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Synthesis of Atropisomeric Diamides with Remotely Related Stereogenic Axes by Stereoselective Additions to Imines

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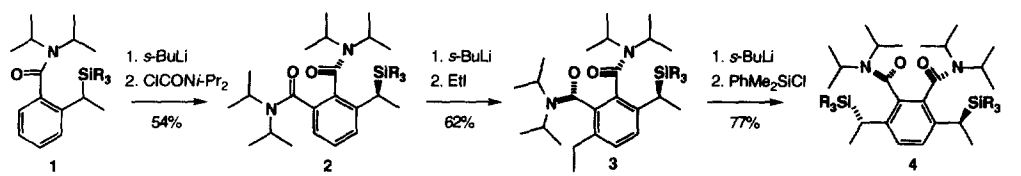
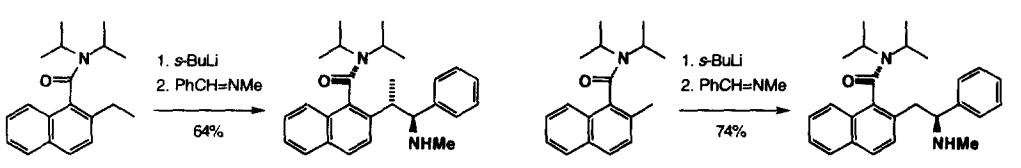
Abstract: Atroposelective addition of axially chiral laterally lithiated 2-alkyl-1-naphthamides to 6-substituted 2-(*N*-methylformimino)benzamides leads, after equilibration of the new stereogenic axis to its more stable conformation, to single atropisomeric diastereoisomers of diamides bearing remotely related stereogenic axes separated by one or two stereogenic centres. The newly created MeNH-bearing stereogenic centre "relays" stereochemical information from the first axis to the second.

In previous publications, we have demonstrated that the stereogenic axis of a rotationally restricted tertiary aromatic amide can control, with high levels of kinetic stereoselectivity, new stereogenic centres.[1] We have also shown that stereogenic centres adjacent to stereogenic axes can influence, under thermodynamic control, the preferred conformation or configuration at the axis.[2] These two types of atroposelectivity – kinetic and thermodynamic – are both evident in the accompanying paper,[3] where we demonstrate that additions of organolithiums to 2-imino-1-naphthamides are stereoselective, and give *syn* amine products which, on heating, also show a thermodynamic preference for the *syn* atropisomer. We have used a combination of thermodynamic control over new axes and kinetic control over new centres to relay stereochemical information from a stereogenic centre through one or two stereogenic axes to a remote 1,5- or 1,6-related stereogenic centre (Scheme 1).[2]



Scheme 1: Relaying stereochemistry through stereogenic axes[2]

In this Letter we show how stereochemical information may be relayed from stereogenic axis to stereogenic axis, via stereogenic centres – reversing the strategy of Scheme 1. The one-step process allows the formation of single diastereoisomers of atropisomeric diamides incorporating a pair of remotely (1,8) related axially stereogenic amide groups separated by one or two stereogenic centres. Atropisomeric diastereoisomers containing two non-biaryl axes were first reported in 1969,[4] but the only subsequent examples are **3** and **4**, whose relative stereochemistry is an unavoidable consequence of the proximity of their axes.[2]



Scheme 2 Atroposelective addition of laterally lithiated amides to imines[5]

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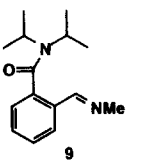
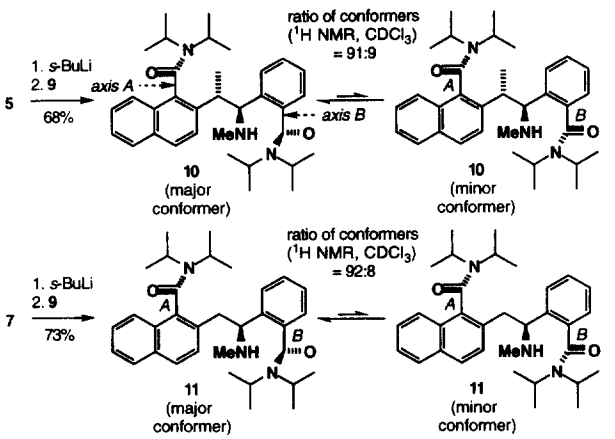
Our starting point was the atroposelective imine addition shown in Scheme 2.[5] Laterally lithiated 2-alkyl aromatic amides give reliably high 1,4 and 1,5-stereocontrol in their additions to benzaldimines. Importantly for the present goal, these reactions generate a new stereogenic centre adjacent to a second aromatic ring. Knowing that benzylic stereogenic centres bearing MeNH groups adjacent to aromatic amide groups exert thermodynamic control over the conformation of the amide,[3] we decided to repeat the imine additions to **5**[6] and **7**[7] with **9** as the electrophile.[8]



9



Scheme 3: Stereoselective addition to an iminobenzamide

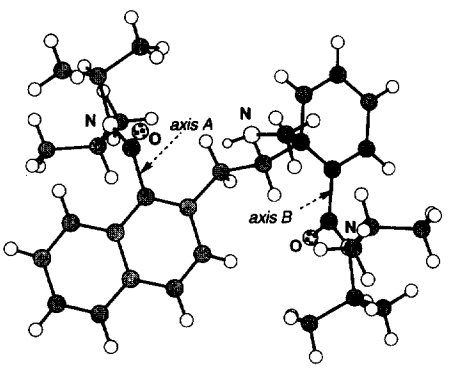
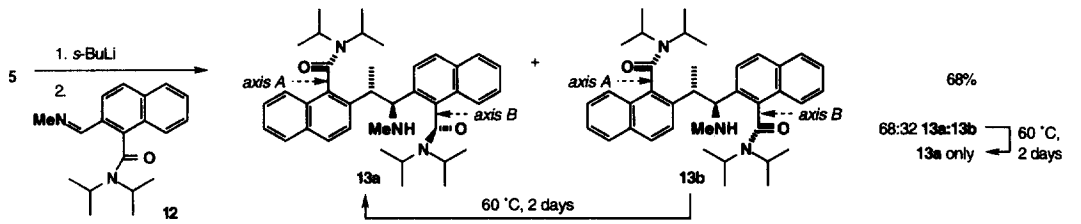


Figure 1: X-ray crystal structure of **11**

The key feature of the products **10** and **11** is the conformation about the new Ar–CO bond (axis B). In their ^{1}H NMR spectra, mixtures of diastereoisomeric conformers about axis B[9] are clearly visible (91:9 ratio in **10**; 92:8 in **11**), and precedent[3] led us to expect hydrogen-bonding would ensure the major conformer bore MeNH and the amide C=O of axis B *syn*. However, from the X-ray crystal structure of **11** (Fig. 1) we deduced that the major conformer had MeNH and the amide C=O of B *anti*.[10] Fig. 1 also shows that the two stereogenic centres have relative configurations controlled by the stereogenic axis A and in line with the precedent shown in Scheme 2. The unexpected[3] conformational preference about axis B must be due to the large CH(Me)Ar or CH_2Ar substituent now competing on steric terms with MeNH for influence over the axis: Figure 2 shows the preferred conformation close to the axis in each conformer of **10**.[11] NH——O=C hydrogen bonding[3] is not strong enough to overcome the repulsive force between the bulky N*i*-Pr_2 group and CH(Me)Ar or CH_2Ar: N*i*-Pr_2 lies *syn* to the smaller NHMe group in both cases.

In order to convert a conformational preference into a diastereoselective reaction, we needed to convert conformers about axis B to atropisomers by including a second restricting group in the 6-position of the benzamide ring.[9] Accordingly, we repeated the addition of laterally lithiated **5** to the 2-imino-1-naphthamide **12**. The reaction generated a mixture of two diastereoisomeric atropisomers **13a** and **13b** in 68% yield. This was no surprise: both starting materials **5** and **12** are chiral and racemic, and we expect a mixture of diastereoisomers to result.[12] In order to allow the MeNH–bearing centre to exert the same thermodynamic control over axis B as it had in **10** we needed to overcome the (now higher) barrier to rotation about the new axis B of **13**. Heating a solution of **13** in $CDCl_3$ to 60 °C for 2 days did just this, and allowed the mixture of **13a** and **13b** to equilibrate to a single atropisomer **13a**, whose crystal structure is shown in Figure 3. Axis A is unaffected by the thermal equilibration, presumably because its stereochemical relationship with the adjacent



Scheme 4: Controlling a remote stereogenic axis

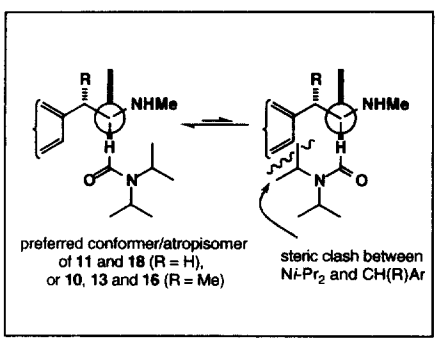


Figure 2: Preferred conformation about axis B

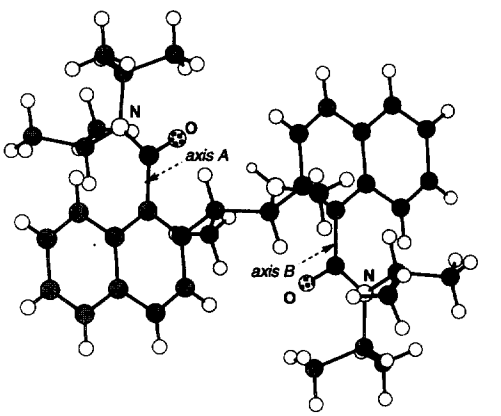
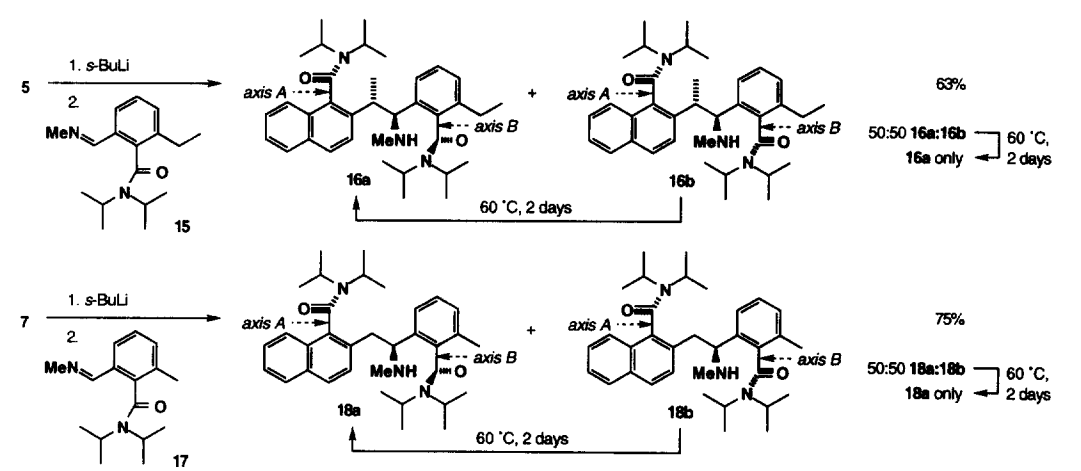


Figure 3: X-ray crystal structure of **13a**

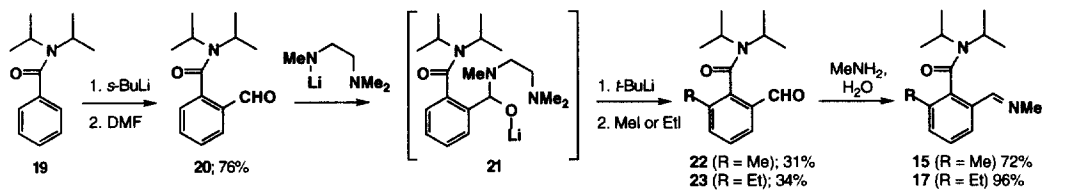
centre is already the thermodynamically more stable of the two possible.[11] The simple lithiation–imine addition–equilibration procedure of Scheme 4 allows the amide at axis A to control, 7 bond-lengths away, the stereochemistry of axis B via two intervening relay centres.

We also managed to get remote stereocontrol over a 2,6-disubstituted benzamide axis. We chose to use imines **15** and **17**, whose 2-alkyl groups might provide a site for subsequent stereoselective reactions. Addition of lithiated **5** to **15** and **7** to **17** gave 1:1 mixtures of atropisomeric diastereoisomers of **16** and **18** respectively in good yield. Equilibration of both **16** and **18** successfully gave the single atropisomers **16a** and **18a** (Scheme 5), whose relative stereochemistry was assumed to be the same as that of **11** and **13a**.[13]



Scheme 5: Control over a benzamide axis

Imines **15** and **17** were made by the sequential double ortholithiation[14] of benzamide **19** shown in Scheme 6. We expected problems with ortholithiation in the presence of a 2-alkyl group,[15] so we introduced the formyl group first (**20**)[16] and then protected it as its trimethylethylenediamine adduct **21** during the alkylation .[17] The alkylated aldehydes **22** and **23** were converted to the imines **15** and **17** with 40% aqueous $MeNH_2$.



Scheme 6: 6-Alkyl-2-iminobenzamides by sequential double ortholithiation

The syntheses of **13a**, **16a** and **18a** are the first diatereoselective preparations of compunds containing two non-biaryl stereogenic axes. The route involves 1,8-stereocontrol: the transfer, in a single chemical step, of stereochemical information from axis A – via two relay centres – to axis B. One of the relay centres is in fact inessential to the method, as the synthesis of **18a** demonstrates.

Acknowledgements

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References and Footnotes

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8. Imine **9** was made in 87% yield by stirring the aldehyde **20** with 40% aqueous methylamine.
9. Tertiary aromatic amides bearing one *ortho* substituent typically undergo rotation about Ar–CO at rates k_{Ar-CO} = 1 to 10^3 s^{-1}. This is slow enough for diastereoisomeric conformers to be discernible by ^1H NMR. Two *ortho* substituents are needed for atropisomers to exist (k_{Ar-CO} < ca. 10^{-3} s^{-1}). See ref. 6.
10. The conformers of **11** can interconvert under the conditions of the crystallisation, so the crystal strutcure *may* not represent the preferred conformation in solution. However, the same conformational preference is evident in the crystal structure of **13a**, whose conformers are atropisomers which cannot interconvert under the conditions of the crystallisation.
11. The "conformational interlocking" apparent in benzamides bearing 2-(1-trialkylsilyl)ethyl and 2-(1-trialkylstannyl)ethyl substituents is probably operating here: see ref. 2 and the discussion in ref. 1. The conformational preferences arise because both Me and NHMe are smaller than CH(R)Ar [R = H, Me or NHMe].
12. Both centres are controlled by axis A, whose stereodirecting influence over-rides the expected (ref. 3) ability of axis B to control the direction attack on the imino groups.
13. Why axis A of **18** should not epimerise is unclear, since unlike axis A of **17** it has no adjacent centre to control it while axis B epimerises. The stability of this conformation of axis A may be at least partly due to the presence of a weak hydrogen-bond between NH and C=O of axis A. (The corresponding O–N interatomic distance is 3.28 Å, N–H–O angle 8.2° in the X-ray crystal structure of **11**; O–N distance 3.25 Å, N–H–O angle 12.8° in **13a**.)
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