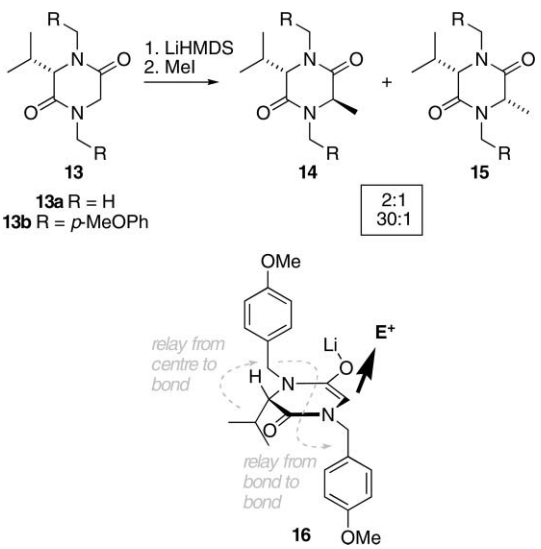
A more subtle means of achieving stereocontrol from a distance makes use of a controlling centre to orientate not temporary *configuration* but simply to bias the *conformation* of that part of the molecule lying between the reaction site and controlling influence. Still very elegantly demonstrated the power of such methods for stereocontrol where the conformation of a macrocyclic ring relays the stereochemistry.[8] A conformational relay effect accounts for the protecting group dependence of the stereoselectivity exhibited by alkylation reactions of the phenylmorpholinones **9** (Scheme 4).[9] Changing the planar *N*-Boc protecting group of **10a** to the conformationally mobile *N*-benzyl group of **10b** *inverts* the 1,3-diastereoselectivity in the alkylation of **12**, the sodium enolate of **9**. The Boc group is stereochemically inert, and an "inherent" *anti* stereoselectivity is observed in reactions of **12a**. However, in **12b** the steric interaction between the phenyl-bearing centre and the *N*-benzyl group forces the benzyl group onto the top face of the molecule, and favours alkylation from



Scheme 4 Relay *via* an *N*-benzyl group.

the bottom face. The *N*-benzyl group of **12b** facilitates the relay of stereochemical information from the old centre to the new.

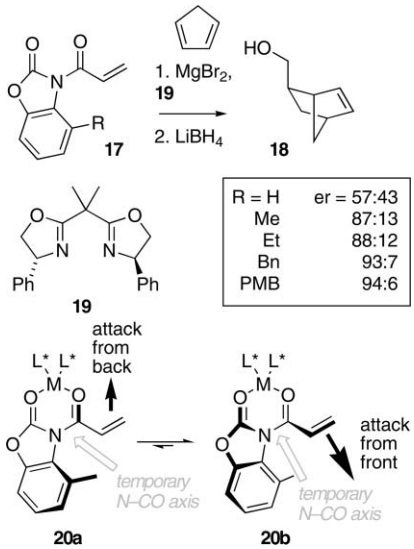
In the alkylations of diketopiperazines **13**, a switch of protecting group from conformationally inconsequential *N*–Me to conformationally powerful *N*–*p*-methoxybenzyl by contrast *enhances* selectivity (Scheme 5).[10] While **13a** (R = H) is alkylated with 2 : 1 diastereoselectivity, **13b** (R = *p*-MeOPh) is alkylated with diastereoselectivity of 30 : 1. Modelling suggests that the enolate **16** derived from **13b** adopts a conformation (Scheme 5) in which steric repulsion between the adjacent isopropyl and *p*-methoxybenzyl group favours conformations with this group lying *anti* to the isopropyl group. In turn, this *N*-substituent pushes the second *N*-substituent onto the bottom face, directing the electrophile to approach the enolate from above. Effectively, stereochemical information is relayed *via* both benzyl groups to the reacting centre.



Scheme 5 Stereochemical relay *via* two *N*–PMB groups.

Renaud has developed a related concept[11] in which stereochemistry is relayed from a chiral *catalyst* to a relatively distant reaction centre through the conformation of an intervening bond (Scheme 6).[12] The agent of the relay takes the form of an "achiral

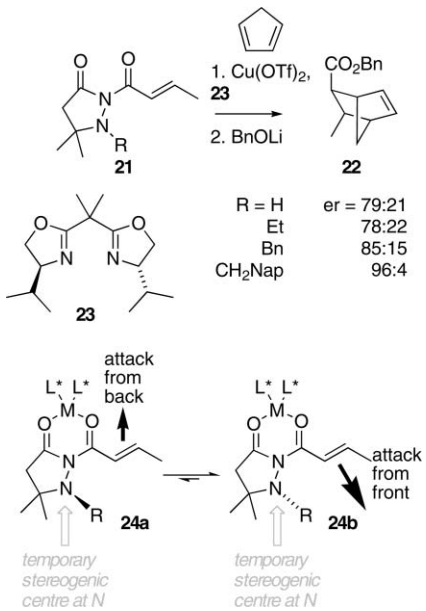
This journal is © The Royal Society of Chemistry 2006



Scheme 6 Stereochemical relay through a transient N–CO axis.

auxiliary", an oxazolidinone derivative of 2-aminophenol. Complexation of chiral Lewis acid $MgBr_2 \cdot$**19** to acryloyl oxazolidinone **17** is proposed to favour one of the two diastereoisomeric conformations **20** about the exocyclic N–CO bond, and indeed increasing the size of R from H through Me, Et, Bn and PMB gave a corresponding increase in product enantiomeric ratio (er)[13] from 57 : 43 to 94 : 6 as the differentiation between the faces of the acrylamide is increased.

In related reactions of **21**, a temporary, labile (*i.e.* kinetically unstable) stereogenic nitrogen centre relays stereochemistry from the chiral catalyst to a reaction centre (Scheme 7).[11,14] The "achiral auxiliary" in this case is a pyrazolidinone, readily available by the conjugate addition of hydrazine to 3,3-dimethylacrylate. The



Scheme 7 Stereochemical relay through a transient stereogenic centre at N.

synthesis allows for easy variation of the substituent R, and the results suggest that this group R has an important role to play in relaying the effect of the chiral Lewis acid to the reaction site: the bigger the group R the higher the selectivity. The tetrahedral N atom inverts rapidly, but in the presence of a chiral Lewis acid it prefers one of the two configurations shown as **24a** or **24b**, converting the achiral (or *prochiral*) auxiliary into a chiral auxiliary. The chiral ligand biases the stereochemistry at N which in turn, being relatively close to the reaction centre, controls the face-selectivity of the Diels–Alder reaction.

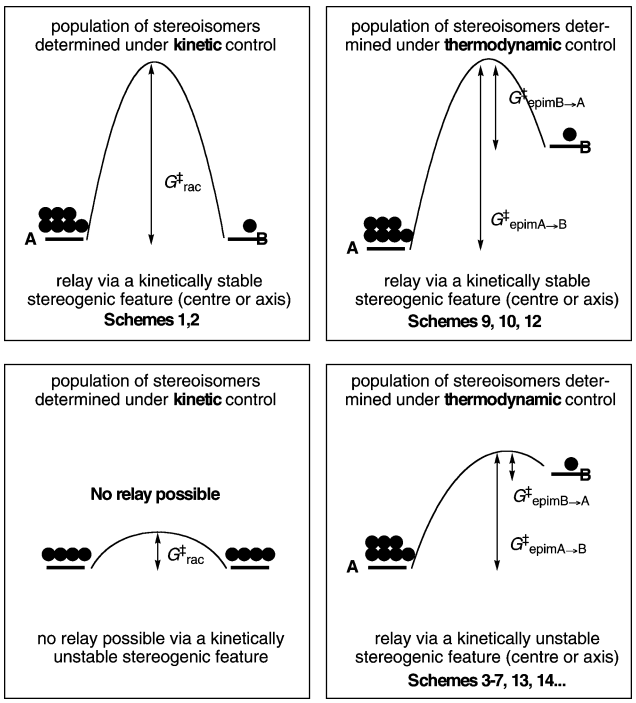
A similar effect is evident in the conjugate addition of nucleophiles to **21** in the presence of chiral magnesium Lewis acids.[15] Introducing larger *N*-substituents R apparently turns on the relay effect.

Relays of stereochemical information from chiral catalysts have an inbuilt drawback: the catalyst must activate the reaction centre and therefore interact with it in some way: the source of asymmetry can never be truly removed spatially from its effect.

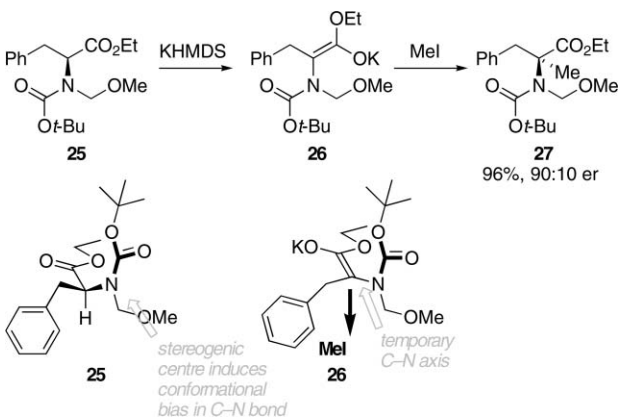
Unlike in Schemes 1 and 2, the stereochemical features proposed to give rise to the observed relay effects in Schemes 3–7 have a lifetime which is short on the laboratory timescale (though presumably long relative to the half-life of the reaction itself[16,17]). For example, although they have features of a chiral axis, the N–CH_2Ar bonds of **12b** and **16** and the N–CO bonds of **20** are not atropisomeric at the temperature of the reaction – in other words their chirality relies solely on the thermodynamic influence of a nearby centre, not on a kinetic barrier to bond rotation. The evidence that a true relay effect is involved is therefore necessarily circumstantial – the dependence of the level of stereoselectivity in the reactions on the presence or absence of certain proposed stereochemical features. While the result of these reactions is not in doubt, it has not yet proved possible in these systems to study spectroscopically the conformation and stereodynamics of the bonds concerned. Scheme 8 illustrates schematically the various possibilities for achieving stereochemical relay.

The idea of temporarily storing information in an *atropisomeric* bond (*i.e.* one with kinetically stable stereochemistry which is not labile on the timescale of the reaction, and which for example can be studied by low temperature NMR techniques) was expanded by Curran[18] into the concept of "prochiral auxiliaries". Curran envisaged that atropisomeric stereochemistry generated under kinetic control would subsequently relay stereocontrol to further centres in a substrate. The idea has never been fully realised in its original form, and the most significant recent developments in the use of temporary atropisomeric chirality to relay stereochemical information have made use of thermodynamic rather than kinetic control over the temporarily stereogenic bond.

Kawabata and Fuji have shown that appropriately protected amino acids **25** may be alkylated apparently with retention of configuration *via* the hindered enolate **26** (Scheme 9).[19] Extensive kinetic investigations have shown the origin of this "through time" relay effect (generally termed "chiral memory",[20] and to be contrasted with the "through space" relays above) is the conformation of the starting amide, coupled with the kinetic stability of the atropisomeric intermediate enolate. As the enolate **26** is formed from what semi-empirical calculations suggest to be



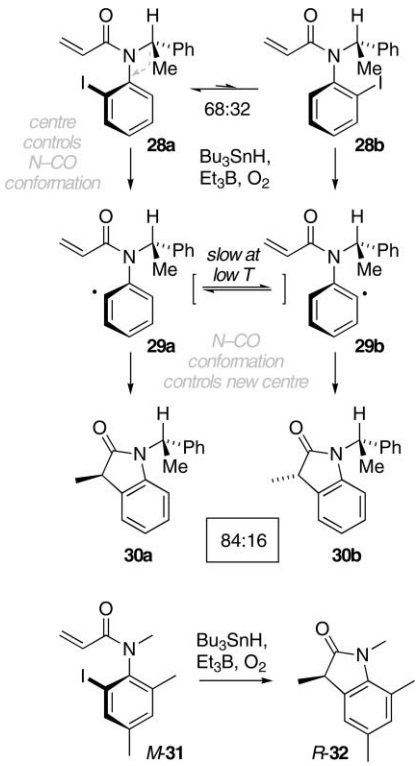
Scheme 8 Kinetic and thermodynamic control in strategies for stereochemical relay. A and B represent two alternative stereo- or conformational isomers of the centre or bond facilitating the relay, in which one is more highly populated than the other due to either kinetic or thermodynamic control. A and B may or may not interconvert on the laboratory timescale.



Scheme 9 Chiral memory – stereochemical relay through time.

the major conformer of **25**, the preferred orientation of its NR_2 group persists. Because C–N bond rotation is slow, and alkylation of the atropisomeric enolate is diastereoselective, the product **27** is formed largely retentively (90 : 10 er). Thus thermodynamic control over conformation is trapped and given kinetic stability by the formation of the atropisomeric (at low temperature) enolate **26**, whose axial configuration persists even once the original controlling centre has disappeared.[19,21]

Being very fast, radical reactions can often display chiral memory effects, and Curran has reported a reaction in which comparison of the temperature dependence of the stereoselectivity and of the starting conformer distribution suggests that both chiral memory and chiral relay effects are in operation (Scheme 10).[17] The stereogenic centre of **28** biases the population of the two amide conformers in such a way that radical cyclisation gives principally **30a** rather than **30b**. At low temperature the radicals **29** cyclise faster than they can interconvert, and while there is some stereochemical leakage from **29b** to **30a** the product ratio is largely the result of the ratio of conformers of **28**. The importance of the axis in relaying stereochemistry is evident in related reactions of resolved *M*-**31** which gives **32** with 90% stereospecificity.[22]

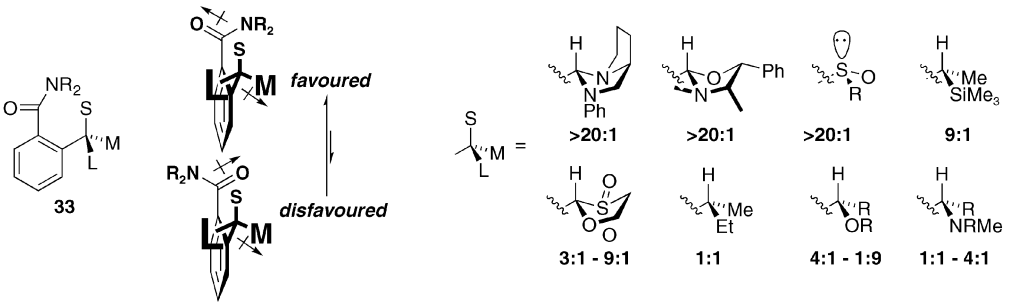


Scheme 10 Chiral memory in radical cyclisations.

Our own work[23,24] has established the surprising ease with which stereogenic centres placed adjacent to certain functional groups – in particular tertiary aromatic amides such as **33** – are able to govern their orientation, often with very high degrees of conformational control. Scheme 11 summarises some of the substituents which display this ability, notably sulfoxides such as **36**, which give rise to conformational ratios about Ar–CO of up to 200 : 1.[25]

The relatively slow rate of rotation about bonds in aromatic amides[26] meant that we have been able to quantify conformational ratios by NMR, and we have used the ability of a stereogenic centre to control the orientation of a functional groups as a means of synthesising new classes of non-biaryl atropisomers enantioselectively.[27,28] However, given that we were also well aware that atropisomeric amide axes are able to control the formation of new stereogenic centres,[29,30] it occurred to us that by placing these two aspects of stereoselectivity in series we could use a rotationally restricted amide as a means of relaying

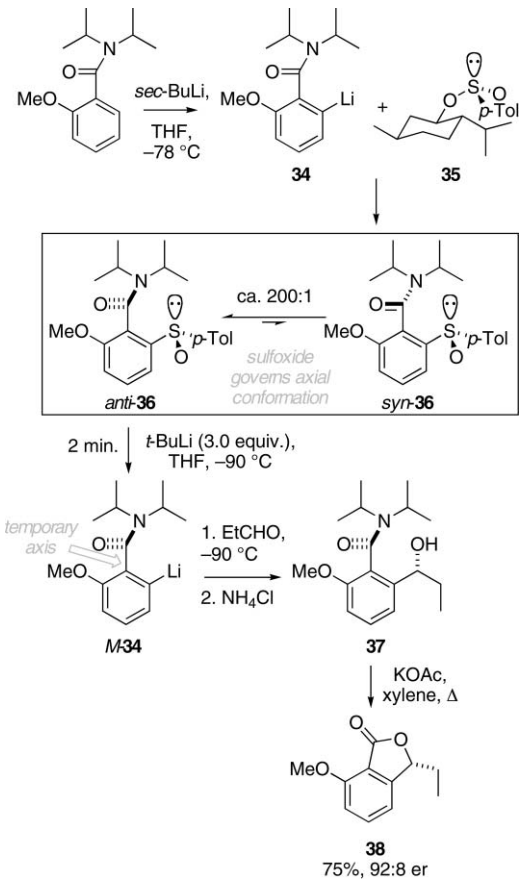
 This journal is © The Royal Society of Chemistry 2006



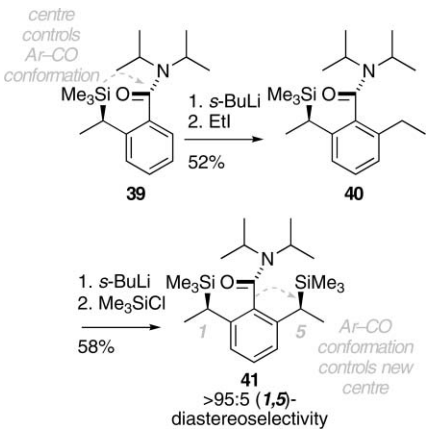
Scheme 11 Typical conformational ratios in tertiary amides bearing adjacent stereogenic centres.

stereochemical information (Scheme 12). The sulfoxide group of **36** is introduced straightforwardly by quenching the lithiated amide (±)-**34** with Andersen's menthyl sulfinate **35**. The sulfoxide is then removed by sulfoxide–lithium exchange, and like the enolate **26**, organolithium *M*-**34** retains its absolute stereochemistry at least over a period of minutes at low temperature, long enough to relay its stereochemistry to the new stereogenic centre of **37**. Lactonisation gave *ent*-*O*-methylisoochracein **38** in 92 : 8 er.[31]

Amide conformation can be used as a means of relaying stereochemical information through space as well as time. Our first spatial stereochemical relay[24,32] used the racemic silane **39**, in which steric effects impose an 88 : 12 conformational preference on the amide (quantified by NMR in $CDCl_3$ at room temperature), to synthesise the meso amide **41** (Scheme 13). The lithio derivative of **40** has low kinetic stability on the laboratory timescale, even at low temperature,[33] but the persisting conformational influence of the adjacent silyl-bearing centre ensures the success of the relay.



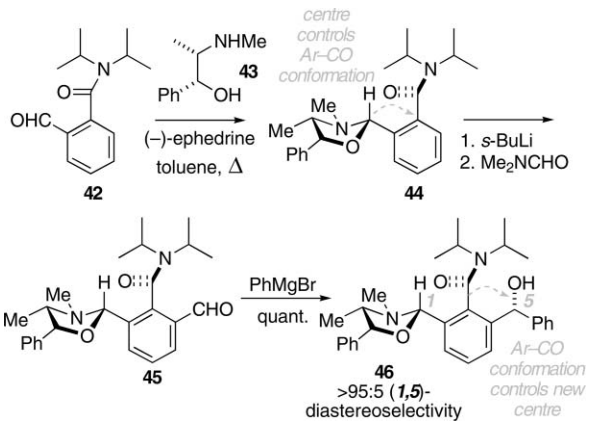
Scheme 12 Chiral memory *via* the Ar–CO axis of a tertiary aromatic amide.



Scheme 13 1,5-Stereochemical relay through an amide axis.

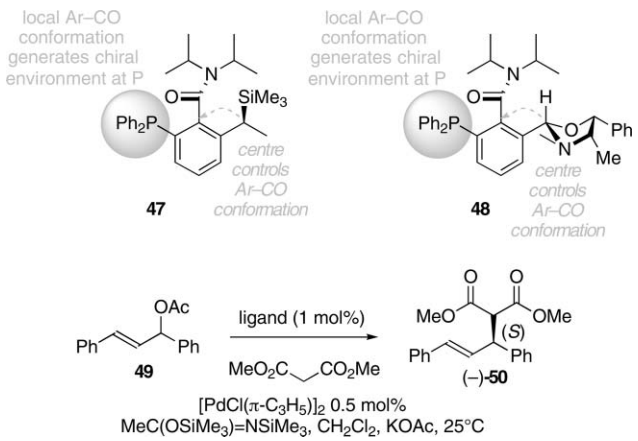
A reliable source of conformational control over aromatic amides, and one which is easily introduced in enantiomerically pure form, is the (−)-ephedrine-derived oxazolidine featured in **44**. It was known that condensation of an aromatic aldehyde with (−)-ephedrine **43** leads preferentially to one of the two possible diastereoisomeric oxazolidines.[34] Intriguingly, though, an adjacent amide will adjust its conformation to ensure that the oxygen atoms of oxazolidine and carbonyl group, and likewise their bulky substituted nitrogen atoms, lie on opposing faces of the ring which bears them.[24,35] Thus condensation of **42** with **43** gives **44**, which adopts preferentially the conformation shown and retains that conformation through the formylation and addition reactions leading to **46**. Stereoselectivity of Grignard additions is governed by amide conformation,[30] and reaction of **45** with PhMgBr is fully diastereoselective (Scheme 14).[24]

In all of the examples above, stereochemical relay induces asymmetry at an otherwise locally achiral remote site in a molecule. That otherwise achiral site could alternatively be a point



Scheme 14 1,5-Stereocontrol by stereochemical relay from an oxazolidine.[36]

of coordination for a metal. Scheme 15 and Table 1 show how the phosphines **47**[28] and **48**,[36] whose chirality in the vicinity of phosphorus is the consequence of stereochemical relay from their chiral centres *via* the amide, can be moderately effective chiral ligands in the palladium-catalysed asymmetric allylic substitution of acetate **49** by dimethyl malonate (Scheme 15).

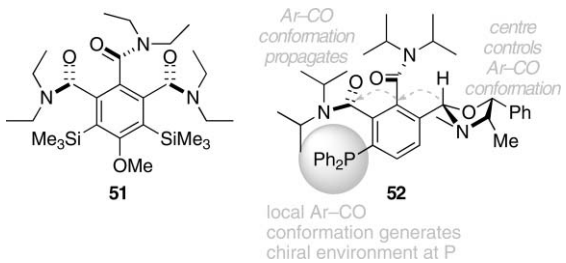


Scheme 15 Enantioselective allylic substitution catalysed by palladium in the presence of amidophosphine ligands.

In 1989, the crystal structure of **51** was reported.[37] The benzene-1,2,3-tricarboxamide adopts the conformation shown in Scheme 16: each amide carbonyl group points in a direction opposing its neighbours – presumably controlled by steric or electronic (dipole) interactions or both. On the assumption that

Table 1 Ligands for the enantioselective substitution of **45**

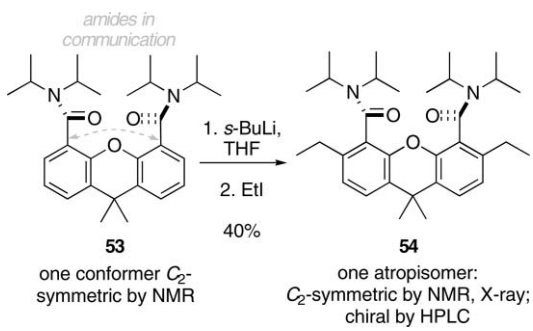
Entry	Ligand	Time	Yield	Product	er
1	**47**	3 days	60%	(−)-**50**	95 : 5
2	**48**	24 h	93%	(−)-**50**	91 : 9
3	**52**	24 h	85%	(+)-**50**	23 : 77



Scheme 16 Conformational interactions between adjacent amides.

the preference for nearby tertiary amide groups to adopt mutually opposing conformations persists in solution, we made the amide **52**, a homologue of the ligand **48**.[36] The phosphine was included in an allylic substitution reaction and gave moderate enantiomeric excess (Table 1, entry 3), but importantly the major enantiomer of the product **50** was opposite to that generated in the presence of the ligand **48**. This is exactly what is to be expected if the amides lie opposed to one another: the local environment of the phosphorus atom in **52** is enantiomeric with the local environment of the phosphorus centre of **48**, despite the stereochemistry originating from the same enantiomer of ephedrine.

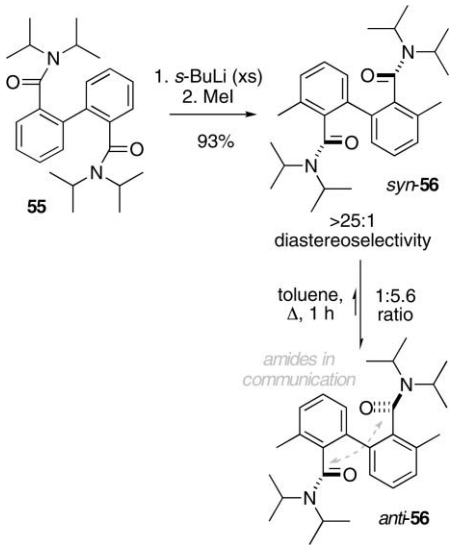
The *anti* alignment preferred in aromatic dicarboxamides turns out to be quite general, even with more remote relationships between the amide substituents.[38] The NMR spectrum of xanthene-1,8-dicarboxamide **53**, for example, contains a single 6 H singlet corresponding to the *gem*-dimethyl group, and double lithiation and electrophilic quench yields a compound **54** which in principle contains two stereogenic axes and may therefore exist as a pair of diastereoisomers. However, only a single diastereoisomer is obtained, which NMR showed to be C_2 symmetric, HPLC on a chiral stationary phase showed to be chiral and racemic, and X-ray crystallography showed to have the stereochemistry shown in Scheme 17.[39]



Scheme 17 *Anti*-preference in a xanthene-1,8-dicarboxamide.

Even amides borne on separate non-rigidly interconnected aromatic rings have a strongly preferred conformation. Amide **56** contains two stereogenic axes, but double ortholithiation of **55** gave only a single diastereoisomer *syn*-**56** (Scheme 18). We were able to prove its stereochemistry by HPLC on a chiral stationary phase: a separation into two enantiomers was just visible, indicating formation of racemic, C_2-symmetric *syn*-**56** rather than achiral, centrosymmetric *anti*-**56**.[40] However, this

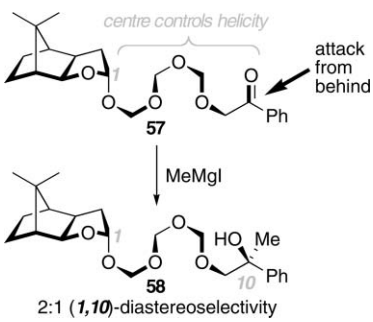
 This journal is © The Royal Society of Chemistry 2006



Scheme 18 Kinetic and thermodynamic stereocontrol in biphenyl-1,1′-dicarboxamides.

C_2-symmetric diastereoisomer turned out to be the less stable of the two, because heating in toluene gave a mixture of compounds in which the second, achiral diastereoisomer prevailed. The amides have a clear thermodynamic preference for the S_2-relationship, and biaryl 2,2′-dicarboxamides fall into the class of molecules which are "flexible with a defined shape".[41]

The question that posed itself at this point was how far stereochemistry could be communicated using conformational preference alone as the means of stereochemical relay. In 1988, Noe[42] had reported some chemistry which, though characterised by only poor stereoselectivity, gave the first indication that conformational control allows communication of stereochemical information over long distances. The anomeric effect forces paraformaldehyde oligomers to adopt a helical conformation in solution, and by tethering short chains of paraformaldehyde to a source of chirality it appears to be possible to induce the helix in **57** to prefer one of two diastereoisomeric conformations. Stereochemical information is transmitted to the new chiral centre in **58** by Grignard attack on a ketone. Stereoselectivity drops with chain length, but still reaches 2 : 1 for the 1,10-relationship formed in the reaction shown in Scheme 19. The importance of the polyether helix in mediating an interaction between the origin



Scheme 19 Relay of stereochemistry *via* a helix.

and terminus of the stereochemical relay was confirmed by control experiments showing that a hydrocarbon chain of the same length failed to induce selectivity.

Given that amides even with rather remote relationships are also capable of communicating with one another, we hoped to be able to use pairs of conformationally communicating groups to mediate remote stereocontrol by a form of staged stereochemical relay. The concept is illustrated in Fig. 1. A set of otherwise freely rotating groups *u–z* adopt, under the influence of a stereocontrolling influence at A, a single orientation which results in the transmission of information about the shape of A through *u–z* to B. Cowburn and Welland had demonstrated a similar concept using quantum dot magnets spaced 135 nm apart:[43] stereochemical relay using amide dipoles could reduce the scale of the system by a factor of about 300.†

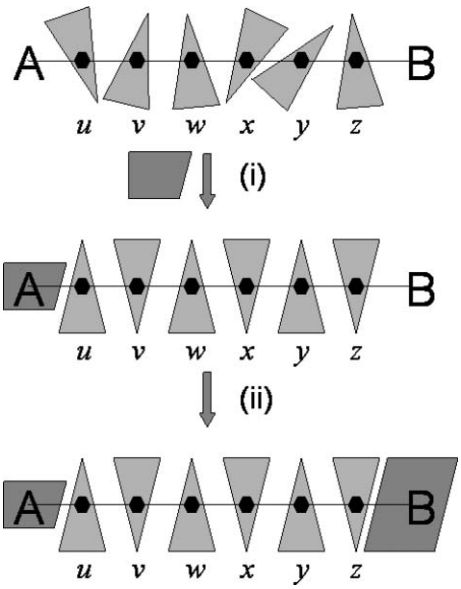
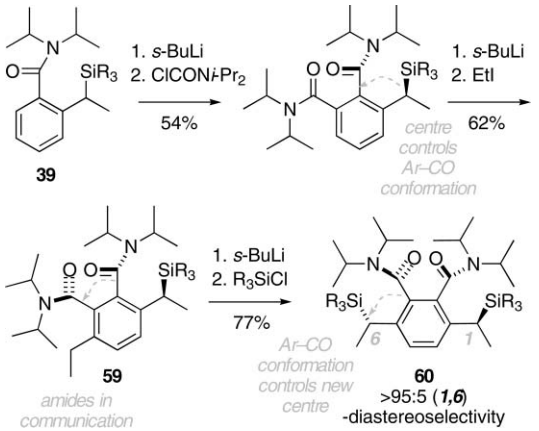


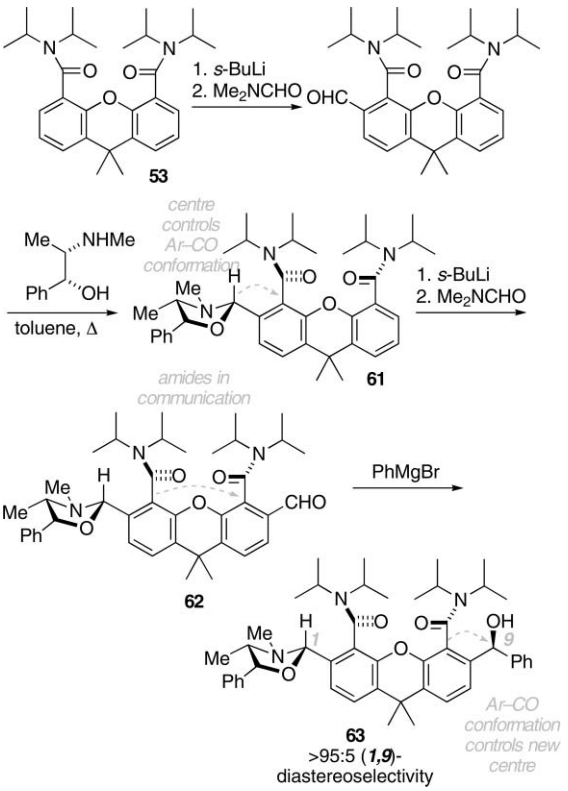
Fig. 1 A strategy for the conformational relay of information from A to B. Groups *u–z* are freely rotating but on incorporation (i) of a stereochemical influence at A adopt an "all-*anti*" alignment, allowing information about the shape of A to be relayed to B *via u–z*. (ii) Formation of new stereochemistry at B can take place diastereoselectively despite the remoteness of A.

Stages in the development of this idea are shown in Schemes 20,[32] 21[39,44] and 22.[40] In Scheme 20, the conformation of the axis adjacent to the stereogenic centre of **39** is relayed round the ring by introduction of a second axis into **59** adjacent to the first. When the second stereogenic centre of **60** is constructed adjacent to this axis, its stereochemistry is under the ultimate control of the centre lying *para* across the ring.[32] In Scheme 21, the idea is taken a stage further: the two amides of **53** are already related by the *anti* conformational preference of such systems; introduction of an ephedrine-derived oxazolidine into **61** forces both axes to adopt a single absolute conformation. The stereochemistry of the oxazolidine is relayed through both amides and allows the subsequent addition of a nucleophile to the carbonyl group of **62** to proceed with complete 1,9-stereochemical control, and **63** is

† The 1 and 8 positions of a xanthene ring are about 4.6 Å apart.



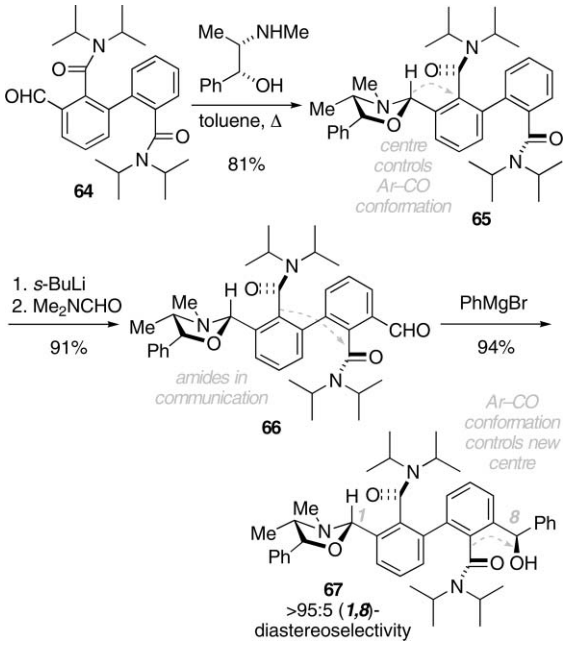
Scheme 20 Remote 1,6-stereocontrol relayed through a benzene-1,2-dicarboxamide.



Scheme 21 Remote 1,9-stereocontrol relayed through a xanthene-1,8-dicarboxamide.

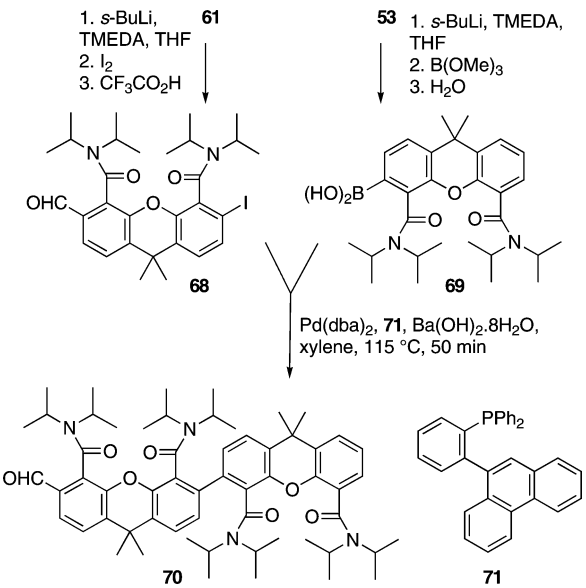
formed as a single diastereoisomer.[39,44] In Scheme 22, the amides also adopt conformations which allow the molecule as a whole to minimise its dipole moment. Thus the oxazolidine of **65** controls both amide groups and thus also ultimately directs nucleophilic attack on the remote carbonyl group of **66**, leading to complete 1,8-stereocontrol in **67**.[40]

The next logical step was to make some molecules containing both the features of both 1,8-xanthenedicarboxamides



Scheme 22 Remote 1,8-stereocontrol relayed *via* a biphenyl-1,1′-dicarboxamide.

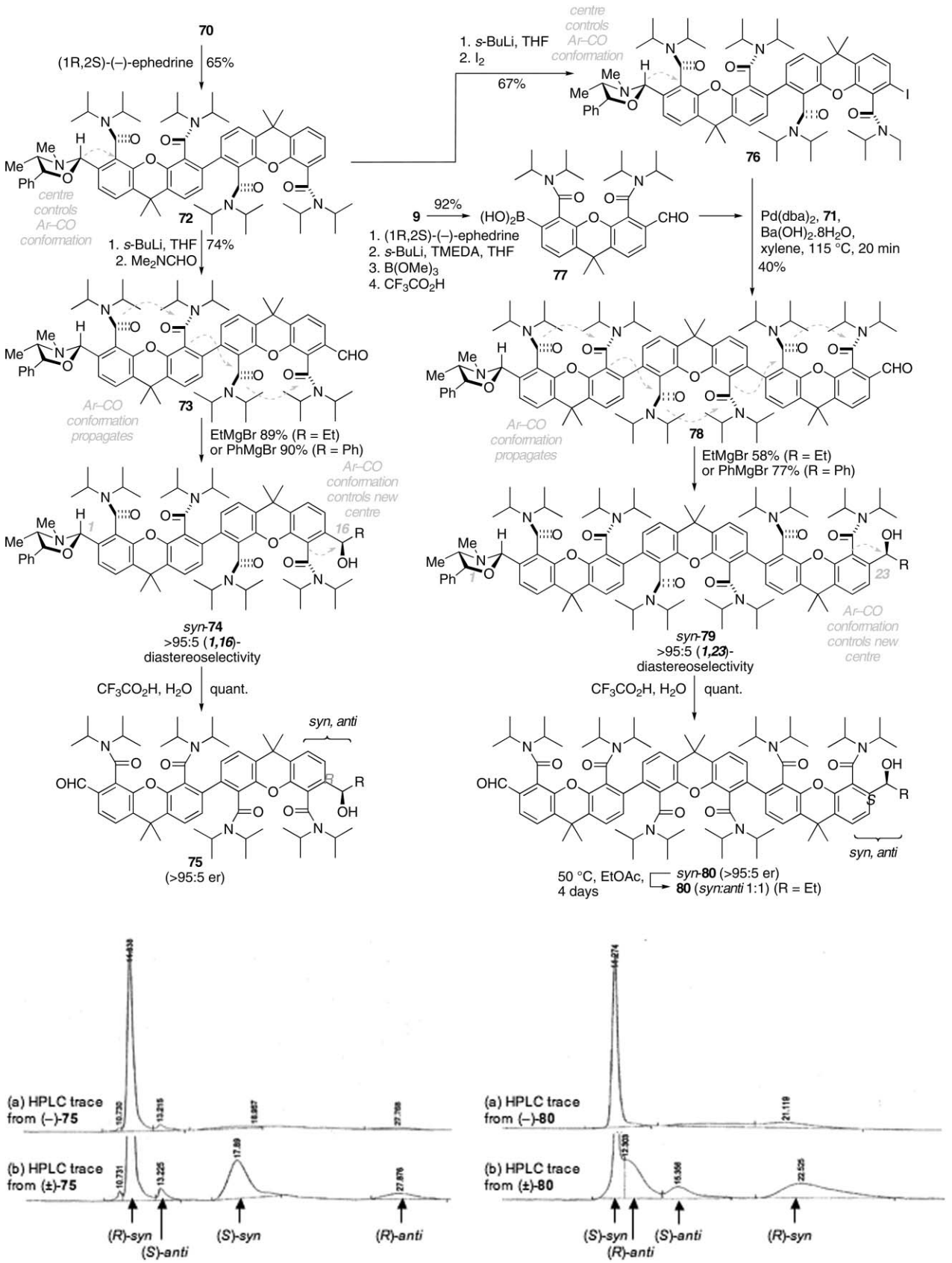
and biphenyl-2,2′-dicarboxamides. Extensive work to establish optimum conditions for Suzuki couplings allowed us to synthesise the conformationally uniform (by NMR) bis-xanthene **70** *via* the route shown in Scheme 23.[44]



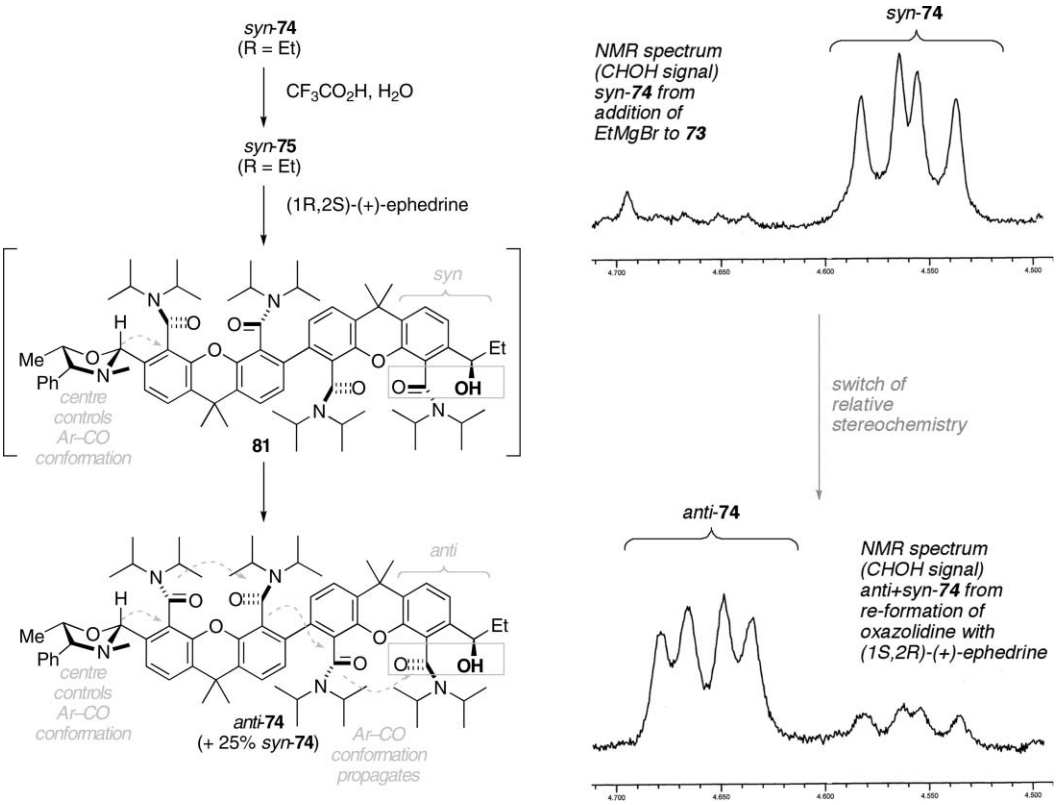
Scheme 23 Synthesis of a bis-xanthene.

From **70**, a further series of lithiations, functionalisations and coupling gave two aldehydes, **73** and **78**, in which the electrophilic centre is separated from a terminal (−)-ephedrine-derived oxazolidine by a chain of four or six amide groups respectively. The X-ray

 This journal is © The Royal Society of Chemistry 2006



Scheme 24 Stereochemical relay in a bis- and tris-xanthene.



Scheme 25 Switching relative stereochemistry from a distance

crystal structure of **78** shows all six amides arranged with their dipoles successively opposed.

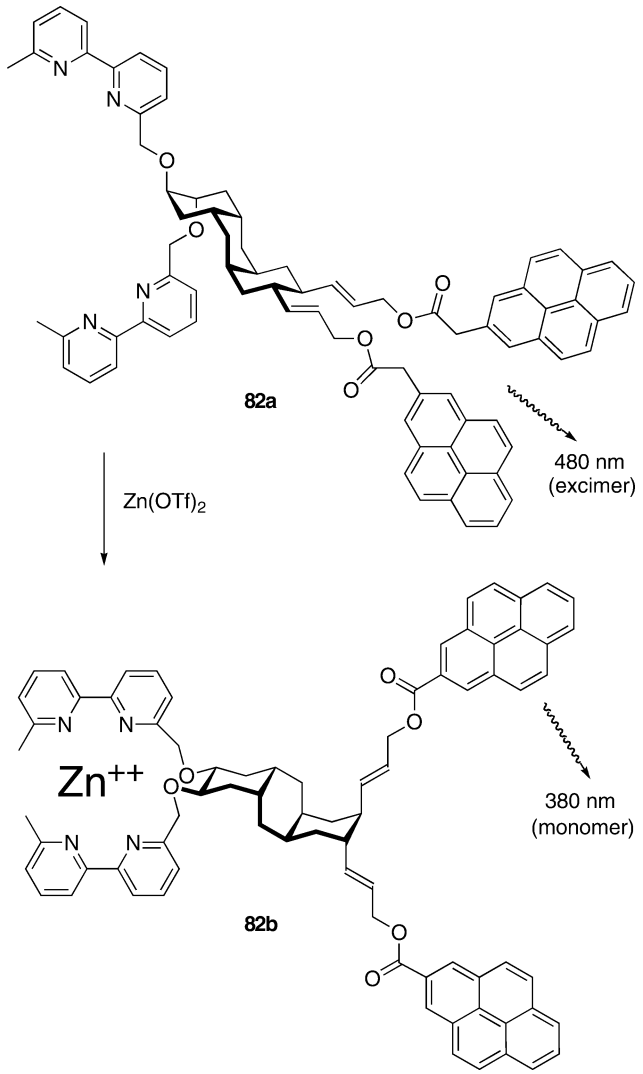
Nucleophilic addition of EtMgBr and PhMgBr to each aldehyde generated a single stereoisomer of the product **74** or **79**, as judged by NMR and by HPLC (Scheme 24), in reactions displaying relayed unprecedented 1,16- and 1,23-remote stereocontrol. Stereochemical homogeneity at the newly formed centre was confirmed by hydrolysis of the oxazolidines to yield aldehydes **75** and **80**. Comparison of the HPLC traces of these aldehydes with those of authentic mixtures of stereoisomers showed some degree of thermal epimerisation (from the deprotection step), but allowed the degree of stereocontrol at the new centre to be quantified as >95 : 5 (Scheme 24).[44]

Alternative explanations for the stereocontrol achieved in **74** and **79**, such as association between the oxazolidine ring of one molecule with the Grignard reagent as it adds to another, were ruled out by showing for example that diastereoselectivity is unchanged in reactions of racemic oxazolidines. Conclusive evidence that stereochemical information may be relayed through the amides was obtained simply by re-condensing **74** (R = Et) with ephedrine enantiomeric with that first used to form the oxazolidine (Scheme 25). Initially, presumably, **81** is formed, but under the conditions of the oxazolidine formation, the amides of **81** relax into their preferred orientation. Necessarily, the relative stereochemistry between the last amide in the sequence and the stereogenic centre adjacent to it becomes inverted, and this local inversion of relative stereochemistry is clearly evident in the chemical shifts of the C*H*OH signals of the two samples of **74** (Scheme 25).

The chemistry in Schemes 24 and 25 shows conformational information being relayed through a molecule in a manner which parallels the allosteric conformational changes in enzymes and receptors which relay information in biological molecules. So far the "output" of the conformational change has been a stereoselective reaction, detectable chromatographically or spectroscopically. Other inputs and outputs can be envisaged, though: for example, Krauss and Koert[45] have developed molecules which use conformational information to mediate signal transduction between a metal binding site and a fluorophore (Scheme 26). Tricyclic **82** adopts the preferred conformation shown as **82a**, but on treatment with zinc a switch occurs to the ring-flipped **82b**. Evidence for the ring flip is provided by NMR or by a change in the fluorescence spectrum as the pyrene fluorophores move apart.[46]

The possibility that the synthetic methodology of remote stereocontrol might be applied to a challenge in nanotechnology – signal transduction and processing – is intriguing, and it is clear that the future in this area is very bright. There are huge opportunities for the combination of various types of conformational control elements to lead not just to systems capable of relaying information but of processing and storing that information as well.

 This journal is © The Royal Society of Chemistry 2006



Scheme 26 Conformational relay of binding information to a fluorophore.

Acknowledgements

We are grateful for ongoing support from the EPSRC, Leverhulme Trust, GlaxoSmithKline, Organon, AstraZeneca, Novartis and Pfizer.

References

1 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
2 W. S. Knowles, *Angew. Chem., Int. Ed.*, 2002, **41**, 1998; R. Noyoi, *Angew. Chem., Int. Ed.*, 2002, **41**, 2008; K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2024.
3 K. Mikami, M. Shimizu, H.-C. Zhang and B. E. Maryanoff, *Tetrahedron*, 2001, **57**, 2917.
4 Y. Tamai, T. Hattori, M. Date, H. Takayama, Y. Kamikubo, Y. Minato and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1141; M. Date, Y. Tamai, T. Hattori, H. Takayama, Y. Kamikubo and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, 2001, 645; P. Linnane, N. Magnus and P. Magnus, *Nature (London)*, 1997, **385**, 799; N. Magnus and P. Magnus, *Tetrahedron Lett.*, 1997, **38**, 3491.
5 I. Fleming, G. R. Jones, N. D. Kindon, Y. Landais, C. P. Leslie, I. T. Morgan, S. Peukert and A. P. Sarkar, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1171.
6 I. Paterson and A. N. Hulme, *J. Org. Chem.*, 1995, 3288.
7 E. J. Thomas, *Chem. Commun.*, 1997, 411; E.-M. Moffatt and E. J. Thomas, *Tetrahedron*, 1999, **55**, 3723.
8 W. C. Still and V. J. Novack, *J. Am. Chem. Soc.*, 1984, **106**, 1148.
9 S. D. Bull, S. G. Davies, D. J. Fox and T. G. R. Sellers, *Tetrahedron: Asymmetry*, 1998, **9**, 1483. Stereochemical relay around a five-membered ring *via* a Boc group has also been proposed – see: M. Oba, T. Terauchi, J. Hashimoto, T. Tanaka and K. Nishiyama, *Tetrahedron Lett.*, 1997, **38**, 5515.
10 S. D. Bull, S. G. Davies, S. W. Epstein, M. A. Leech and J. V. A. Ouzman, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2321.
11 O. Corminboeuf, L. Quaranta, P. Renaud, M. Liu, C. P. Jasperse and M. P. Sibi, *Chem.–Eur. J.*, 2003, **9**, 29.
12 L. Quaranta, O. Corminboeuf and P. Renaud, *Org. Lett.*, 2002, **4**, 39.
13 R. E. Gawley, *J. Org. Chem.*, 2006, **71**, 2411.
14 M. P. Sibi, L. Venkatraman, M. Liu and C. P. Jasperse, *J. Am. Chem. Soc.*, 2001, **123**, 8444.
15 M. P. Sibi and M. Liu, *Org. Lett.*, 2001, **3**, 4181.
16 We assume this is generally the case. Even if it is not, the explanations presented for the stereochemical relays may still hold, but the situation will be complicated by the relative reactivities of the conformers involved. See ref. 17 and N. S. Zefirov, *Tetrahedron*, 1977, **33**, 2719.
17 M. Petit, A. J. B. Lapierre and D. P. Curran, *J. Am. Chem. Soc.*, 2005, **127**, 14994.
18 D. P. Curran, G. R. Hale, S. J. Geib, A. Balog, Q. B. Cass, A. L. G. Degani, M. Z. Hernandes and L. C. G. Freitas, *Tetrahedron: Asymmetry*, 1997, **8**, 3955.
19 T. Kawabata, H. Suzuki, Y. Nagae and K. Fuji, *Angew. Chem., Int. Ed.*, 2000, **39**, 2155.
20 K. Fuji and T. Kawabata, *Chem.–Eur. J.*, 1998, 373.
21 For a recent summary of reactions displaying chiral memory effects, see: M. A. Bonache, G. Gerona-Navarro, M. Martín-Martínez, M. T. García-López, P. López, C. Cativela and R. González-Muñiz, *Synlett*, 2003, 1007 and references therein. This paper describes a memory effect which does *not* rely on retention of conformation.
22 D. P. Curran, W. Liu and C. H.-T. Chen, *J. Am. Chem. Soc.*, 1999, **121**, 11012; D. P. Curran, C. H.-T. Chen, S. J. Geib and A. J. B. Lapierre, *Tetrahedron*, 2004, **60**, 4413; M. Petit, S. J. Geib and D. P. Curran, *Tetrahedron*, 2004, **60**, 7543.
23 J. Clayden, *Chem. Commun.*, 2004, 127.
24 M. S. Betson, J. Clayden, M. Helliwell, P. Johnson, L. W. Lai, J. H. Pink, C. C. Stimson, N. Vassiliou, N. Westlund, S. A. Yasin and L. H. Youssef, *Org. Biomol. Chem.*, 2006, 424.
25 M. S. Betson, J. Clayden, M. Helliwell and D. Mitjans, *Org. Biomol. Chem.*, 2005, 3898.
26 A. Ahmed, R. A. Bragg, J. Clayden, L. W. Lai, C. McCarthy, J. H. Pink, N. Westlund and S. A. Yasin, *Tetrahedron*, 1998, **54**, 13277.
27 J. Clayden, D. Mitjans and L. H. Youssef, *J. Am. Chem. Soc.*, 2002, **124**, 5266; J. Clayden, L. W. Lai and M. Helliwell, *Tetrahedron*, 2004, **60**, 4399; J. Clayden, M. Helliwell, C. McCarthy and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3232.
28 J. Clayden, P. Johnson, J. H. Pink and M. Helliwell, *J. Org. Chem.*, 2000, **65**, 7033.
29 J. Clayden, *Synlett*, 1998, 810; P. Bowles, J. Clayden, M. Helliwell, C. McCarthy, M. Tomkinson and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2607; J. Clayden, N. Westlund, R. L. Beddoes and M. Helliwell, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1351; J. Clayden, N. Westlund and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1379; J. Clayden, M. Helliwell, J. H. Pink and N. Westlund, *J. Am. Chem. Soc.*, 2001, **123**, 12449; J. Clayden, J. H. Pink, N. Westlund and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2002, 901.
30 J. Clayden, C. McCarthy, N. Westlund and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1363.
31 J. Clayden, C. C. Stimson and M. Keenan, *Synlett*, 2005, in press.
32 J. Clayden, J. H. Pink and S. A. Yasin, *Tetrahedron Lett.*, 1998, **39**, 105.
33 J. Clayden, C. C. Stimson, M. Keenan and A. E. H. Wheatley, *Chem. Commun.*, 2004, 228.
34 C. Agami and T. Rizk, *J. Chem. Soc., Chem. Commun.*, 1983, 1485; C. Agami and T. Rizk, *Tetrahedron*, 1985, **41**, 537.
35 J. Clayden and L. W. Lai, *Tetrahedron Lett.*, 2001, **42**, 3163.
36 J. Clayden, L. W. Lai and M. Helliwell, *Tetrahedron: Asymmetry*, 2001, **12**, 695.

37 R. J. Mills, N. J. Taylor and V. Snieckus, *J. Org. Chem.*, 1989, **54**, 4372.
38 M. S. Betson, J. Clayden, H. K. Lam and M. Helliwell, *Angew. Chem., Int. Ed.*, 2005, **44**, 1241.
39 J. Clayden, M. N. Kenworthy and L. H. Youssef, *Tetrahedron Lett.*, 2000, **41**, 5171.
40 J. Clayden, A. Lund and L. H. Youssef, *Org. Lett.*, 2001, **3**, 4133.
41 R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 2054.
42 C. R. Noe, M. Knollmüller and P. Ettmayer, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1379.
43 R. P. Cowburn and M. E. Welland, *Science*, 2000, **287**, 1466.
44 J. Clayden, A. Lund, L. Vallverdú and M. Helliwell, *Nature (London)*, 2004, **431**, 966.
45 R. Krauss and U. Koert, *Synlett*, 2003, 598.
46 H.-G. Weining, R. Krauss, M. Seydack, J. Bendig and U. Koert, *Chem.–Eur. J.*, 2001, **7**, 2075.

This journal is © The Royal Society of Chemistry 2006