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Conformationally Interlocked Amides: Remote Asymmetric Induction by Mechanical Transfer of Stereochemical Information

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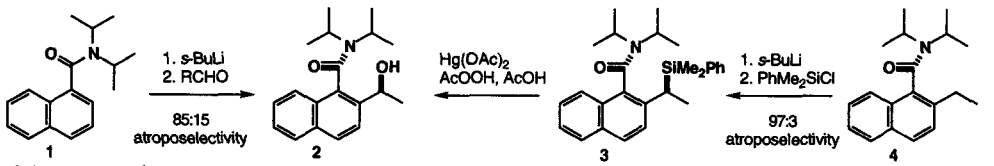
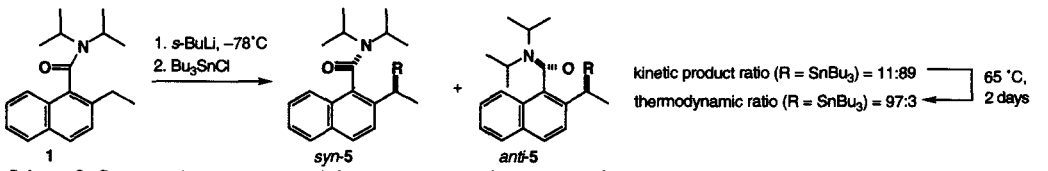
Abstract: The axial conformation of an aromatic tertiary amide group may be powerfully influenced by an adjacent stereogenic centre. Because the amide axis can also control the *formation* of new chiral centres, the amide can act as a "relay centre" for the transmission of stereochemical information. Conformational interlocking of adjacent amide groups on an aromatic ring means that a pair of amide groups can be used in series to mediate asymmetric induction between remote stereogenic centres, for example those lying *para* across an aromatic ring.

The conformation of a tertiary amide substituent on an aromatic ring can exert powerful *kinetic* control over the formation of a nearby stereogenic centre.[1-10] We first demonstrated this with the addition of ortholithiated 1-naphthamides **1** to aldehydes, in which the two atropisomeric[11] diastereoisomers of the product **2** are formed in ratios of up to 90:10.[2,3] More recently, we reported that the amide exerts an even more powerful influence over the lateral lithiation reactions of benzamides and 1-naphthamides:[5] **3** is formed as a single stereoisomer from **4** via a configurationally stable organolithium,[6] and we have used reactions similar to this to mediate remote (1,5) asymmetric induction.[7]



Scheme 1: Amide conformation controls the formation of new stereogenic centres

The configuration of a stereogenic centre can exert powerful *thermodynamic* control over the conformation of a nearby tertiary amide group. A striking example of this was provided by the atropisomeric tributylstannyl-substituted naphthamides **5** (R = $SnBu_3$) (Scheme 2).[6] Although in this instance kinetic stereochemical control over the lateral lithiation–electrophilic quench gave mainly the *anti* atropisomer, thermal equilibration converted it almost entirely to the *syn* atropisomer.



Scheme 2: Stereogenic centres control the conformation of tertiary amides

In this Letter we show how it is possible to exploit the readiness of a tertiary amide substituent both to respond to and to transmit stereochemical information by using it as a "relay centre" for remote asymmetric induction – we describe, for example, a method for the relative stereocontrol of (1,6)-related stereogenic centres situated *para* to one another across an aromatic ring.

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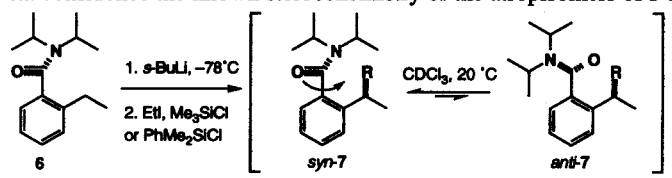
While 2-substituted tertiary 1-naphthamides and 2,6-disubstituted tertiary benzamides have the potential for atropisomerism,[12-16] tertiary benzamides bearing a single 2-substituent are conformationally labile about the Ar–CO bond – rotational barriers are typically 60-75 kJ mol^{-1}, corresponding to half-lives of the order of 0.001 s to 1 s at 20 °C.[17-20] These barriers nonetheless correspond to slow rotation on the NMR timescale, and benzamides **7** bearing chiral substituents (synthesised by lateral lithiation[21,22] of **6**) clearly show two diastereoisomeric conformers *syn*- and *anti*-**7** (corresponding to the *syn*- and *anti*- atropisomers of the naphthamides **5**) in their ^{1}H NMR spectrum at 20 °C (Scheme 3). As the Table shows, the relative population of the two conformers depends heavily on the substituent R at the stereogenic centre and parallels the equilibrium ratios obtained by thermally epimerising the corresponding atropisomers of **5**,[5] allowing us to assign with confidence the known stereochemistry of the atropisomers of **5** to the conformers of **7**.



Scheme 3: Conformers of 2-substituted benzamides 7

R =	product, yield (%)	conformers *syn*-7:*anti*-7 ratio (by NMR)	atropisomers *syn*-5:*anti*-5 equilibrium ratio (*ref.*)
Et	**7a**, 94	55:45	60:40 (*5*)
Me_3Si	**7b**, 87	87:13	94:6 (*5*)
$PhMe_2Si$	**7c**, 91	92:8	–
Bu_3Sn	–	–	97:3 (*6*)

Table: Conformational ratios for benzamides 7 and naphthamides 5

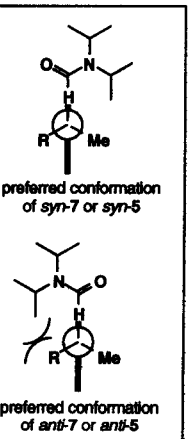
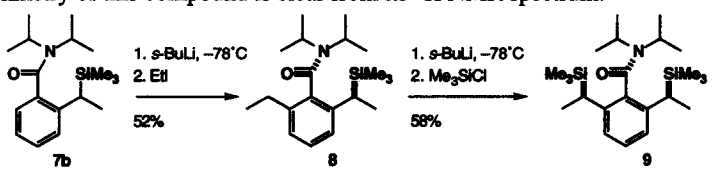


Figure 1

The lowest energy conformations of *syn* and *anti*-**5** and **7**[23] appear in Figure 1 – the crystal structure of *syn*-**5** (R = Et)[5] also shows the C–H bond at the stereogenic centre eclipsing the Ar–CO bond. This clarifies the origin of the conformational preferences of the amides, both in magnitude and direction: severe crowding between bulky Bu_3Sn, Me_3Si or Me_2PhSi groups and the amide N*i*-Pr_2 group favour a single conformer, while with R = Et, the preference for *syn*-**7** over *anti*-**7** (or *syn*-**5** over *anti*-**5**) is less marked.

The near conformationally-uniform **7b** could be trapped as a single atropisomer simply by introducing a second *ortho* substituent (Scheme 4). Only one product **8** out of two possible diastereomeric atropisomers was obtained on treatment of **7b** with *s*-BuLi at –78 °C and then EtI:[24] the stereoisomeric purity of the product[25] reflects the relative population of the two conformers of starting material at –78 °C, which may exceed 98:2. The $SiMe_3$-bearing stereogenic centre has now exerted complete stereochemical control over the new stereogenic Ar–CO axis, and this axis can in turn control a new stereogenic centre. Lateral lithiation of **8** with *s*-BuLi, followed by a Me_3SiCl quench, gave the *meso* amide **9** with >90:10 stereocontrol. The symmetry of this compound is clear from its ^{1}H NMR spectrum.[26]



Scheme 4: Relaying stereochemical information through an amide axis

10

The next challenge was to see whether stereochemical information could be passed not just from stereogenic centre to stereogenic axis and from stereogenic axis to stereogenic centre, but also from one stereogenic axis to another. Snieckus' crystal structure of **10**,[27] in which the orientation of the adjacent tertiary amide groups alternates around the ring as shown, suggested the possibility of using conformationally interlocked amide groups to pass stereochemical information around, or across, an aromatic ring.

We trapped the preferred *syn* conformer of the $PhMe_2Si$-substituted benzamide **7c** as a single atropisomer **13**[25] by ortholithiating and quenching with $ClCON(i\text{-}Pr)_2$.[24] The same compound could be made from the bis-amide **11**, available from phthaloyl chloride (Scheme 5). The room-temperature NMR spectrum of **11** is broadened, although it still shows four distinct 6H doublets, which we interpret as pairs of diastereotopic methyl groups in a chiral, C_2 symmetric ground-state conformation with the amide groups aligned *anti*. Analysis of variable temperature NMR experiments on **11** gave a barrier to Ar–CO rotation of 66 kJ mol^{-1}.[19] Adding a 2-ethyl group by ortholithiation–EtI quench sharpened the spectrum,[28] and the product **12** could be deprotonated again entirely at the lateral position[22] and quenched with $PhMe_2SiCl$ to give **13**, again as a single atropisomer.[25] Each route to **13** gives the same isomer but for a different reason – from **7c** the stereogenic centre exerts thermodynamic control over the conformation of the amide, while from **12** the amide exerts kinetic control over the configuration of the new centre.

The sharp ^1H NMR spectrum of **13** suggests that, since rotation about even the less hindered Ar–CO is likely to be slow on the NMR timescale, one conformer – presumably (and on the basis of later results, evidently) with amide groups aligned *anti* – is preferred. And as before, this conformer was trappable as an atropisomer: ortholithiation of **13** and EtI quench gave **14**. At this stage, we have succeeded in passing stereochemical information from centre to axis to axis, and we ended the sequence by passing that information back to a stereogenic centre again: lateral lithiation of **14** with a $PhMe_2SiCl$ quench gave a single,[25] symmetrical isomer of **15**. Its crystal structure, shown in Figure 2, confirms the sense of the transmission of stereochemical information.

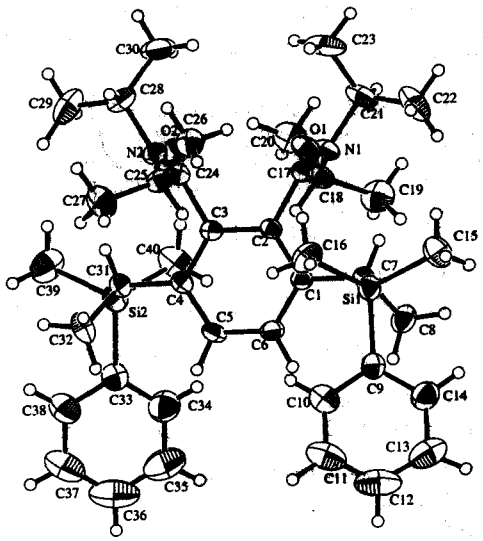
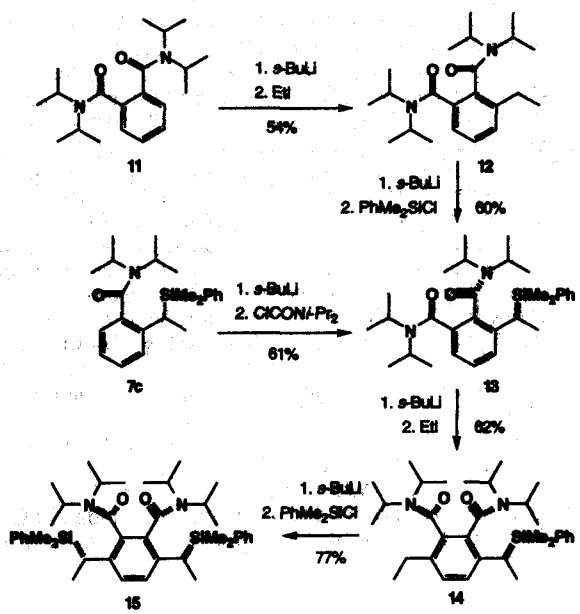


Figure 2: X-ray crystal structure of **15**



Scheme 5: Relaying stereochemical information through two amide axes

The two stereogenic centres of **15** are isolated from one another in space, lying *para* across an aromatic ring.[29] Yet the pair of conformationally interlocked amides provides a medium for stereochemical communication between them – a sort of mechanised molecular telegraphy system. Restriction of conformational mobility has been proposed as a mediator of asymmetric induction in a wide-ranging group of reactions,[30-33] and we are currently extending this concept to related systems.

Acknowledgements

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References and Footnotes

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