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Fast racemisation and slow epimerisation of laterally lithiated amides: stereochemical evidence for the mechanism of inversion of amide-substituted benzyllithiums

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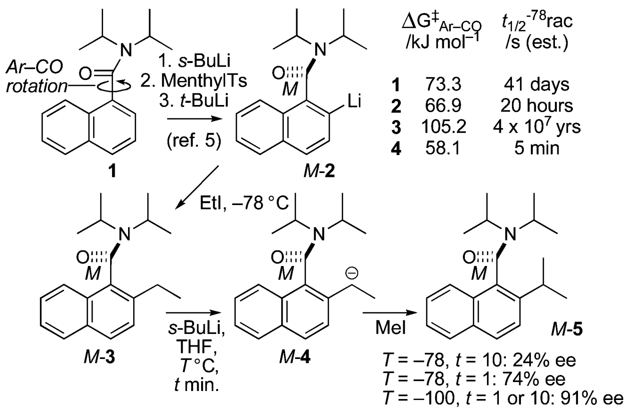
Tertiary 1-naphthamides racemise much more slowly than their laterally lithiated derivatives, and the relative rates of racemisation and epimerisation of these derivatives indicate that the lithium-bearing stereogenic centre inverts *via* a "conducted tour" mechanism, in which the lithium cation is delivered from one face to the other by coordination to the rotating amide group.

Configurational instability has enabled benzyllithiums to be employed in some mechanistically ingenious and simultaneously practically useful asymmetric synthetic methods.[1,2] In this paper we report stereochemical results which allow us to propose with certainty that the racemisation of amide-stabilised benzyllithiums (laterally lithiated amides) involves dissociation of the organolithium into a benzyl anion and a lithium cation, followed by rotation of the amide group to deliver the lithium cation to the other face of the anion with concomitant inversion at the Ar–CO axis.

We have reported[4] that ortholithiated tertiary amides racemise slowly over a period of minutes at −78 °C: **2** has a barrier to Ar–CO rotation of *ca.* 66.9 kJ mol^{-1} compared with 73.3 kJ mol^{-1} for the unlithiated amide **1**.[5] This higher barrier means that the absolute stereochemistry at the Ar–CO axis of the enantiomerically and diastereoisomerically pure sulfoxide is maintained through sulfoxide–lithium exchange and electrophilic quench, allowing the synthesis of the atropisomeric 2-ethyl naphthamides **3** in enantiomerically pure form.

The barrier to enantiomerisation, and hence to ArCO rotation, of the amide **3** is of the order of 105.2 kJ mol^{-1}: it has a half-life for racemisation at room temperature of 42 h. However, in trying to functionalise the amide further by lateral lithiation and electrophilic quench (Scheme 1), we found that its lithiated derivative **4** racemises extremely fast. A product **5** of only 24% ee was recovered when **4** was quenched with MeI 10 min after being formed from *M*-**3** at −78 °C in THF; even after 1 min the ee of **5** was 74%. Only by lithiating *M*-**3** and quenching *M*-**4** at −100 °C was it possible to reduce racemisation to an acceptable degree: **5** was then obtained in 91% ee after 1 or 10 min. From these data we deduce that the half-life for racemisation of **4** at −78 °C is of the order of 5 min,[3] corresponding to a barrier to Ar–CO rotation at this temperature of only 58.1 kJ mol^{-1}. Lithiating **1** increases its rate of racemisation 50 fold, but lithiating **3** increases its rate of racemisation 4 × 10^{12} fold!

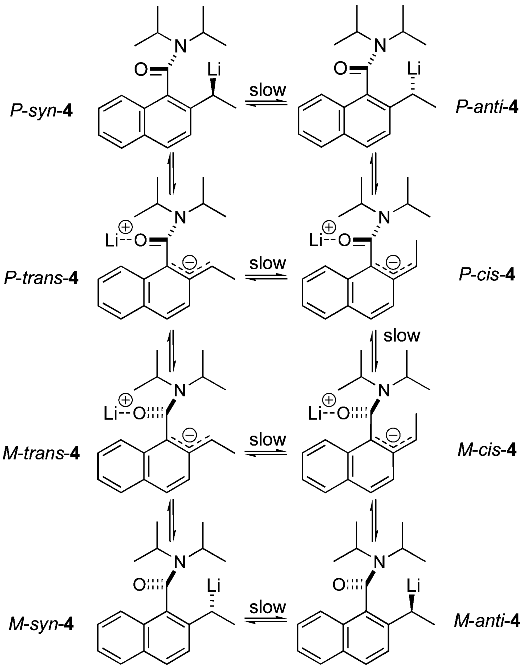


	ΔG$^{‡}_{Ar–CO}$ /kJ mol^{-1}	$t_{1/2}^{-78}$rac /s (est.)
1	73.3	41 days
2	66.9	20 hours
3	105.2	4 x 10^{7} yrs
4	58.1	5 min

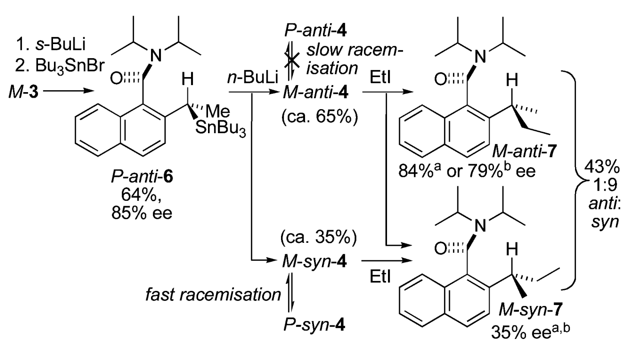
T = –78, *t* = 10: 24% ee
T = –78, *t* = 1: 74% ee
T = –100, *t* = 1 or 10: 91% ee

Scheme 1 Fast racemisation of a laterally lithiated amide.†

We have shown previously that the laterally lithiated amide **4** may exist as two diastereoisomers, which we have represented as *syn*- and *anti*-**4** (Scheme 2). Lithiation of **3** is diastereoselective and generates *syn*-**4**[6,7] and the results in Scheme 1 demonstrate that *M*-*syn*-**4** racemises rapidly. To monitor the racemisation of *M*-*anti*-**4** we investigated its synthesis by tin–lithium exchange (Scheme 3). Lithiation of *M*-**3** at −78 °C in THF followed by a rapid quench with Bu$_3$SnBr gave the stannane *P*-*anti*-**6**‡ in 64% yield and 85% ee. We have noticed before[6,7] that the conversion of *anti*-**6** to **4** is



Scheme 2 Stereoisomers of **4**: structures and interconversions.†



Scheme 3 Rates of racemisation of the diastereoisomers of **4**‡ [a]after 10 min; [b]after 30 min.

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a rare example of a tin–lithium exchange lacking full retentive stereospecificity, and *P*-*anti*-**6** was treated with *n*-BuLi at −78 °C to give a *ca.* 65 : 35 mixture of enantiomerically enriched organolithium *M*-*anti*-**4** and its diastereoisomer *M*-*syn*-**4**. Quenching the resulting mixture of organolithiums with EtI after 10 min gave a 9 : 1 mixture of diastereoisomers of the *sec*-butyl substituted amides *M*-*syn*-**7** and *M*-*anti*-**7** in 43% yield, and by HPLC on a chiral stationary phase we were able to establish that the major product *M*-*syn*-**7** had an ee of only 35% while the minor product *M*-*anti*-**7** had retained 84% ee, essentially the same as the starting stannane *P*-*anti*-**6**. After 30 min, *M*-*anti*-**7** still retained 79% ee.

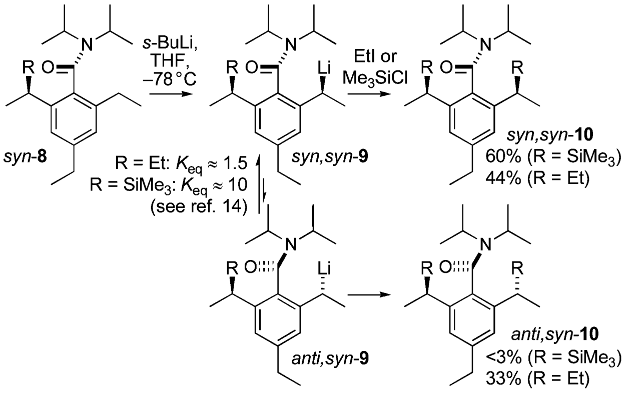
The fact that aging the mixture of *anti*-**4** and *syn*-**4** for 30 min at −78 °C leads to only a small diminution of the ee of *anti*-**7**, but leads to a slump in the ee of *syn*-**7** to a constant 35% is powerful evidence that while *syn*-**4** racemises rapidly, *anti*-**4** racemises only very slowly. Previous work[6,7] showed that organolithium *syn*-**4** reacts with ethyl iodide stereospecifically to yield *syn*-**7** while organolithium *anti*-**4** reacts with ethyl iodide non-stereospecifically to yield a mixture of *syn*- and *anti*-**7**. The ee of the minor diastereoisomer *anti*-**7** therefore gives an accurate measure of the ee of *anti*-**4**, while the ee of *syn*-**7** is a function of the ee of both *anti*-**4** and *syn*-**4**. Furthermore, in line with previous results,[6,7] *syn*-**4** and *anti*-**4** must interconvert slowly too, or *syn*-**4** would contaminate *anti*-**4** and therefore *anti*-**7** with racemic material.

These, and previous,[6,7] results confirm that interconversion of *syn*- and *anti*-**4** (epimerisation) is slow (none detectable after 1 h at −40 °C[6,7]). Epimerisation would in principle occur either by Ar–CO rotation or by inversion at the stereogenic Li-bearing centre (though the latter would be more likely) so at least one of these two independent processes has to be slow. But racemisation of **4**, which we have now found to be fast, must involve *both* Ar–CO rotation *and* inversion at C–Li. This must mean either that a concerted rotation about Ar–CO and inversion at C–Li is occurring much more rapidly than either of the two processes can occur independently, or that the representation of the diastereoisomers of **4** as *syn*- and *anti*-**4** is incorrect.

Possible alternative structures for the diastereoisomers of **4** are shown as *cis*- and *trans*-**4** in Scheme 2, which differ not in relative stereochemistry at two stereogenic centres but instead in the geometry about a partial C=C double bond: they amount to *endo*- and *exo*-isomers of an allyllithium system.[8] The stability of such structures, which have no covalent C–Li bond, and in which the anionic carbon atom is trigonal rather than tetrahedral, is supported by recent experimental and theoretical work.[9] Interconversion of *cis*- and *trans*-**4** is a geometrical isomerisation, whose rate would be completely independent of the rate of racemisation of either diastereoisomer, which occurs on Ar–CO rotation of either geometrical isomer.

An important feature of benzyllithium chemistry is the stereospecificity of their reactions with electrophiles, which may vary from fully retentive to fully invertive.[10] With **4**, for example, silylation and alkylation is retentive while stannylation is invertive. It is difficult to see, however, how stereospecificity in the reactions of *cis*- and *trans*-**4** could be electrophile-dependent, given the lack of a C–Li bond. We therefore propose that the two diastereoisomers of **4** may adopt the structures *syn*- or *anti*-**4** in solution, but that they racemise by Ar–CO rotation in *cis*- and *trans*-**4**. Memory of the relative stereochemistry is retained during the Ar–CO rotation in the geometry of the partial double bond, which is defined by the requirement of Li$^+$ to leave only *syn* to the amide C=O group. Similar "conducted tour" mechanisms have been proposed for racemisation of organolithiums. Lithiated sulfones, for example, racemise by ion pair formation and delivery of coordinated Li$^+$ to the opposite face of the anion by rate-determining bond-rotation.[11]

The reason for the increase in rate of racemisation of *trans*-**4** relative to **3** can be ascribed to delocalisation of negative charge into the carbonyl group which is maximal at the transition state for Ar–CO rotation, when the C=O group and the ring are coplanar.



Scheme 4 Fast epimerisation of laterally lithiated benzamides.[13]

The slow racemisation, and therefore slow Ar–CO rotation, of *cis*-**4** is to be expected given that the blocking effect of the methyl group is much greater in *cis*- than in *trans*-**4**. Indeed, the rate of racemisation of any laterally lithiated amide ought therefore to depend solely on the barrier to Ar–CO bond rotation. This may explain, at least in part, observations which are difficult to rationalise if racemisation of laterally lithiated amides is interpreted as simply inversion at tetrahedral C–Li: (a) lithiated benzamides apparently have lower configurational stability than lithiated naphthamides,[7,12] and (b) lithiation–quench of *syn*-**8** (R = Et) gives mixtures of diastereoisomers of products **10** (Scheme 4):[13] the lithiated intermediate **9** can epimerise, the product ratio representing the equilibrium ratio of the diastereoisomeric conformers *syn*,*syn*-**9** and *anti*,*syn*-**9**.[14]

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Notes and references

† For clarity, THF is omitted from the organolithium structures.

‡ Note that in the stannane **6** the CIP priority rules invert the *M*- and *P*-descriptors relative to all other compounds in the sequence.

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