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Configurational Stability and Stereospecificity in the Reactions of Amide-Stabilised Organolithiums: A Non-Stereospecific Tin-Lithium Exchange

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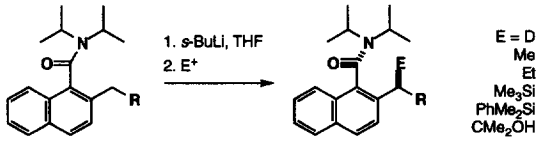
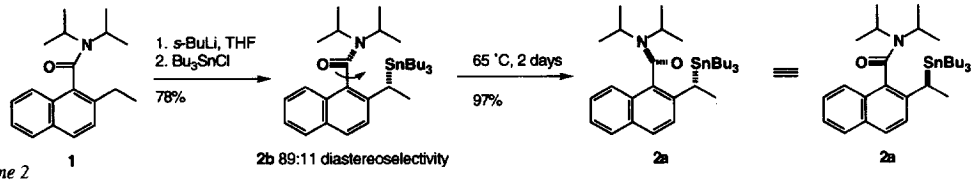
Abstract: Diastereoisomers of laterally lithiated tertiary naphthamides are configurationally stable at the lithium-bearing stereogenic centre at –40 °C. The *syn* diastereoisomer, which may be formed by stereoselective deprotonation or stereospecific transmetallation, reacts stereospecifically, but both the tin-lithium exchange leading to the *anti* diastereoisomer and its subsequent reactions are characterised by an unprecedented lack of stereospecificity. © 1997 Elsevier Science Ltd.

Configurational stability in organolithium compounds is largely confined to those bearing α-heteroatoms,[1-8] and benzylic organolithiums are particularly prone to rapid configurational inversion.[9-12] Intramolecular coordination of the lithium atom slows the inversion process, and laterally lithiated secondary anilides are one class of non-α-heterosubstituted benzylic organolithiums which is configurationally stable at –78 °C, though not at –25 °C.[13,14] Many studies of configurational stability in organolithiums make use of tin-lithium exchange[15] to generate organolithiums of defined stereochemistry:[6-8,13,16,17] these transmetallations are always assumed to proceed with reliable retention of configuration.[18]



Scheme 1 Atroposelective lateral lithiation – electrophilic quench reactions of aromatic amides

In the preceding paper,[19] we reported that the lateral lithiation – electrophilic quench of aromatic amides can be highly atroposelective, and favours the *syn* atropisomeric diastereoisomer for those electrophiles tested (Scheme 1). We now describe our investigations into the mechanism of this stereoselective reaction and our studies of the configurational stability of the intermediate organolithiums. We make use of the rotationally-restricted amide group as a "stereochemical marker", allowing us to distinguish retention from inversion in electrophilic substitutions, and we report what we believe to be the first example of a non-stereospecific tin-lithium exchange.

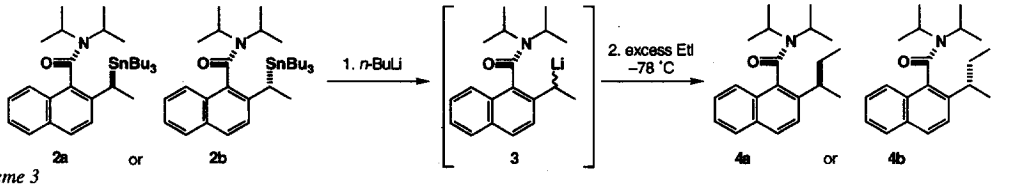


1 2b 89:11 diastereoselectivity 2a 2a

Scheme 2

2-Ethyl naphthamide **1** was lithiated and quenched with Bu_3SnCl to give a mixture of atropisomeric stannanes **2b** and **2a** (Scheme 2). In contrast to the reactions in scheme 1,[19] the major product from this reaction turned out to be the less thermodynamically stable of the two atropisomers, and the racemic **2b** could be converted almost entirely to its racemic diastereoisomer **2a** by heating to 65 °C for 2 days. It is partly for this reason, though more convincingly because of further evidence outlined below, that we believe that asymmetric induction in this reaction proceeds with the opposite sense to that in the reactions in Scheme 1 and we have assigned the major product of this reaction (**2b**) *anti* stereochemistry.[20]

Diastereoisomeric stannanes **2a** and **2b** were separable by flash chromatography, and this gave us the opportunity to investigate the configurational stability of laterally lithiated amides and the origin of the atroposelectivity observed in their reactions. Each stannane was accordingly treated with *n*-BuLi in THF at –78 °C and the resulting green organolithiums **3** were quenched with ethyl iodide to give mixtures of **4a** and **4b** (Scheme 3 and Table, entries 1 and 2).



Scheme 3

Table: Stereospecificity in the transmetallation of stannanes **2a** and **2b**

entry	ratio **2a:2b**	transmetallation conditions	yield (%)	ratio **4a:4b**
1	100:0	–78 °C, 2 h	97[a]	99:1
2	6:94	–78 °C, 2 h	87[a]	60:40
3	100:0	–40 °C, 2 h	94[a]	98:2
4	5:95	–40 °C, 2 h	83[b]	60:40
5	5:95	–78 °C, 30 min → –25 °C, 5 min → –78 °C, 100 min	83[b]	64:36

[a]Isolated yield; [b]Yield determined by HPLC

The outcome is different for different stannanes **2a** and **2b** (entries 1 and 2), so whatever the detailed course of the reaction, the intermediate organolithium **3** cannot be the same in each case and *must therefore have some degree of configurational stability*. Yet the product stereochemistry cannot be determined solely on transmetallation because the ratio of products **4a:4b** does not reflect the ratio of stannanes **2a:2b**.

These selectivities are not snapshots of a slowly equilibrating mixture of organolithiums[8] because they are independent of the temperatures to which the organolithiums are subjected. Entries 3-5 show how the product ratios are invariant even when the intermediate organolithium is kept at –40 °C for 2 h or even warmed briefly to –25 °C. Organolithiums **3** must be configurationally stable. It is remarkable that similar organolithium compounds in the benzamide series are configurationally unstable even at –78 °C,[10] while ours have complete configurational stability at –40 °C.

Given that the organolithium intermediates are configurationally stable, non-stereospecific conversion of **2** to **4** must arise from non-stereospecific *formation* or from non-stereospecific *reaction* of the

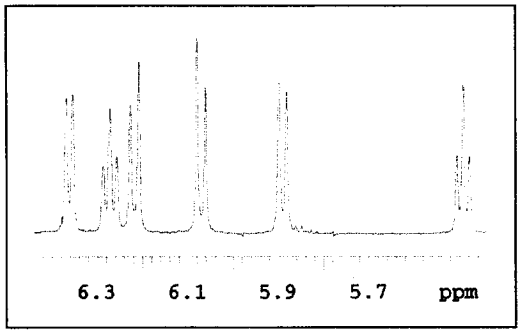


Figure 1 (**2a** + *n*-BuLi)

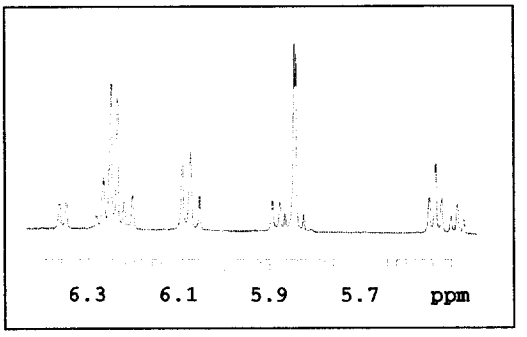


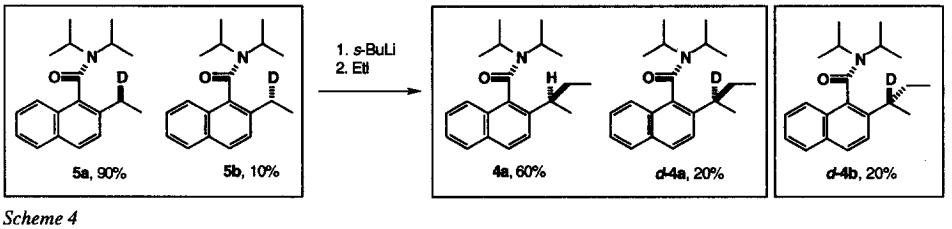
Figure 2 (**2b** + *n*-BuLi)

organolithiums **3**. NMR studies showed that there was a lack of stereospecificity in *both* of these steps.[21] Figure 1 shows part of the ^{1}H NMR spectrum at –40 °C of the organolithium **3a** obtained by treating **2a** with *n*-BuLi in d_8-THF. An identical spectrum is obtained when **1** is deprotonated. Figure 2 depicts the ^{1}H NMR spectrum obtained by transmetallating **2b** – it shows a 35:65 mixture of **3a** and the diastereoisomeric organolithium **3b**: this is to our knowledge the *first reported example of non-stereospecific tin-lithium exchange*. The ratio of organolithiums remained unchanged when the mixture was kept for 1 h at –40 °C.

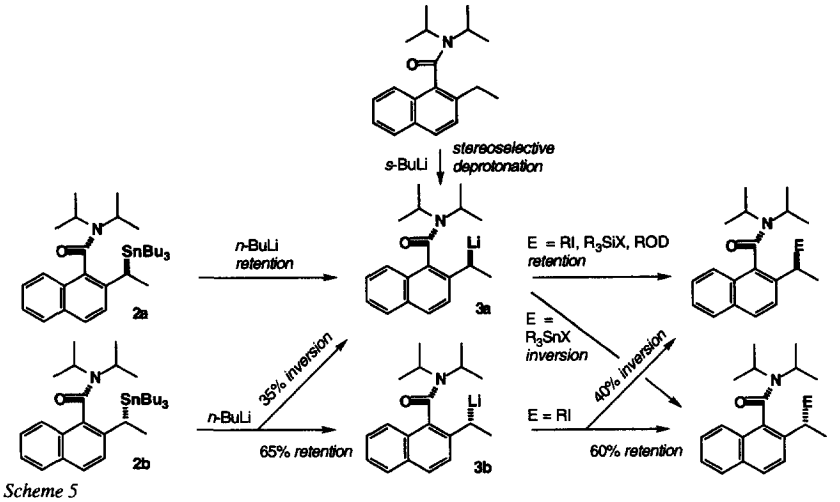
Stannane **2a** transmetallates with 100% stereospecificity; **2b** with only 65% stereospecificity. The degree of stereospecificity in the *electrophilic quenching step* also depends on the relative stereochemistry of the starting materials. The 35:65 ratio of **3a**:**3b** obtained from **2b** gives not a 35:65 ratio of products on electrophilic quench, but 60:40 **4a**:**4b**. We know that pure organolithium **3a**, whether derived from **1** or from **2a**, reacts stereospecifically to give pure **4a**, and the **3a** component of the mixture derived from **2b** must react likewise. The **3b** in this mixture must therefore be reacting non-stereospecifically, giving a 40:60 mixture of **4a**:**4b**.

Final proof of the sense of the stereospecificity (retention or inversion) in the electrophilic quenching step came from two sources. Deprotonation of **1** or transmetallation of **2a** gives the same organolithium **3a** – the one whose NMR spectrum is shown in Fig. 1 – which reacts with ethyl iodide to give **4a**. Yet this organolithium reacts with Bu_3SnCl to give predominantly **2b**. This proves that, for organolithiums **3**, electrophilic substitution of lithium by Bu_3SnCl proceeds with inversion.[22]

Deuteration of **3a**, on the other hand, proceeds with retention: when a 90:10 mixture of **5a**:**5b**, obtained by lithiating **1** and quenching with deuteromethanol,[19] was deprotonated and quenched with EtI, an 80:20 ratio of **4a**:**4b** was obtained (Scheme 4).[23] Loss of stereoselectivity in this reaction (relative to the same reaction of **1**) must be due to the kinetic isotope effect,[24] and shows that the proton removed on lithiating **1** is the one which in **5a** is replaced with D – in other words, that **3a** has *syn* relative stereochemistry, and is deuterated with retention.[25] The known relative stereochemistry[19] of **3a**'s alkylation and silylation products shows that these reactions proceed with retention too. Our overall conclusions are summarised in Scheme 5.



Scheme 4



Scheme 5

Tin-lithium exchange is *not* reliably stereospecific. Great care should be taken in interpreting stereochemical results which rely upon the assumption that it is.

Acknowledgments

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20. For other examples in which stereochemical sense depends on the electrophile see refs 4, 7, 16 and 17.
21. See ref. 7 for a similar loss of stereospecficity.
22. Provided, of course, that this transmetallation proceeds with 100% retention and not 100% inversion.
23. All of **4b** was deuterated, but only a quarter of **4a**. Undeuterated **4a** must arise from stereospecific alkylation of undeuterated **3a** derived from **5a** de-deuterated *syn* to oxygen, while all of the **5b** in the starting material is converted stereospecifically into *d*-**4a**. The remaining *deuterated* material (all of the 20% *d*-**4b** and half of the 20% *d*-**4a**) must then come from the *d*-**3b** produced by inhabitual *anti* selective (due to the kinetic isotope effect) deprotonation of **5a** and provides further evidence that the alkylation reactions of **3b** have only 65% stereospecificity.
24. We know, from the NMR spectrum of the organolithium, that **1** is deprotonated with >95:5 stereospecificity. Assuming the *anti* protons of **1** and of **5a** are removed at the same rate, this gives a *minimum* value of 10 for k_H/k_D. Extremely high values for k_H/k_D have been used to direct the stereochemical outcome of a reaction: see Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993,** *32*, 394.
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