Pergamon

Tetrahedron Letters, Vol. 38, No. 14, pp. 2561-2564, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00401-2

Atroposelectivity in the Reactions of Laterally Lithiated Tertiary Amides

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Abstract: Lateral lithiation – electrophilic quench of 2-substituted *N,N*-dialkyl-1-naphthamides proceeds with high levels of diastereoselectivity in favour of one atropisomer of the product. Similar atroposelectivity may be observed in the reactions of 2-substituted benzamides, provided the products are trapped at low temperature by a subsequent *in situ* ortholithiation – alkylation reaction.
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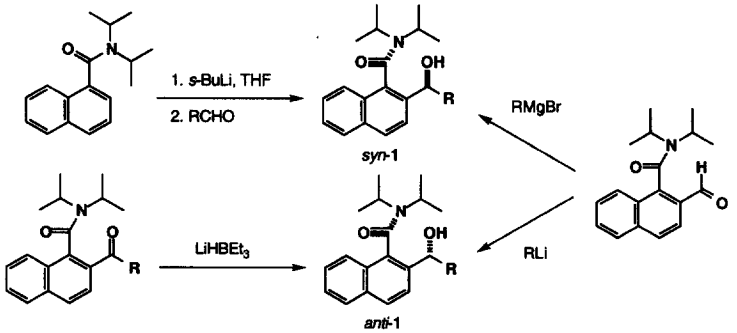
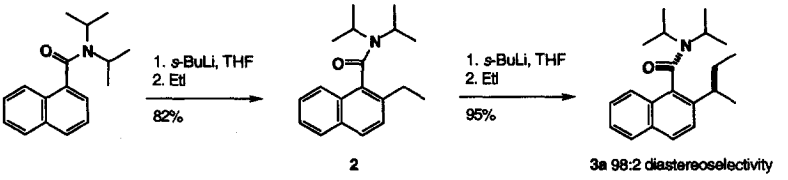
Few substituents rival aromatic *N,N*-dialkyl carboxamide groups in their ability to direct lithiation at both ortho-[1,2] and lateral (i.e. benzylic)[3,4] positions.[5] Reacting metallated *N,N*-dialkyl amides with electrophiles provides a powerful method for regiocontrolled elaboration of aromatic rings,[2] and these metallation-quench procedures have been made enantioselective by using (–)-sparteine as a chiral ligand for lithium.[6,7] In this Letter we show that reactions of laterally lithiated amides proceed with hitherto unnoticed *diastereo*selectivity (atroposelectivity[8]) which can exceed 98:2 in favour of one diastereoisomeric atropisomer of the product.

The potential for atroposelectivity in the reactions of hindered aromatic amides arises because rotation about their C–CO bond is slow,[9,10] and we have previously described atroposelective routes to the alcohols **1** in which the conformation of the amide controls the formation of the new chiral centre (Scheme 1).[11-13] These diastereomeric 2-(1-hydroxyalkyl) naphthamides **1** are all stable compounds, and interconvert only in solution with a half life of several days at room temperature.



Scheme 1 Atroposelective reactions of naphthamides[11,12]

Our investigations into the reactions of laterally lithiated naphthamides began with the 2-ethyl compound **2**. Lithiation with *s*-BuLi in THF at –78 °C gave a green solution which was quenched at the same temperature with EtI. Atropisomer **3a** was obtained in 95% yield, and with a stereoselectivity of 98:2.[14] X-ray crystallography showed that **3a** had the *syn* relative stereochemistry shown in figure 1.



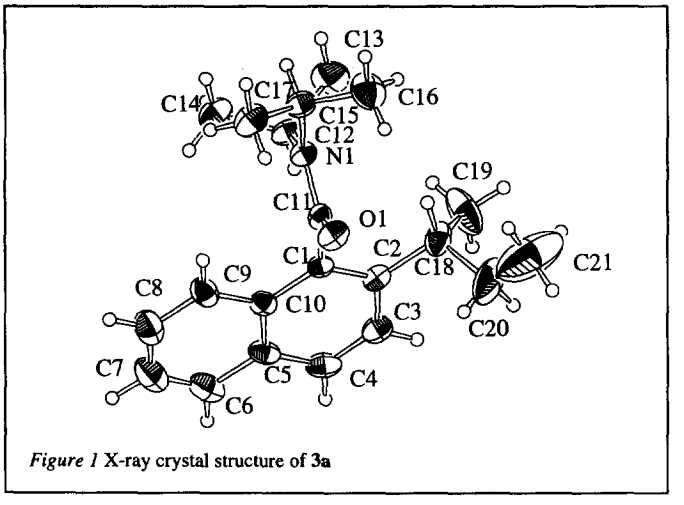
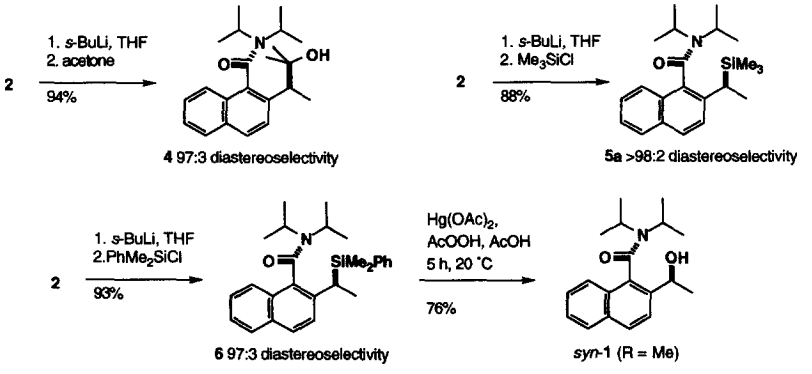
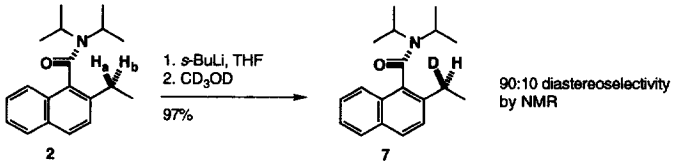


Figure 1 X-ray crystal structure of **3a**

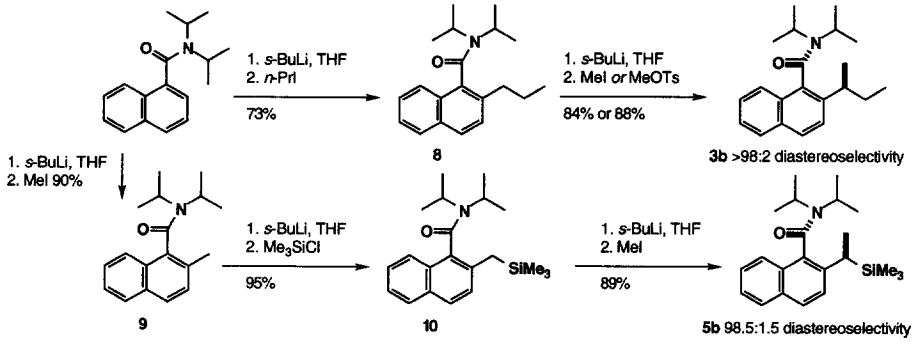
Single compounds **4**, **5a** and **6** (by NMR and HPLC) were likewise obtained when laterally lithiated **2** was quenched with acetone, Me_3SiCl and $PhMe_2SiCl$ respectively. While the relative stereochemistry of **4** remains unconfirmed, we were able to show that **6** (and therefore probably **5a** too) had the same *syn* relative stereochemistry as **3a** by stereospecific oxidation[15,16] of **6** to the known[11,12] alcohol *syn*-**1** (R = Me).



Deuteration of lithiated **2** was atroposelective too. In the ^1H NMR spectrum of **2** in C_6D_6, the diastereotopic protons H_a and H_b are clearly distinguishable, and quenching lithiated **2** with deuteromethanol gave **7** (with 90:10 atroposelectivity), the ^1H NMR of which lacked the downfield member of the diastereotopic pair. NOE studies of **2** provided a stereochemical assignment of the two protons H_a and H_b,[17] and this clearly showed that the major product of the reaction had D *syn* to the amide oxygen as drawn: deuteration proceeds with the same stereochemical sense as alkylation and silylation.



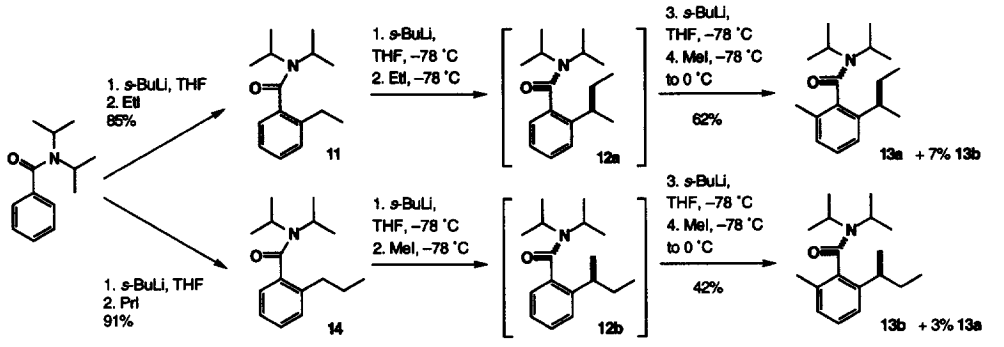
The electrophilic quenching step of these reactions must be under kinetic control, because by introducing the substituents in reverse order we were able to make the other atropisomers of **3** and **5**. Thus, lateral lithiation of the 2-propyl substituted **8** followed by addition to methyl iodide or methyl tosylate[18] gave **3b**, clearly distinguishable from **3a** by NMR and by HPLC. Similarly, silylation of the 2-methyl substituted **9** gave **10**, which was lithiated a second time and quenched with methyl iodide to give **5b**, again a single compound with NMR spectra and HPLC retention times clearly different from those of its diastereoisomer **5a**.



The pairs of atropisomers could be interconverted by heating in solution. Either **3a** or **3b** gave an equilibrium 60:40 mixture of **3a**:**3b** after 2 days at 65 °C; similarly either **5a** or **5b** gave 94:6 **5a**:**5b**.

There is a close parallel between our *diastereo*selective electrophilic quenches of laterally lithiated naphthamides and Beak's *enantio*selective electrophilic quenches of (–)-sparteine-complexed laterally lithiated benzamides.[6] Diastereoselectivity in our reactions owes its very existence to the fact that in the naphthamide series the rate of rotation about the aryl–CO bond is slow at room temperature[9,10] – in the benzamide series the rotamers interconvert rapidly and are not atropisomers.[19-21] However lateral lithiations, including those in which sparteine is used as a chiral ligand,[6] are routinely carried out at –78 °C, and *at this temperature even benzamides carrying a single 2-substituent can exhibit atropisomerism.*[22] It appeared to us quite possible that the electrophilic quench of laterally lithiated benzamides is diastereoselective as well, but that the diastereoselectivity vanishes along with the potential for diastereoisomers on warming to room temperature.

To investigate this, we devised a system in which the ephemeral atropisomers could be captured by locking the conformation of the reaction product with a subsequent transformation *in situ*. We prepared the 2-ethyl-substituted benzamide **11**, laterally lithiated it with *s*-BuLi,[5] and quenched the lithiated species with ethyl iodide, still at –78 °C, to give the stereochemically fragile **12a**. Now, instead of warming to room temperature, a second dose of *s*-BuLi was added, again at –78 °C, which removed the *ortho* proton. A final quench with methyl iodide gave the 2,6-disubstituted benzamide **13** as a 90:10 mixture of two atropisomers, the major one of which we assume to be **13a** by analogy with **3a**. The other atropisomer **13b** could be made in a similar way from the 2-propyl benzamide **14**.



This result clearly has implications for the enantioselective functionalisation of compounds such as **11** and **14** using (–)-sparteine,[6] and raises intriguing questions of cooperation and competition between the diastereoselectivity imposed by the amide group and the enantioselectivity imposed by (–)-sparteine.

Acknowledgments

We thank the Leverhulme Trust and the Royal Society for research grants, Glaxo-Wellcome Ltd for the generous donation of HPLC equipment and Zeneca plc for support through the Strategic Research Fund. We are grateful to Mr Roy Beddoes for determining the X-ray crystal structure of **3a**.

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14. Selectivities were measured by keeping the reaction mixture cold during work-up, and consigning the crude product to the freezer (–18 °C) until it was analysed by HPLC.
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17. The preferred conformation of **2** was deduced, by molecular modelling and by inspection, to be more or less as shown in Figure 2, with the methyl group twisted *syn* to the amide oxygen. The four methyl groups carried by nitrogen were assigned by a combination of literature precedent (see Stewart, W. H.; Siddall, T. H. *Chem. Rev.* **1970,** *70*, 517) and decoupling experiments. Irradiation of the aromatic multiplet containing H^3 gave an NOE in the upfield member only of the diastereotopic pair CH_aH_b; irradiation of Me_a gave an NOE in the downfield member of this pair only.

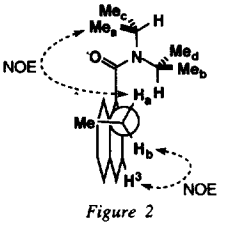

Figure 2

18. Beak has observed leaving-group dependent stereoselectivity in similar systems (ref 6).
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22. The barrier to racemisation of the NEt_2 homologue of **11** is 60 kJ mol^{-1} (ref. 3); this is equivalent to a half-life for racemisation of about 20 min at –78 °C.

(*Received in UK* 7 *February* 1997; *revised* 24 *February* 1997; *accepted* 28 *February* 1997)