FEATURE ARTICLE

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Atropisomers and near-atropisomers: achieving stereoselectivity by exploiting the conformational preferences of aromatic amides

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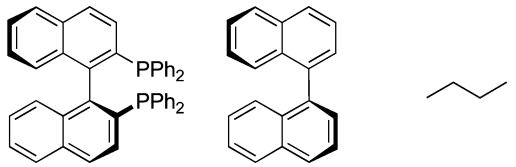
The conformational preferences of aromatic amides are remarkably easy to control with a high degree of selectivity. This article reviews the consequences of this unusual form of stereocontrol, which enables for example the asymmetric synthesis of atropisomers and the ability to achieve remote stereocontrol by conformational relay.

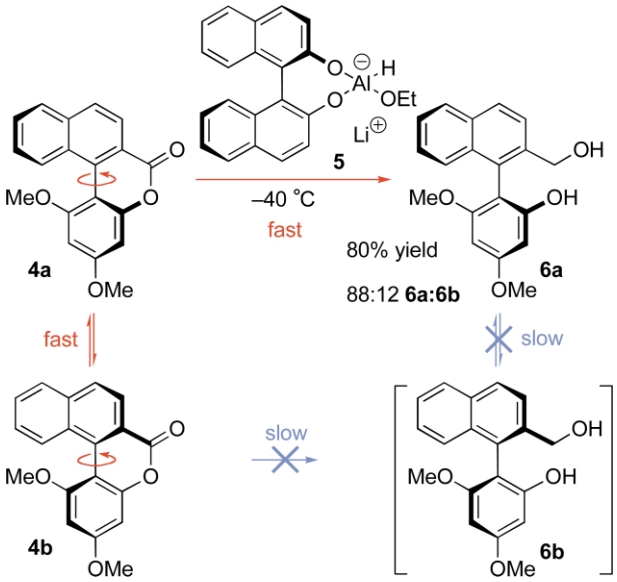
Introduction

The boundary between atropisomers and conformers (and therefore between configuration and conformation) is delineated by Oki's arbitrary definition[1] that atropisomers are conformers which interconvert with a half-life of more than 1000 s at a given temperature. By this definition, BINAP **1** is atropisomeric up to at least 200 °C, 1,1′-binaphthyl **2** ceases to be atropisomeric just below 50 °C,[2] and butane **3** becomes atropisomeric (existing as one achiral and one chiral diastereoisomer) at temperatures below about −220 °C.[3] In the quest for stable atropisomeric systems usable as chiral ligands, chemists have tended to ignore compounds close to Oki's boundary, presumably reasoning that they would be too easily racemised for general use in asymmetric reactions.



1 **2** **3**

But is stereochemical lability always a disadvantage? Maybe so if the conformers or atropisomers concerned are enantiomeric: racemisation by thermal equilibration will lead to loss of stereochemical information. Nonetheless, interconversion of enantiomeric "near-atropisomers" has been exploited by Bringmann in some elegant asymmetric syntheses of atropisomeric natural products using dynamic kinetic resolution.[4] In a simple example, Scheme 1 shows two lactones **4a** and **4b** which are enantiomeric



Scheme 1 Bringmann's method for dynamic *kinetic* resolution in the asymmetric synthesis of a biaryl.[5]

conformers even at −40 °C, interconverting rapidly on the timescale of their reduction by the BINAL reagent **5**. One of them (**4a**) reacts faster than the other, and generates a product **6a** which, because it lacks the bridging lactone linkage, is atropisomeric up to ambient temperature and beyond. As **4a** reacts, equilibrium with **4b** is continually restored, and eventually a product **6a** is formed in good yield and with good enantioselectivity by *dynamic kinetic resolution*.[5]

Atropisomers are perfectly suited to dynamic processes such as this because small changes in structure often have a large impact on their thermal stereochemical stability. Dynamic processes frequently feature in our own work, and many are highlighted in this article, but in nearly all cases these processes are controlled by the *thermodynamic* stability of the molecules themselves and not the *kinetics* of their reactions.

The conformers of **4** are enantiomeric and must therefore be present in a 1 : 1 ratio in their readily attained equilibrium. But if two conformers or atropisomers are diastereoisomeric, they will necessarily differ in energy. Thermal equilibration will lead to a bias towards the more stable conformer. Mikami has applied this idea in a family of ligands containing a "near-atropisomer" (or, in his terminology, *tropos* ligand) whose conformation is governed by the structure of the rest of the complex,[6] and other chemists have developed the idea that the stereocontrolling effect of a relatively isolated or remote stereogenic centre may be amplified if it can influence the conformation of a more substantial portion of a molecule.[7–10]

In our research, we have viewed the equilibration of two diastereoisomeric conformers "near-atropisomers" as a potentially

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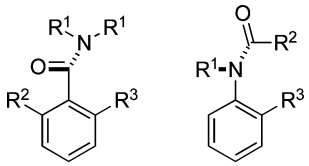
stereoselective reaction: the aspect we need to control is simply the degree of stereoselectivity — in other words the free energy difference between the conformers. Can we identify atropisomeric or near-atropisomeric molecules which can be equilibrated, thermally, to a single conformer, and whose resulting stereochemistry can then be retrieved (in the form of the stereogenic bond of a stable atropisomeric compound) or exploited?

Although commercially available enantiomerically pure atropisomers such as BINAP are all made by resolution, there have been recent notable successes in the asymmetric synthesis of atropisomers by *kinetically* controlled coupling reactions or *kinetically* controlled dynamic resolutions.[11,12] In this article, I shall review some methods for the synthesis of atropisomers based upon *thermodynamic* control, and show how insights we have gained during this work have started to lead us beyond the asymmetric synthesis of atropisomers to the point where we are able to control and exploit conformation in a more widely applicable sense.

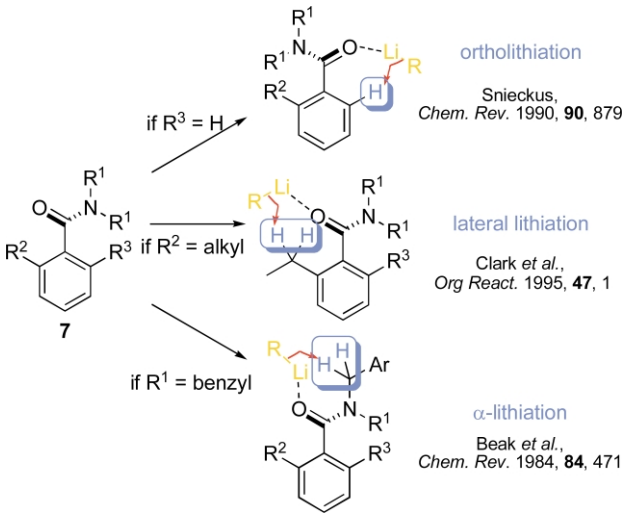
Aromatic amides: synthetically versatile atropisomers

The majority of ambient-temperature atropisomeric molecules familiar to chemists are biaryls, and the class of atropisomeric biaryls includes some of the most successful chiral ligands ever made.[14] Non-biaryl atropisomers[15] remained largely a stereochemical textbook curiosity[3] until a few research groups around the world demonstrated a series of atroposelective reactions in which the stereochemistry of the non-biaryl atropisomer was able to govern the formation of a new stereogenic centre.[16–21] For reasons associated with the rigidity of the amide linkage, the most studied of these non-biaryl atropisomers have been either benzamide derivatives **7** or anilides **8**.



7 **8**

We chose to develop the stereoselective chemistry of the amides **7** (with R = *i*-Pr or R = Et — though we prefer the former because the NMR spectra are clearer, barriers to bond rotation are marginally higher, and the compounds are generally more crystalline) not just because of their interesting conformational properties but also because of the structural variation which can be introduced courtesy of their versatile ortho-,[22–25] lateral[26] and α-lithiation[27] chemistry (Scheme 2).[13] Barriers to isomerisation in the benzamide

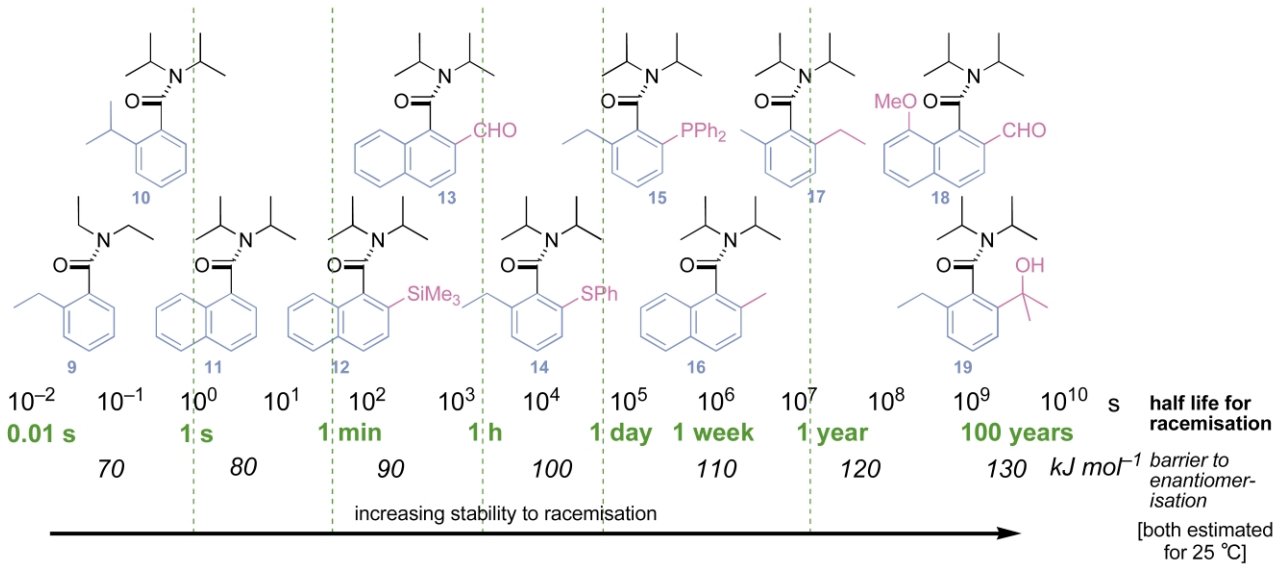


Scheme 2 Lithiation chemistry of tertiary aromatic amides **7**.[13]

series depend principally on the nature of the substituents ortho to the amide,[28] the very substituents which can be modified using lithiation chemistry. Tertiary aromatic amides **7** are among the best of all ortholithiation directors[25] and we were able to use ortholithiation to make a range of benzamide and naphthamide derivatives and to study their rates of racemisation[29] and the stereoselectivity of their reactions.[30]

Stereochemical stability and lability in amides

We soon found that *complete* stereochemical stability can be achieved only in the most hindered of amides. Scheme 3 shows half-lives for racemisation of a representative series of substituted benzamides and 1-naphthamides. The most stereochemically stable are *peri*-substituted naphthamides:[31] 2,8-disubstitution in a 1-naphthamide **18** yields half-lives for racemisation which can be measured in years (approximate half-lives quoted are in solution at



Scheme 3 Some representative aromatic amides and their half-lives for racemisation and barriers to bond rotation (enantiomerisation).

25 °C). Amides such as **19** bearing a fully substituted carbon at one *ortho* position and any non-hydrogen substituent at the other are similar: **19** has a half-life for racemisation at 25 °C of 30 years.[32] Other 2,6-disubstituted benzamides or 2-substituted 1-naphthamides are typically atropisomeric at ambient temperature, but have rather shorter half-lives for racemisation.[29,32] Two kinds of *ortho*-substituent undermine enantiomeric stability — substituents based on second row elements (amides with Si,[29] P,[32] or S-based[33] 2-substituents typically racemise with very low barriers) and freely-rotating trigonal substituents (formyl substituents in particular).[29,34,35] Interestingly, the size of the substituents at nitrogen (as long as they are not H) has a relatively minor effect of the rate of racemisation; with a pair of non-identical *N*-substituents R^1, the smaller of the two controls the rate of racemisation.[29,36]

Tertiary benzamides with a single *ortho* substituent present an interesting case because they are typically not atropisomeric, but their conformers interconvert slowly on the NMR timescale. Thus **11** shows, in its NMR spectrum, all the features of a chiral molecule (diastereotopic pairs of methyl signals for example) yet it cannot be resolved. Variable temperature (VT) NMR[29,37] and more recently saturation transfer studies[36] have allowed us to quantify the rates of rotation in these molecules.

The amides in Scheme 3 have no stereochemical features apart from the Ar–CO axis. But introduce a stereogenic centre into a molecule such as **20** with a two-fold rotational axis, and the two otherwise enantiomeric conformers or atropisomers *anti*-**20** and *syn*-**20** become diastereoisomeric, and therefore necessarily of different stability. And because they interconvert slowly on the NMR timescale, the ratio of diastereoisomers can be observed simply by running an NMR spectrum. Amide **20** for example, exhibits an 87 : 13 mixture of diastereoisomeric conformers in its NMR spectrum at ambient temperature in $CDCl_3$ (Fig. 1).

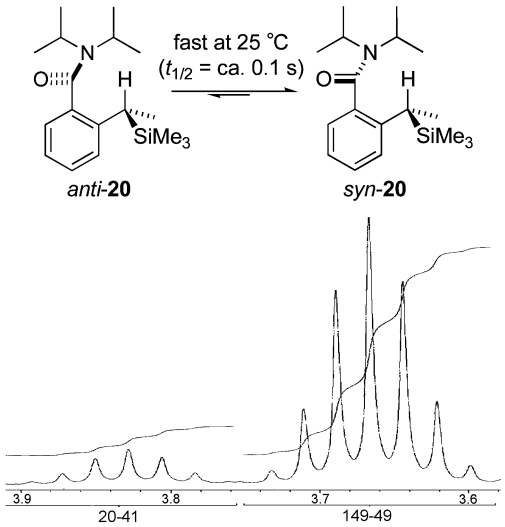
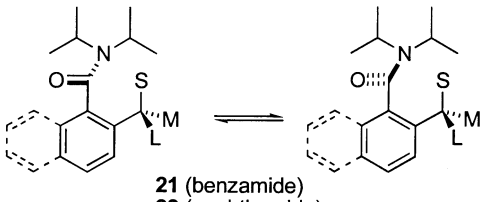


Fig. 1 A portion of the ^{1}H NMR spectrum of **20**, illustrating the presence of two diastereoisomeric conformers.

Conformational control

A difference in free energy between two diastereoisomeric conformers of about 7 kJ mol^{-1} at ambient temperature is sufficient to make one predominate over the other in a ratio of 94 : 6.[38] We have now established a group of five or so classes of stereogenic centre which, when placed adjacent (*ortho*) to the Ar–CO axis of an aromatic amide, are able to achieve stereocontrol at least at this level — and even much higher in some cases. At the temperatures indicated in Table 1, all of the compounds represented by the general structures **21** and **22** (with S, M and L representing three different, though not necessarily sterically differentiated, groups) equilibrate to the thermodynamically-controlled ratios of conformers (for **21**, measured by NMR) or atropisomers (for **22**, measured by NMR or HPLC) indicated.

Table 1 Conformational preferences in benzamides **21** and naphthamides **22** bearing chiral 2-substituents



21 (benzamide)
22 (naphthamide)

Entry	S, M, L =		R =	Ratio of conformers	*T*/°C	Ref.
1	H, Me	**21a**	—	55 : 45	25	56
2		**22a**	—	60 : 40	65	51
3	H, OH, R	**22b**	Me	38 : 62	62	29
4		**22c**	Et	42 : 5	55	29
5		**22d**	Bu	36 : 64	62	29
6		**22e**	Ph	36 : 64	60	29
7		**22f**	*t*-Bu	89 : 11	110	55
8	H, Me, $SiMe_2R$	**20**	Me	87 : 13	25	56
9		**21g**	Ph	92 : 8	25	56
10		**22g**	Me	94 : 6	65	51
11	H, Me, $SnBu_3$	**22h**	—	97 : 3	65	52
12	H, O, N, Ph	**21i**	—	> 95 : 5	25	57
13		**22i**	—	> 95 : 5	110	57
14	H, N, N, Ph	**22j**	—	> 90 : 10	110	58
15	S, O, R	**22k**	Me	> 95 : 5	25	33
16		**22l**	*t*-Bu	> 98 : 2	25	
17		**22m**	Ph	> 98 : 2	25	
18		**22n**	*p*-Tol	> 99 : 1	25	

The ability of these stereogenic centres to control the conformation of an adjacent axis is itself a form of stereoselectivity, but one in which thermodynamic control and not kinetic control governs the stereochemical outcome. Thermodynamic stereocontrol has classically been used widely in ring synthesis — for example, equilibration to allow an all-equatorially substituted cyclohexane or an *exo*-substituted bicycle — and is operative in crystallisation-induced stereoselective transformations.[39–47] It has been shown to be an important strategy for achieving enantioselectivity with

organolithium compounds.[48] Some applications to biaryl synthesis are discussed below, but the use of thermodynamic stereocontrol outside of these areas is rare.[49,50]

What is striking in Table 1 is the way in which high levels of control arise even from simple "off the shelf" systems — the stereogenic centres involved were most certainly not the result of an extensive search — indeed quite the opposite. Our first observation of the effect was with **22g** and **22h**, which we made as part of an investigation of kinetic stereoselectivity in the lateral lithiation of 2-ethyl substituted amides.[51–54] The discovery of the effect with **22j** and **22i**, our first trials with easily-formed stereogenic centres of defined configuration, followed shortly afterwards. **22f** was a deliberate attempt to see if another type of easily formed centre would provide stereocontrol,[55] and **22m** was first accidentally observed during a stereoselective sulfide oxidation. So far, the only amides bearing a chiral 2-substituent which we have made but which have only a weak (< 85 : 15) conformational preference have been the *s*-butyl substituted compounds **21a/22a** and the various alcohols **22b–e**.

X-Ray crystallography allowed us in all cases to be certain of the stereochemistry of the major atropisomers of **22**, and to deduce the probable stereochemistry of the major conformers of **21**, and we initially assumed that the origin of the conformational preference was steric, as represented by Fig. 2. The smallest group borne by the

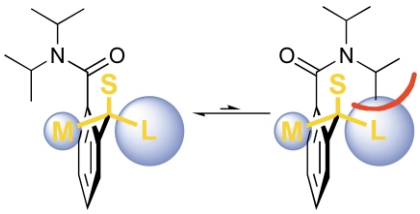


Fig. 2 Steric control over amide conformation.

stereogenic centre, S, would lie more or less eclipsing the amide, with the medium and large groups M and L occupying the two faces of the naphthalene ring system. The amide would then prefer a conformation which minimises interaction with the L group. However, the discovery that even methylsulfoxides such as **22k** exhibit high levels of conformational preference forced us to consider the possibility that dipole repulsion plays an important role in determining the stereochemistry of these compounds (Fig. 3). The true picture must be a combination of both factors, and ongoing modelling work is determining the importance of each.[59]

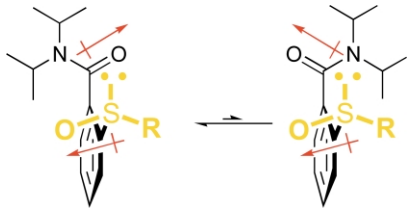
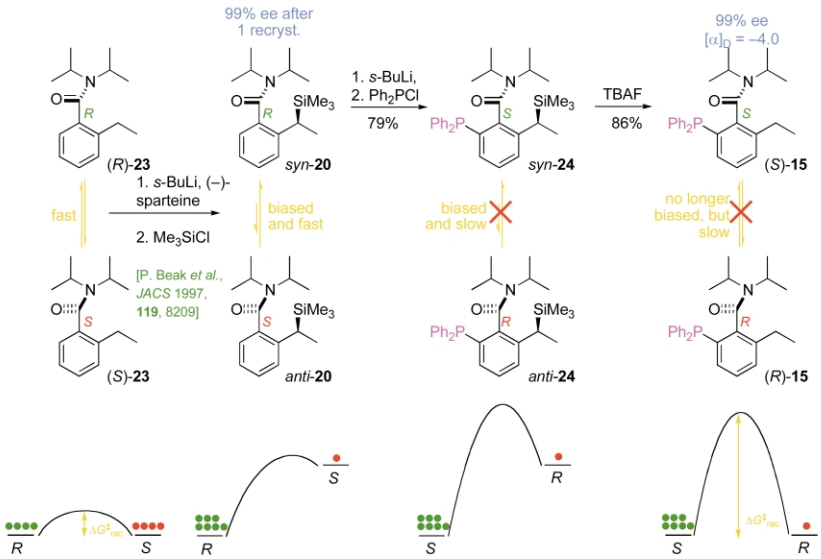


Fig. 3 Electronic control over amide conformation.

Asymmetric synthesis of atropisomers under thermodynamic control

This demonstration of the ability of stereogenic centres to govern the conformation of an adjacent axis was the breakthrough we needed in our attempts to find a general way of making atropisomeric amides **7** enantioselectively. The atroposelective synthesis of enantiomerically pure atropisomers had previously been confined to the biaryl field, with specific solutions to specific synthetic problems.[60] Thermodynamic control is particularly suited to compounds for which stereoisomeric interconversion can be achieved *via* a simple mechanism — thermally-induced bond rotation in the case of atropisomers. Meyers showed that thermodynamic control can be used in the asymmetric synthesis of biaryls,[61] and Uemura has published some nice examples of contrasted kinetic *versus* thermodynamic control in the synthesis of biaryls *via* arenechromium tricarbonyl complexes.[35,62,63] Some recent atroposelective syntheses of members of the vancomycin-teicoplanin class of antibiotics,[64–70] were achieved *via* thermodynamic control over the stereogenic Ar–Ar and Ar–OAr axes.

We have employed two conceptually different approaches to the asymmetric synthesis of non-biaryl atropisomers under thermodynamic control. An example of the first is shown in Scheme 4.[32] A stereogenic centre is constructed enantioselectively adjacent to an otherwise freely rotating (*i.e.* kinetically unconstrained) axis. In this instance, we used Beak's (−)-sparteine-directed silylation of the rapidly racemising 2-ethylbenzamide **23**,[71] which (after recrystallisation) allows us to make **20** in 99% ee. As discussed above, **20** prefers to adopt principally conformation *syn*-**20**. There is only a low kinetic barrier to rotational interconversion between the conformers of **20**, but this changes when the major *conformer* is trapped as a major *atropisomer* by increasing the steric hindrance to rotation about the axis. Lithiation and substitution of **20** introduces a kinetic barrier to conformer (now atropisomer) interconversion, and allows the major atropisomer *syn*-**24** to be obtained, after purification, enantiomerically and diastereoisomerically pure.



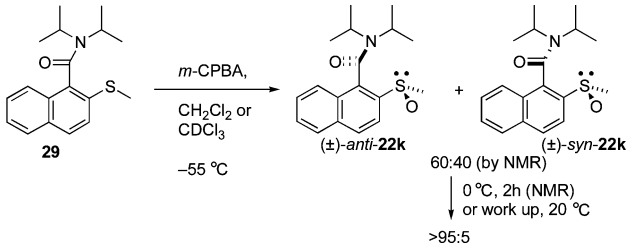
Scheme 4 Asymmetric synthesis of an atropisomeric amidophosphine under thermodynamic control.

Finally, removal of the stereogenic centre (by desilylation in this case) leaves a single atropisomeric enantiomer of the phosphine (*S*)-**15**, which, despite the loss of a thermodynamic preference for one atropisomer over the other, is unable to relax to thermodynamic equilibrium with (*R*)-**15** because of the residual kinetic barrier to rotation provided by the Et and PPh_2 groups. The method is amenable to various electrophiles, though in this form it always leaves an ethyl group at the 2-position of the benzamide.[32]

The second, practically more straightforward, method is illustrated in Scheme 5, which starts with a racemic atropisomer **13**. This compound is converted to a diastereoisomeric mixture of atropisomers, each diastereoisomer enantiomerically pure, by reaction with an enantiomerically pure "resolving agent". In the example illustrated here,[57] the resolving agent is (−)-ephedrine **25**, but a proline-derived diamine **27**[58] and (+)-pseudoephedrine **28**[57] are also successful. Resolution is achieved not by discarding 50% of the material but simply by heating, which overcomes the barrier to interconversion of atropisomers and dumps most of the material into the energetic well of the *anti* atropisomer of **22i**. Low temperature removal of the auxiliary (and reduction, to avoid the difficulties alluded to earlier of preventing racemisation of a 2-formylated atropisomer) provides (*R*)-**26** in 94% ee. Overall, resolution is achieved dynamically (no material is wasted) but under *thermodynamic* and not *kinetic* control. "Dynamic thermodynamic resolution" is a recently established feature of asymmetric organolithium chemistry,[72] and the same set of stereochemical events, illustrated diagrammatically in Scheme 5, occurs here.

The residual ethyl and hydroxymethyl groups of **15** and **26** prompted us to seek other "resolving agents" which could be removed in a more versatile manner. Our furthest advance in this area has been the use of the sulfoxides **22k–n**, which boast a remarkable collection of properties: easy to introduce in enantiomerically pure form, possessing low kinetic barriers to epimerisation but powerful conformation-controlling ability, and easily replaced in a constructive sulfoxide-lithium exchange step.

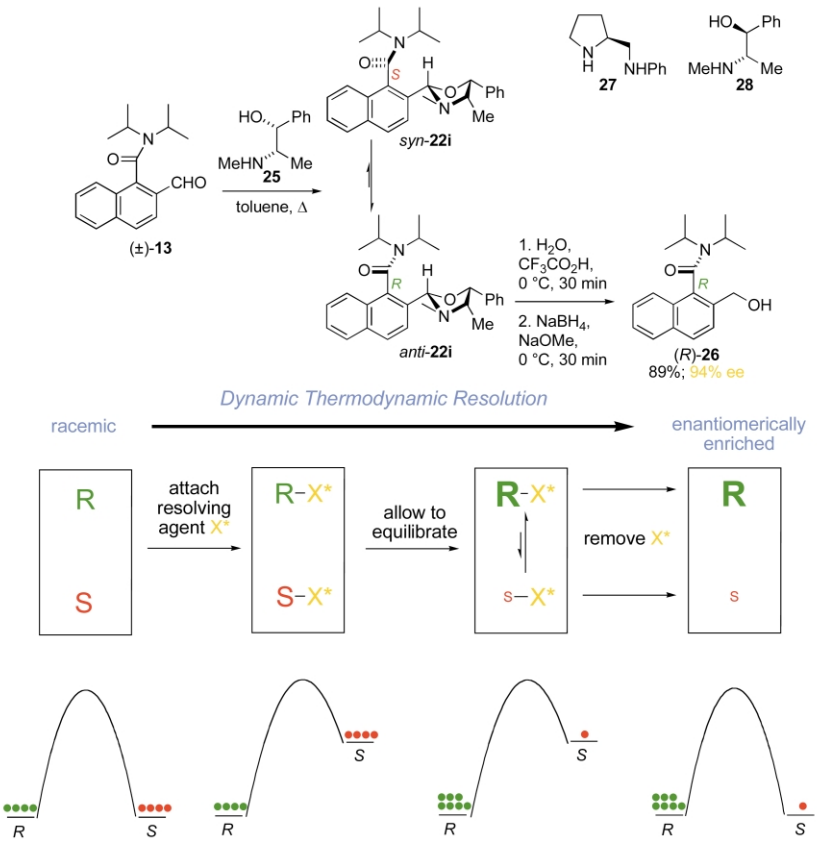
We first noticed the power of the controlling influence of the sulfoxide group when we were attempting amide-directed sulfide oxidation of **29** (Scheme 6): after work up at room temperature,



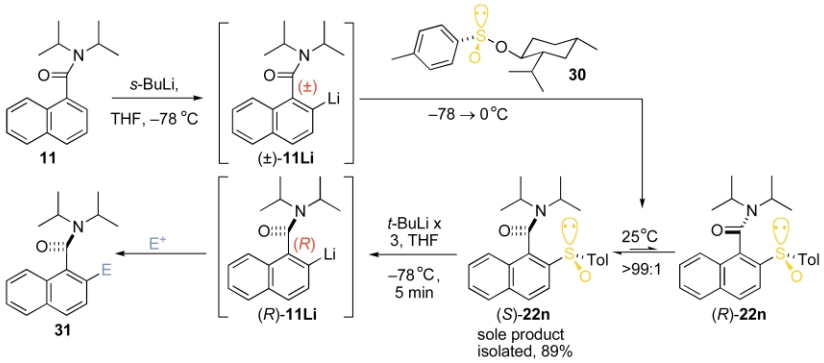
Scheme 6 Thermodynamic control in the stereoselective oxidation of an amidosulfide.

selectivity for *anti*-**22k** was near perfect, but investigation by NMR of the kinetic selectivity of oxidation at −55 °C showed much poorer selectivity: a sure sign that thermodynamic control is operative. By NMR, we could observe an initial 60 : 40 ratio of diastereoisomers of **22k** equilibrate to essentially diastereoisomeric purity within 2 h at 0 °C or in a matter of minutes at room temperature.[33] The remarkably low kinetic barrier reflects sulfur's position in the second row of the periodic table, as discussed above, but is far from a disadvantage, as it allows us to avoid the heating required for the thermal equilibration of **22i**.

This was all in the racemic series, but of course similar sulfoxides **22n** can be formed enantioselectively from **11** in one step using the method of Anderson[73,74] — nucleophilic substitution at sulfur of diastereoisomerically and enantiomerically pure (−)-menthyl sulfinate **30**. Ortholithiation of **11** and reaction with **30** gives material which is presumably initially formed as a mixture of conformers, but which is isolated solely as conformer (*S*)-*anti*-**22n** (Scheme 7), because equilibration of the diastereoisomeric atropisomers on work up gives extremely high (> 99 : 1) levels of



Scheme 5 Dynamic thermodynamic resolution in the asymmetric synthesis of atropisomers.



Scheme 7 Dynamic thermodynamic resolution *via* lithium-sulfoxide-lithium exchange.

thermodynamic conformational control (Table 1). A further property of the sulfoxide now comes into play: it can be removed by sulfoxide-lithium exchange, returning organolithium **11**Li in enantiomerically pure form. At this stage we have effectively carried out a dynamic thermodynamic resolution of **11**Li using the sulfoxide as the resolving agent. The enantiomerically pure atropisomeric ortholithiated amide **11**Li is of sufficient configurational stability to be intercepted by a range of electrophiles and give products **31** with high enantiomeric purity (Table 2).

Table 2 Asymmetric synthesis of atropisomeric amides **31**

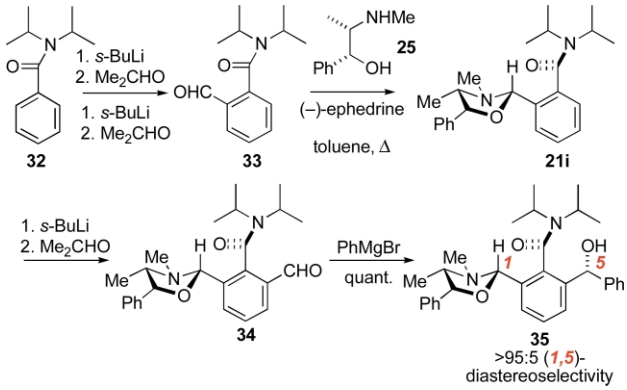
Entry	1	2	3	4	5	6	7
E =	Me	Et	Br	I			
Yield (%)	91	97	91	92	94	94	91
Ee (%)	98	96	> 99	99	> 99	92	94

Stereochemical relay

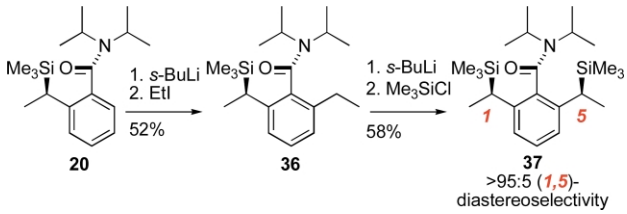
The asymmetric syntheses of atropisomers illustrated in Schemes 4, 5 and 7 convert the stereochemistry of a readily obtained stereogenic centre into asymmetry at an axis. If the stereochemistry, instead of "coming to rest" in the axis, is passed on beyond the axis to more remote parts of the molecule, a *stereochemical relay* can result, with the axis just a "staging post" in the transmission of stereochemistry. Other chemists[7,8] have probed the idea of using conformation to relay stereochemistry, but, because of the well-defined spectroscopic features of tertiary amides, the details of their role in the conformational transmission of stereochemical information are much clearer than those of the relaying groups in other published examples. Previous work[30] has shown that amide axes are able to control a variety of stereoselective addition reactions, so the relay sequence turns out to be relatively easy to achieve.

Scheme 8 shows a simple example. The chirality of the (−)-ephedrine-derived oxazolidine of **22i** governs the preferred conformation of the (non-atropisomeric) amide axis, and because the stereoselectivity of Grignard addition to 2-formylbenzamides is governed by amide conformation,[76] nucleophilic addition to **34** is fully diastereoselective.[75] 1,5-Stereocontrol is achieved through the mediation of the amide group. A similar effect is evident in Scheme 9, where a single diastereoisomer of the product **37** is formed because the conformation of **20** is retained in **36**, and the amide axis of **36** controls the stereochemistry of its lithiation and electrophilic substitution to generate **37**.[56]

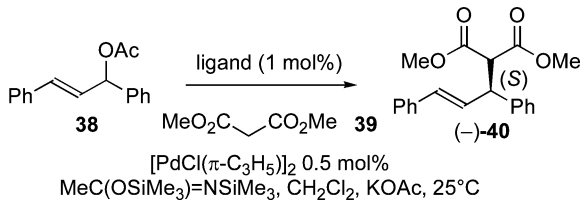
In these examples, stereochemical relay induces asymmetry at an otherwise achiral site in a molecule. That an otherwise achiral site can be a point of coordination for a metal, and Scheme 10 and Table 3 show how the phosphines *syn*-**24** (Scheme 4)[32] and **45**,[75] whose chirality in the vicinity of phosphorus is the consequence of



Scheme 8 1,5-Stereocontrol by stereochemical relay from an oxazolidine.[75]



Scheme 9 1,5-Stereocontrol by stereochemical relay from a 1-silylethyl group.[56]



Scheme 10 Enantioselective allylic substitution catalysed by palladium in the presence of amidophosphine ligands.

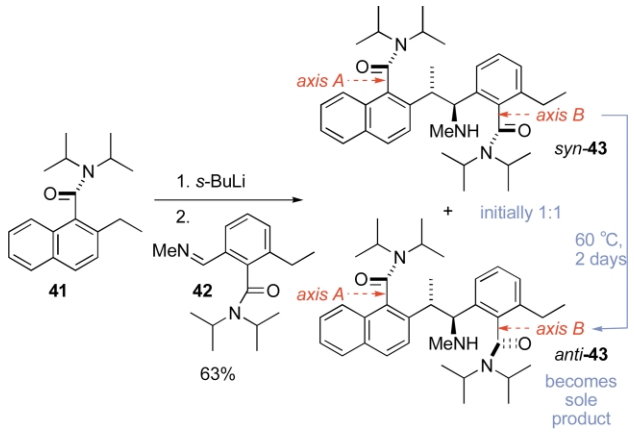
Table 3 Ligands for the enantioselective substitution of **38**

Entry	Ligand	Time	Yield (%)	Product	Ee (%)
1	*syn*-**24**	3 days	60	(−)-**40**	90
2	**45**	24 h	93	(−)-**40**	82
3	**46**	24 h	85	(+)-**40**	53

stereochemical relay from their chiral centres *via* the amide, can be moderately effective chiral ligands in the palladium-catalysed asymmetric allylic substitution of acetate **38** by malonate **39**.

The synthesis of the diamides **43** illustrates a reversal in role of the stereogenic axes and centres in a stereochemical relay. Lateral lithiation–electrophilic quenching with imines allows an axis to

govern the conformation of a pair of new stereogenic centres.[78] In the case of **43**, formed when **41** is lithiated and added to **42** (Scheme 11), one of those centres finds itself adjacent to a chiral axis, and

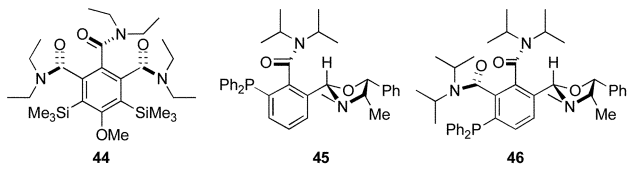


Scheme 11 Remote thermodynamic control over a second Ar–CO axis.[77]

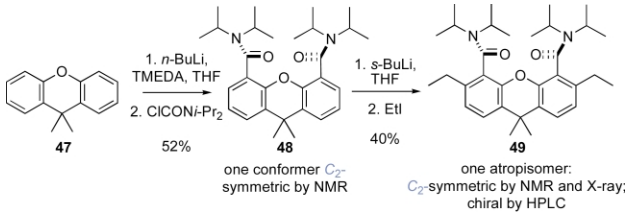
because imine **42** is itself chiral, addition of racemate **41** to racemate **42** initially leads to the formation of a pair of diastereoisomers in a 1 : 1 ratio. The two atropisomeric diastereoisomers are not however of equal energy, and heating them equilibrates the second amide axis (marked axis B in Scheme 11) to yield solely more stable *anti*-**43**, in which axis A has governed axis B *via* stereochemical relay through the stereogenic centres.[77]

Propagation of conformation

In 1989, the crystal structure of **44** was reported.[79] The benzene-1,2,3-tricarboxamide adopts the conformation shown below: 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 the preference for nearby tertiary amide groups to adopt mutually opposing conformations persists in solution, we made the amide **46**, a homologue of the ligand **45**, from **21i**.[75] The phosphine was included in an allylic substitution reaction and gave moderate enantiomeric excess (Table 3), but importantly the ee was in the opposite sense to the ee generated in the presence of the ligand **45**. This is exactly what is to be expected if the amides lie opposed to one another: the local environment of the phosphorus atom in **46** is enantiomeric with the local environment of the phosphorus centre of **45**, despite the use of the same enantiomer of the ephedrine.



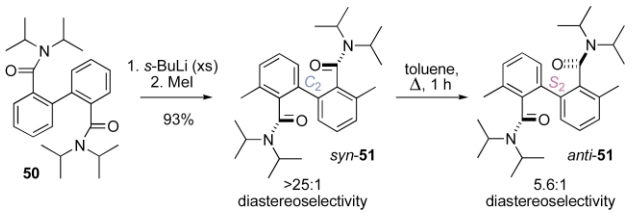
Given the bulk of the substituents involved, the tendency of amide groups to lie opposed to one another is perhaps unsurprising. However, the effect turns out to be quite general, occurring in diamides even with more remote relationships between the amide substituents. We made **48**, for example, by lithiation of the xanthene **47** (Scheme 12).[80] The NMR spectrum of **48** contains a single 6 H singlet corresponding to the *gem*-dimethyl group, and double lithiation and electrophilic quench yields a compound **49** which in principle contains two stereogenic axes and may therefore exist as a pair of diastereoisomers. However, only a single diastereoisomer was obtained, a diastereoisomer 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 structure shown in Scheme 12.[80]



Scheme 12 *Anti*-preference in a xanthene-1,8-dicarboxamide.

Even amides borne on separate non-rigidly interconnected aromatic rings have a strongly preferred conformation. Amide **51** contains two stereogenic axes; in principle therefore two possible diastereoisomers. Given that the biaryl axis in this case will not be stereogenic, one of these stereoisomers, *anti*-**51**, will be centrosymmetric (S_2 symmetric) and therefore achiral; the other, *syn*-**51**, will be C_2 symmetric and therefore chiral.

In the event, double ortholithiation of **50** (Scheme 13) gave only a single diastereoisomer *syn*-**51**, and we were easily able to prove



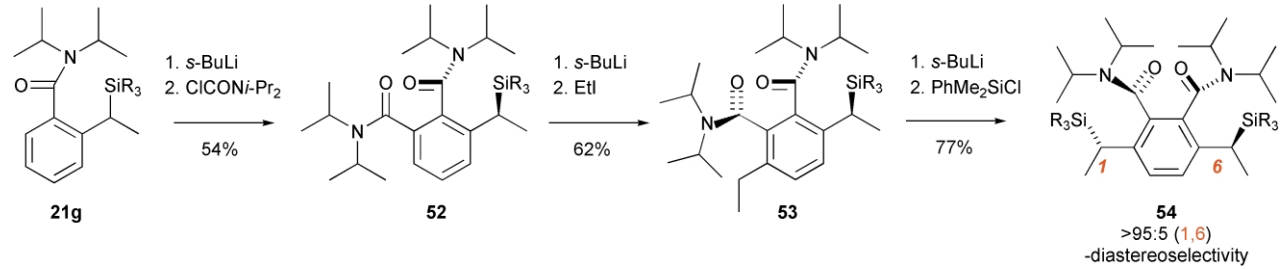
Scheme 13 Kinetic and thermodynamic stereocontrol in biphenyl-1,1′-dicarboxamides.

its stereochemistry by HPLC on a chiral stationary phase: a separation into two enantiomers was just visible, indicating chiral, C_2-symmetric *syn*-**51** rather than achiral, centrosymmetric *anti*-**51**.[81] However, this C_2-symmetric diastereoisomer turned out not to be the more 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.

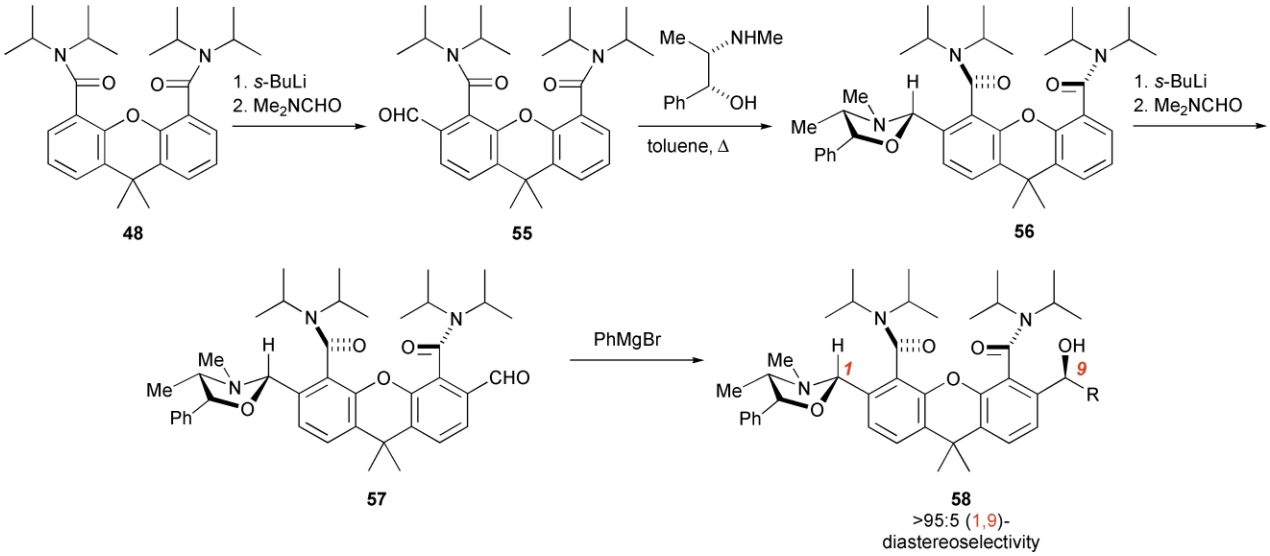
Remote stereocontrol by stereochemical relay

Given that amides even with rather remote relationships are capable of communicating with one another, we expected to be able to use these pairs of "conformationally interlocked" groups to mediate remote stereocontrol in a form of stereochemical relay. Four stages in the development of this idea are shown in Schemes 14,[56] 15[80] and 16.[81] In Scheme 14, the conformation of the axis adjacent to the stereogenic centre of **21g** is relayed round the ring by introduction of a second axis into **52** adjacent to the first. When the second stereogenic centre of **54** is now constructed adjacent to this axis, its stereochemistry ends up being controlled by the centre lying *para* across the ring.[56] In Scheme 15, the idea is taken a stage further: the two amides of **48** are already related by the *anti* conformational preference of such systems; introduction of an ephedrine-derived oxazoline into **56** forces both axes to adopt a single absolute conformation. The stereochemistry of the oxazoline is relayed through both amides and allows the subsequent addition of a nucleophile to the carbonyl group of **57** to go with complete (1,9)-stereochemical control.[82] A similar sequence of events allows the oxazolidine of **61** to directed nucleophilic attack on the remote carbonyl group, leading to complete 1,8-stereocontrol in **62**.[81]

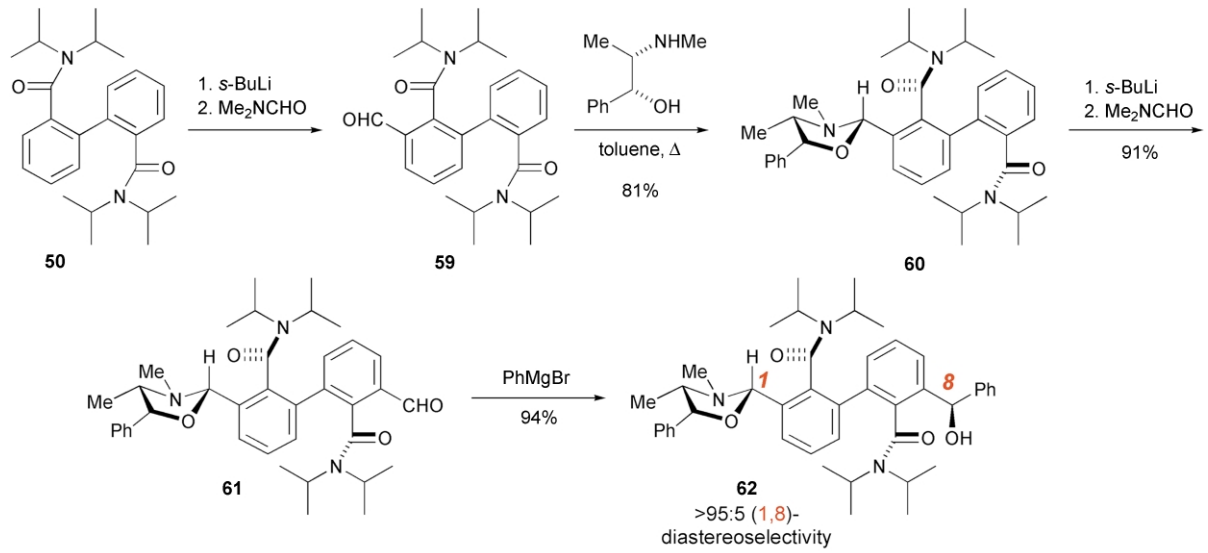
Although remote stereochemical control has been achieved over more bond-lengths than in these examples,[83,84] Scheme 15 probably represents most remote stereocontrol yet achieved in terms of linear separation between the origin and destination of the stereochemical information. This chemistry certainly represents the first time conformational control has been used in this way, relaying information about the absolute configuration of a stereogenic centre through a molecule[10] in much the same way that allosteric



Scheme 14 Remote (1,6) stereocontrol relayed through a benzene-1,2-dicarboxamide.



Scheme 15 Remote (1,9) stereocontrol relayed through a xanthene-1,8-dicarboxamide.



Scheme 16 Remote (1,8) stereocontrol relayed *via* a biphenyl-1,1′-dicarboxamide.

conformational changes in enzymes and receptors relay information in biological molecules.

Conclusion

Stereochemical control over axial conformation is readily achieved just by letting molecules do what they want to do: we allow the molecules to adopt their most stable conformation and then exploit the consequences. Trapping conformational preference in an atropisomeric axis permits general asymmetric syntheses of atropisomers. Letting the new axis itself control the configuration of further stereogenic centres opens the way for remote stereochemical relays — a form of long-range information transfer still open for further exploitation.

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through her X-ray crystallographic studies. Finally, none of the work described here would have been possible without the support of industrial sponsors and funding bodies: EPSRC, Leverhulme Trust, Royal Society, Roche, AstraZeneca, GlaxoSmithKline and the EU Erasmus/Socrates Programme.

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