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LETTERS

Anion Translocation in Organolithiums: A Mechanism for the Lithiation and Cyclisation of Tertiary Naphthamides

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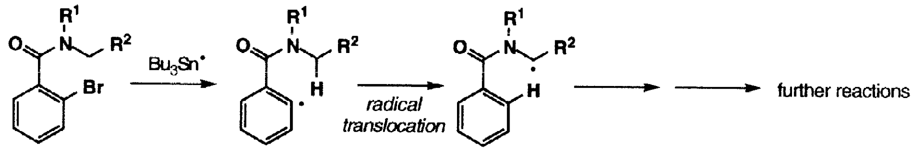
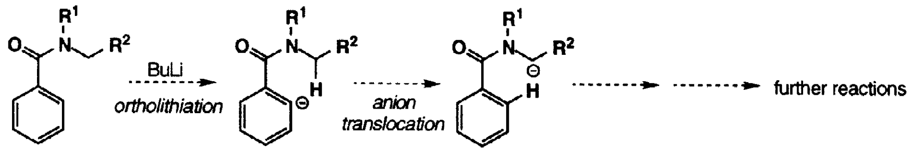
Abstract: Deuterium labelling shows that an intramolecular proton transfer ("anion translocation") is a key step in the mechanism leading to an α-lithiated tertiary naphthamide and thence to the products of anionic cyclisation. The kinetic isotope effect means that proton transfer from the *ortho* position can become the sole mechanism for α-lithiation, though for undeuterated amides a parallel mechanism also operates in which lithiation occurs directly at the position α to nitrogen.

Radical translocation – the intramolecular radical abstraction of a hydrogen atom – is a key step in some important radical reactions, and ingenious reaction sequences involving radical translocation from an amide protecting group have been used to generate α-nitrogen substituted radicals.[1] In principle, the anionic equivalent of these radical translocation reactions, in which an anion (organolithium) formed under kinetic control undergoes an intramolecular proton transfer, could provide new routes to α-nitrogen substituted organolithiums (Scheme 1b). Such "anion translocation" reaction sequences have not been generalised in synthetic chemistry,[2] but in this Letter we describe a reaction which proceeds, at least in part, by this process, and points to the potential development of anion translocation as a new synthetic strategy.

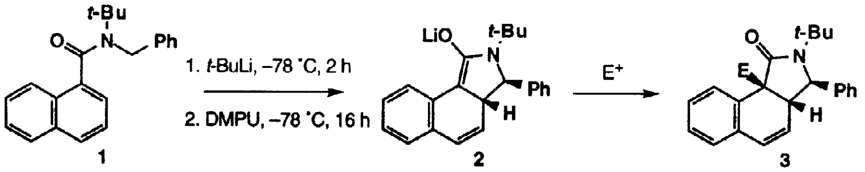


Scheme 1a: Radical translocation from an amide



Scheme 1b: Anion translocation from an amide

We recently described an anionic cyclisation reaction of N-benzyl naphthamides (Scheme 2).[3] Treatment of *N-t*-butyl-*N*-benzyl-1-naphthamide **1** with *t*-BuLi and then DMPU[4] yields a tricyclic enolate **2** which can be quenched stereoselectively with electrophiles to give functionalised benzo[*e*]isoindolinones **3**.



Scheme 2: Anionic cyclisation of N-t-butyl-N-benzylnaphthamide 1

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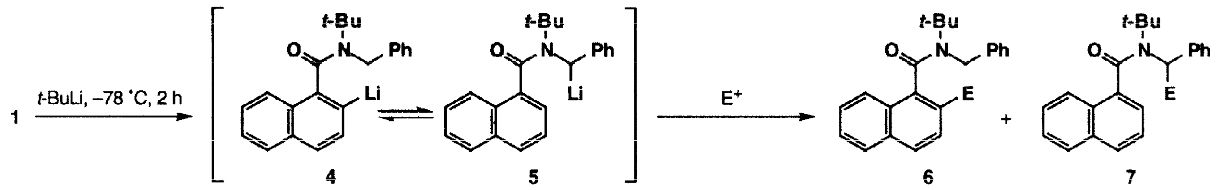
The mechanism of the cyclisation is intriguing: lithiation occurs in the absence of DMPU, but the organolithium intermediate does not cyclise until DMPU is added. Table 1 shows the results of trapping the uncyclised intermediate organolithium, prior to addition of DMPU: amide **1** was lithiated with *t*-BuLi at –78 °C, left for a period of 2 h and then quenched with an electrophile (Scheme 3)



Scheme 3: Electrophilic trapping of the organolithium intermediate

Table 1: Trapping the organolithium intermediate

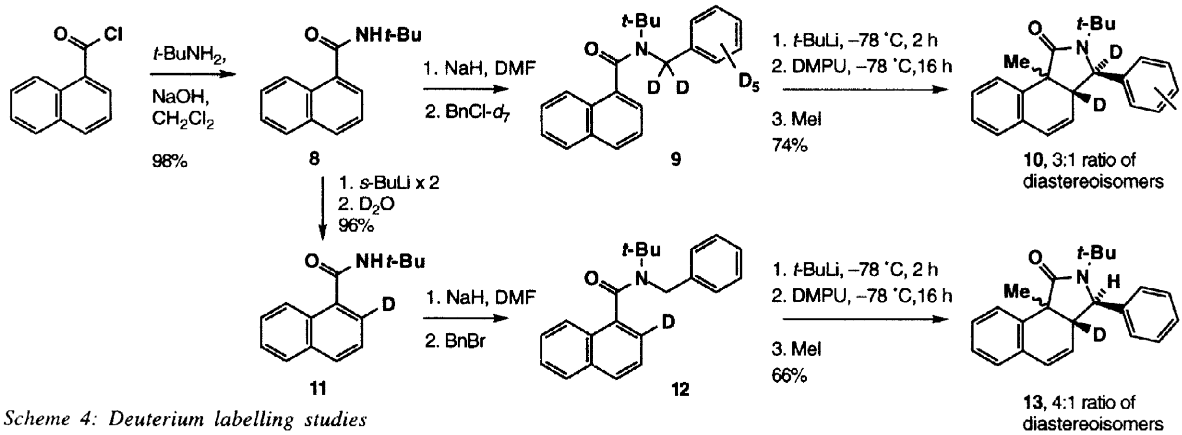
Entry	Electrophile	E =	Yield **6** (%)[a]	Yield **7** (%)[a]	Ratio **6**:**7**[b]
1	D_2O	D	59		1:2
2	MeI	Me	28	56	1:2
3	EtI	Et	33	13	2:1
4	Me_3SiCl	Me_3Si	n/d	n/d	>10:1
5	DMPU (2 min) then MeI	Me	4	62[c]	1:10

[a] Isolated yield. Remainder of the crude product is largely made up of some cyclisation product **3** and small amounts of remaining **1**. [b] Ratio from ^1H NMR of crude product. [c] Plus 23% of a mixture of diastereoisomers of **3**.

The trap never gave entirely one product, and indicated that the organolithium from which the enolate **2** forms in the cyclisation is in fact a mixture of *ortho*- and α-lithiated compounds **4** and **5**. The electrophile-dependent outcome furthermore suggests that the organolithiums **4** and **5** are in equilibrium. Quenching with reactive electrophiles such as MeI or D_2O gives a 1:2 mixture of *ortho* and α products **6** and **7**, and we view this ratio as the nearest estimate we have of the actual ratio of **4**:**5** in solution. Less reactive electrophiles gave a greater proportion of the *ortho* product **6** – for EtI the ratio reverses to 2:1 **6**:**7**, while with Me_3SiCl, only the *ortho* product **6** was detectable (albeit in low yield) in the product mixture. It seems that equilibration of **4** and **5** is rapid, with **5** slightly more stable but the **4** more reactive. MeI and D_2O provide a snapshot view of this equilibrium; EtI and TMSCl react selectively with **4** at a rate comparable with or slower than the rate at which the two species interchange. Table 1 gives us our first glimpse of an anion translocation, since this must be the mechanism by which **4** and **5** interconvert.

Adding DMPU to the mixture makes it cyclise, and how it does this is at least partly revealed by entry 5 of Table 1, which shows the result of adding DMPU but allowing insufficient time for the organolithiums to cyclise: DMPU forces the *ortho* organolithium **4** to undergo anion translocation to give the α organolithium **5**. We know that this anion translocation must take place during the cyclisation, because only **5** can cyclise, yet yields for **1**→**3** (Scheme 2) are often near quantitative.

How does the mixture of organolithiums **4** + **5** arise? Unlike many other tertiary amides, *N*-*t*-butyl amides are conformationally uniform, with the *t*-butyl group *syn* to oxygen.[5] This appears to prevent a "complex-induced proximity effect"[6] operating in the lithiation α to nitrogen (as is precedented for other tertiary amides).[7] Complex-induced ortholithiation of the naphthamide is however possible,[8] and the presence of the ortholithiated species **4** in the mixture suggested to us that *all* of the lithiated material might originate by ortholithiation followed by rapid formation of an equilibrium mixture of **4** + **5** through anion translocation.[9] We tested this theory with some deuterium-labelled compounds. Alkylation of the sodium anion of *N*-*t*-butyl-1-naphthamide **8** with d_7-benzyl chloride gave the Bn-d_7-labelled amide **9**, and ortholithiation of the same secondary amide **8**, followed by D_2O quench to give **11** and then amide alkylation with BnBr, gave the *ortho*-*d*-labelled amide **12**.



Scheme 4: Deuterium labelling studies

When **9** was treated with *t*-BuLi and then DMPU in THF at –78 °C, followed by methyl iodide, it gave a good yield of a mixture of stereoisomers of **10**, with 100% deuterium labelling at the *3a* (ring junction) position. This confirms a mechanism in which the *ortho* proton is removed to give Bn-d_7-**4** which subsequently undergoes anion translocation by deuteron transfer to give an *ortho-d* organolithium **5** which then cyclises. Cyclisation of a mixture of **9** and **1** gave only unlabelled **3** (E = Me) and fully labelled (<1% d_6) **10**, proving that the transfer is intramolecular.

When we carried out the same reaction on **12**, with the deuterium label at the *ortho* position, we got another result entirely. Cyclisation occurred to **13** with the deuterium label intact at the *ortho* position, indicating a mechanism in which *t*-BuLi has lithiated **12** α to nitrogen directly, by-passing the ortholithiated species **4**.

The two reaction courses must be a consequence of the kinetic isotope effect, which can have very high values of k_H/k_D (>20) at –78 °C.[10] We found that it was fully possible to direct alkylation to the *ortho* or the α position purely by using deuterium substitution (Scheme 5): when **9** was lithiated and methylated (in the absence of DMPU, to prevent cyclisation) **14** (and <10% α-methylated product) was obtained; when **12** was lithiated and methylated only **15** (and no *ortho*-methylated product) was obtained.[11,12]

Scheme 5: Deuterium directs the regioselectivity of alkylation

The answer to how much of the equilibrating mixture of unlabelled organolithiums **4** and **5** arises through each of the two possible routes for deprotonation – and hence which is the true mechanism of our cyclisation – was finally provided by competition experiments in which a mixture of **1** and **9** or **1** and **12** was lithiated with a deficit of *t*-BuLi (0.5 eq) and quenched with MeI, as summarised in Table 2. Undeuterated **1** lithiates faster than either **9** or **12**, and the degree to which the rate of lithiation of each falls short of the rate of lithiation of **1** gives a crude estimate of the contribution that lithiation at their respective deuterated positions makes to the overall rate of lithiation. The results suggest that only one third of the **5** formed from **1** by *t*-BuLi is generated by ortholithiation–anion translocation, and the rest by deprotonation at the α position.

$$\begin{matrix}\mathbf{1}+\mathbf{9}\\ \text{or}\\ \mathbf{1}+\mathbf{12}\end{matrix}\ \xrightarrow[\quad]{\begin{matrix}\text{1. } t\text{-BuLi (0.5 eq)}\\ \text{2. MeI}\end{matrix}}\ \text{remaining } \mathbf{1} + \text{remaining } \mathbf{9} \text{ or } \mathbf{12} + \mathbf{5}\ (R = Me) + \mathbf{6}\ (R = Me) + \mathbf{14} + \mathbf{15}$$

Table 2: Isotopic labelling and relative rates of reaction

	Starting material contains:[a]			Product contains:[a]			Relative rate of lithiation of:		
Entry	**1** (%)	**9** (%)	**12** (%)	**1** (%)	**9** (%)	**12** (%)	**1**	**9**	**12**
1	54	46	0	14	32	0	1	0.41	–
2	55	0	45	26	0	27	1	–	0.76

[a]by mass spectroscopy

Whatever the preferred mechanism of the cyclisation itself, intramolecular anion translocation is a viable route to organolithiums at sites of lower kinetic acidity, and we hope to apply this idea more generally.

Footnotes and References

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2. For a recent isolated example, see Fleming, I.; Mack, S. R.; Clark, B. P. *Chem. Commun.* **1998**, 715. Interconversion of isomeric organolithiums by *inter*molecular deprotonation is well-precedented: see, for example, Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.
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10. For examples of very high values of k_H/k_D, see Hoppe, D.; Paetzow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394.
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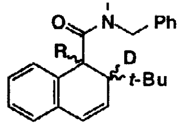
12. By-products (10-20% yield) from the lithiation reactions of **12** are the *t*-butyl addition compounds **16**.



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