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Synthesis of Atropisomeric 2-(1-Aminoalkyl)-1-naphthamides by Stereoselective Addition of Organolithiums to a 2-Imino-1-naphthamide

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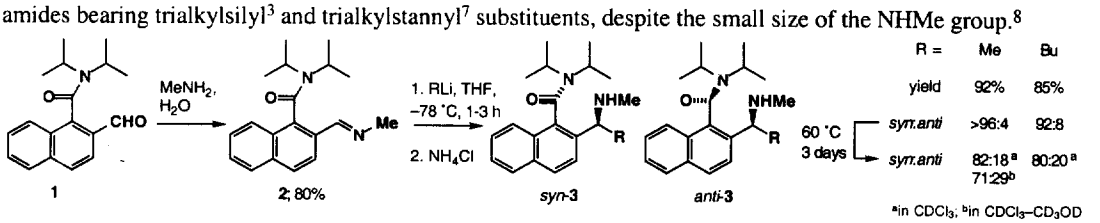
Abstract: Unlike the corresponding aldehydes, 2-(*N*-methylformimino)-*N,N*-dialkyl-1-naphthamides react highly atroposelectively with simple organolithium reagents to give atropisomeric amines whose *syn* stereochemistry is thermodynamically preferred over *anti*.

Aromatic tertiary amides flanked by two *ortho* substituents are usually atropisomeric (axially chiral) because of slow rotation about the Ar–CO bond.[1] Rotationally restricted tertiary amide substituents can be powerful agents for stereocontrol,[2] particularly in lithiated amides,[3] even at relatively remote centres.[4,5] *Nucleophilic* additions to 2-acyl-1-naphthamides are in general less stereoselective.[6] We attributed the poor, metal-dependent stereoselectivity of the additions to 2-formyl-1-naphthamides **1** to free rotation about the Ar–CHO bond which allows the aldehyde to adopt any of a number of conformations and limits the use of nucleophilic additions to carbonyl groups in atroposelective synthesis.

In this Letter we show that substitution of the carbonyl group for an imine (–CH=NMe) remedies this situation and permits highly stereoselective nucleophilic additions of organolithiums to an axially chiral 1-naphthamide. The products are atropisomeric aromatic amides bearing methylamino (MeNH) substituents.

The imine **2** was made from the aldehyde **1**[1] by stirring with 40% aqueous $MeNH_2$. **2** was treated with methyllithium or butyllithium in THF at –78 °C, and then quenched after 1-3 h with ammonium chloride to give the atropisomeric amines *syn*-**3**. ^{1}H NMR showed that the reaction proceeded with high levels of atroposelectivity: >25:1 *syn*:*anti* for addition of MeLi and 12:1 *syn*:*anti* for addition of BuLi. The X-ray crystal structure of *syn*-**3** (R = Me) proved the *syn* stereochemistry of the major atropisomer (Figure 1). This was unexpected – organolithium additions to **1** are moderately *anti*-selective[6] – but can be explained by assuming the CH=NMe group twists away from the N*i*-Pr_2 group (either for solely steric reasons, or assisted by chelation of Li by the imine N and amide O), and is then attacked on its less hindered face (Figure 2).

To compare these compounds *syn*-**3** with their *anti* diastereoisomers, we epimerised them by heating to 60 °C in $CDCl_3$. After 3 days, thermodynamic equilibrium had been attained: the equilibrated mixture of the two diastereoisomers still contained mainly the *syn* isomer, but in a ratio of 82:18 (R = Me) or 80:20 (R = Bu) with *anti*-**3**. This thermodynamic *syn* preference approaches the strong (>90:10) *syn* preference observed with amides bearing trialkylsilyl[3] and trialkylstannyl[7] substituents, despite the small size of the NHMe group.[8]



Scheme 1: Atroposelective addition to an imino-naphthamide

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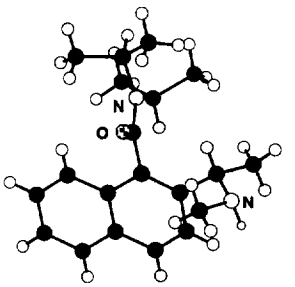


Fig. 1: Crystal structure of syn-3 (R = Me)

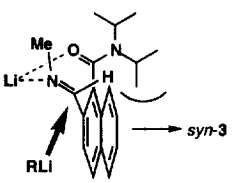
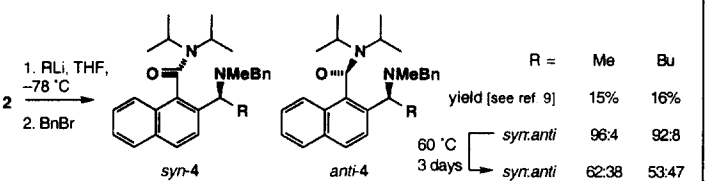


Fig. 2: Attack on 2



Scheme 2: Atroposelective synthesis of tertiary amines from 2

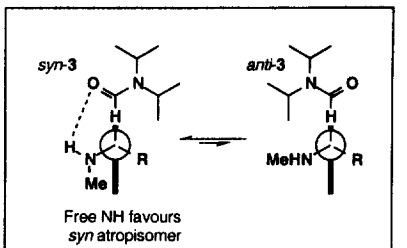


Fig. 3a: Conformational preference in 3

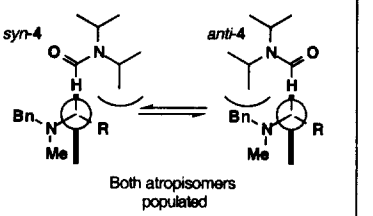


Fig. 3b: Conformational preference in 4

To probe the reason for the thermodynamic *syn*-selectivity, we repeated the alkyllithium additions to imine **2**, but quenched the products with BnBr rather than NH_4Cl. It was necessary to warm the reaction mixtures to 0 °C to obtain complete *N*–alkylation, but nonetheless the tertiary amines **4** were obtained with the same level of *syn* selectivity as **3**.[9] Heating **4** (R = Me or Bu) to 60 °C for 3 days decreased the ratio of *syn*:*anti* atropisomers to 62:38 (R = Me) or 53:47 (R = Bu) – significantly more *anti* atropisomer than for the secondary amines **3**. This strongly suggests that the thermodynamic preference for the *syn* atropisomer of **3** is not principally a steric effect (since increasing the size of the NHMe group by alkylation would then increase the thermodynamic *syn* selectivity to avoid NMeBn–N*i*-Pr_2 interactions), but may be a hydrogen-bonded effect (Figure 3a). The lower thermodynamic *syn* selectivity obtained on epimerising **3** (R = Me) in the presence of deuteromethanol (Scheme 1) supports this explanation. The more equal population of the two atropisomers of **4** would be due to the similar sizes of Me or Bu and NR_2 (Figure 3b).[8]

Acknowledgements

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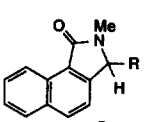
References and Footnotes

1. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.
2. Clayden, J. *Synlett* **1998**, 810.
3. Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2561.
4. Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997**, *38*, 8487.
5. Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105.
6. Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577.
7. Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565.
8. For a discussion of control of amide conformation by an adjacent stereogenic centre, and the importance of the size of the groups carried by the centre, see ref. 5
9. The low yield is due to cyclisation of the *N*-lithio amine product onto the amide (to give a lactam **5**) which outpaces *N*-alkylation by BnBr. LDA is eliminated, which re-deprotonates **5** α to nitrogen, and the anion formed is alkylated to give **6** in 64% (R = Me) or 54% (R = Bu) yield. The reaction giving **3** (Scheme 1) also produces traces of **5** (4% after 1 h; 15% after 3 h).



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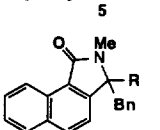

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