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# Diastereoselective ortholithiation and conformational control in stereospecific dearomatising anionic cyclisations

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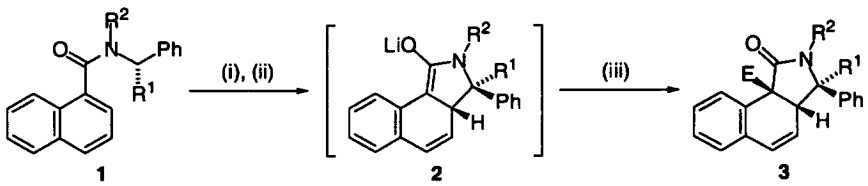
**Abstract**

The dearomatising anionic cyclisation of tertiary naphthamides bearing chiral *N*-substituents (such as α-methylbenzyl) is stereospecific and retentive not because of a configurationally stable organolithium intermediate but because the starting material exists as two atropisomers at −78°C, of which only one is lithiated. The initially formed ortholithiated amide can be trapped with MeI to give single diastereoisomers of atropisomeric amides bearing chiral *N*-substituents. Given time, even in the absence of DMPU, the ortholithiated amide undergoes anion translocation to an α-lithiated species, which can cyclise only to one diastereoisomer of the product, leading to the observed stereospecificity. 

In the accompanying Letter[1] we described the dearomatising anionic cyclisation of tertiary 1-naphthamides **1** bearing chiral *N*-α-alkylbenzyl substituents. The cyclisation of **1** to the enolate **2** is fully stereospecific, and proceeds with >99% retention (Scheme 1). The enolates **2** may be trapped with a variety of electrophiles to yield the enantiomerically pure, highly substituted pyrrolidinones **3**. In this Letter we present the results of our investigation into the mechanism of the cyclisation and the source of its stereospecificity.




1 2 3

Scheme 1. Stereospecific dearomatising anionic cyclisation. (i) *t*-BuLi, THF, −78°C, 2 h; (ii) DMPU (6 equiv.), −78°C, 16 h, (iii) $E^+$

At first sight, stereospecificity seemed to be due to the intermediacy of a configurationally stable organolithium **5** which, it could be imagined, forms and reacts with overall retention.[2] However,

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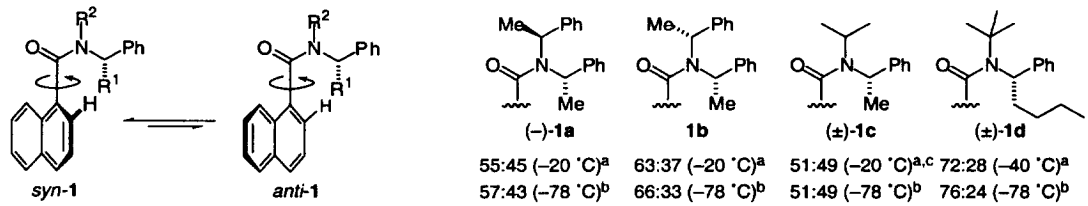
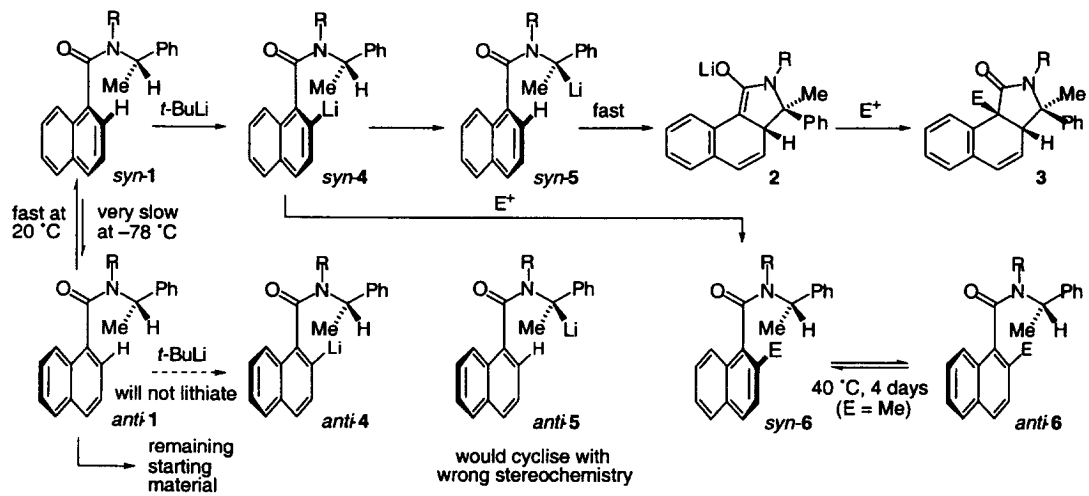
several aspects of the reaction lead us to believe the *conformation of the starting material* mediates the stereochemical control.

Naphthamides **1** bearing chiral *N*-substituents exist as a mixture of diastereoisomeric conformers, each of which is visible as a separate set of signals in the $^1$H NMR spectrum at 20°C. These conformational ratios, determined by $^1$H NMR at –20°C or –40°C, are shown in Scheme 2.[3] The conformers interconvert by rotation about the Ar–CO bond[4] a process which in similar compounds has an activation energy $\Delta G^{\ddagger}$ of about 75 kJ mol$^{-1}$.[5] At room temperature the Ar–CO rotation is fast, but at –78°C we expect this rotation to have a half-life of several hours — rather longer than the lifetime of the cyclisation reaction itself. Naphthamides **1** are, therefore, essentially mixtures of diastereoisomers at this temperature, and the calculated diastereoisomeric ratios at –78°C are given in Scheme 2.




Scheme 2. Ratios of conformers for chiral 1-naphthamides. [a]*syn*:*anti* ratio determined by $^1$H NMR in $CDCl_3$; [b]calculated *syn*:*anti* ratio assuming constancy of $-RT\ln K$; [c]NMR also shows a pair of rotamers with opposite C–N geometry, which together contribute about 20% of the total mixture

If the lithium-bearing centre of the supposed reaction intermediate **5** were configurationally stable, **5** too would exist as two diastereoisomers represented in Scheme 3 as *syn*-**5** and *anti*-**5**. Furthermore, if it were the stereospecific reaction of **5** which controlled the absolute product stereochemistry, then only one of these (*syn*-**5**) can the α-methylbenzyl group approach the naphthalene ring to give the correct relative product stereochemistry. Cyclisation of *anti*-**5** would put Ph *endo* to the tricyclic system, unless it underwent inversion of relative stereochemistry or reaction with stereospecificity opposite to *syn*-**5**. So, either **5** is not configurationally stable (in which case we need another explanation for the stereospecificity of the cyclisation) or only one conformer of the starting material is converted to product.




Scheme 3. Mechanisms for stereospecific anionic cyclisation

The second of these alternatives certainly appears to be true. Even with an excess of *t*-BuLi (up to 1.8 equiv.), it is impossible to force any of these reactions to completion (Table 1, entries 1–4). Significantly,

Table 1
By-products from cyclisation reactions (conditions of Scheme 1)

| entry | starting material | *syn*-**1** : *anti*-**1**[a] | ratio **1**:**3**[b] | $E^+$ | E | cyclised **3**, % yield | trapped **6**, % yield | recovered **1**, % yield |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | 57:43 | [c] | MeOH | H | 49 | – | 25 |
| 2 | **1b** | 66:33 | [c] | MeOH | H | 44 | – | 52 |
| 3 | **1c** | 51:49 | [c] | MeOH | H | 53 | – | 42 |
| 4 | **1d** | 76:24 | 77:23 | MeOH | H | 53 | – | [c] |
| 5 | **1d** | 76:24 | 82:18 | $CD_3OD$ | D | 73 | <5[d] | 11 |
| 6 | **1d** | 76:24 | 74:26 | MeI | Me | 66 | 0[b] | 15 |

[a] calculated ratio of starting conformers at −78 °C; [b] by NMR of crude product; [c] not determined; [d] by MS

when determined, the crude ratio of product to starting material matches closely the calculated ratio of starting material conformers at −78°C, and in no case does the yield significantly exceed the calculated proportion of the major conformer. It seems that stereospecificity is attained because only one of the two diastereoisomeric conformers of the starting material is able to react.

If this is indeed the case, two possibilities still remain. Either all of the starting material **1** is lithiated but only one conformer of the organolithium **5** cyclises (this *would* require a configurationally stable intermediate organolithium — otherwise the two conformers *syn*-**5** and *anti*-**5** are simply enantiomeric), or only one conformer *syn*-**1** of the starting material is lithiated — this then cyclises, leaving unlithiated starting material (this would not require the intermediate organolithium *syn*-**5** to be configurationally stable).[2]

The difference between the two alternatives lies in whether the starting material which does not cyclise is nonetheless lithiated. The reactions in entries 5 and 6 of Table 1 indicate that the remaining uncyclised starting material is not lithiated, or the products would include some deuterated or methylated starting material such as **6** (E=D or E=Me). Lithiation itself therefore appears to be stereoselective.

The final proof that it is indeed conformation which differentiates the material that lithiates and cyclises from that which does not came when we omitted the cyclisation-promoting DMPU from the lithiation of **1** and shortened the reaction time to allow insufficient time for cyclisation to occur. The results of these experiments are shown in Table 2. Entry 1 shows that, after 2 h, the starting material had lithiated but not all cyclised, since it could be deuterated in low yield. This reaction (entry 1) returned 32% cyclised material, and 40% of the 63% remaining starting material was deuterated.[6] Presumably, it is this deuterated material (25% of the total) which would go on to cyclise while the remaining material (60% of starting material; 38% of the total) is never lithiated and never cyclises. The fragmentation pattern in the mass spectrum showed that deuteration occurred only on the naphthalene ring to give **6** (E=D), and chiral HPLC of the starting material [including **6** (E=D)] showed that it was still enantiomerically pure. We already know that these cyclisations may proceed via an initially formed *ortho*-lithiated species **4** which 'translocates' to an α-lithiated species **5**,[7] and **4** is the only organolithium trappable after 2 h, maybe because **5** cyclises as soon as it forms.[8] Under similar conditions, the majority of lithiated **1b** had already cyclised (entry 2).

Even if only one conformer of the starting material is lithiated, with E=D, conformers *syn*-**6** and *anti*-**6** interconvert rapidly at room temperature and both are observed in the product mixture. But with E=Me, *syn*-**6** and *anti*-**6** become atropisomers with sufficient conformational stability for characterisation even at room temperature.[5] We therefore used MeI instead of $CD_3OD$ to trap the uncyclised organolithiums **4**. After 6 h or 1 h, most of the lithiated starting material has cyclised and we got back mainly the

Table 2
Trapping the uncyclised organolithium

| entry | starting material | reaction time | $E^+$ | E | cyclised **3**, % yield | trapped **6**, % yield | remaining **1**, % yield |
|---|---|---|---|---|---|---|---|
| 1 | **1c** | 2 h | $CD_3OD$ | D | 32 | 25[a,b] | 38[b] |
| 2 | **1b** | 2 h | $CD_3OD$ | D | 23 | 7[a] | 47 |
| 3 | **1c** | 6 h | MeI | Me | 39 | 5 (*syn*-**6** only)[c] | 20[c] |
| 4 | **1b** | 1 h | MeI | Me | 14 | 10 (*syn*-**6** only)[c,d] | 60[c] |
| 5 | **1c** | 5 min | MeI | Me | 0 | 20 (*syn*-**6** only)[c,e] | 80[c] |
| 6 | **1b** | 5 min | MeI | Me | 3[b] | 21 (*syn*-**6** only)[c] | 75[c] |

[a]by MS; [b]enantiomerically pure by HPLC on chiral stationary phase; [c]by NMR; [d]9% isolated by HPLC; [e]7% isolated by HPLC

methylated cyclised product **3** (E=Me) along with the starting material and only small amounts of trapped **6** (entries 3 and 4). But after just 5 min, although lithiation is not complete, both **1b** and **1c** gave a crude reaction product containing essentially only starting material and *a single atropisomer* of the *ortho*-methylated *syn*-**6** (E=Me)[3] (entries 5 and 6). *syn*-**6** (E=Me, R=α-methylbenzyl) was isolated by HPLC and epimerised in solution at 40°C to establish the existence of the other diastereoisomeric atropisomer *anti*-**6**, confirming its absence from the reaction product mixture, and proving that the stereoselectivity of the reaction arises because only one conformer can lithiate: ortholithiation is diastereoselective.[9]

To summarise, the overall stereochemical course of the cyclisation is as follows. At −78°C, the starting material partitions itself into two slowly interconverting diastereoisomeric conformations *syn*-**1** and *anti*-**1**. One (fortunately the major, *syn*-**1**) undergoes rapid ortholithiation to give *syn*-**4**; the other, *anti*-**1**, for whatever reason, cannot lithiate. The ortholithiated species *syn*-**4** (which may be trapped) translocates to an α-lithiated species **5**, which may or may not be configurationally stable at the Li-bearing centre, but whose Ar–CO axis preserves the memory of the original absolute stereochemistry.[10] Compound **5**'s existence is too fleeting for it to be trapped, and it rapidly cyclises back onto the aromatic ring either with retention of configuration, or simply in order to place Ph *exo* to the new tricyclic system, to give the enolate **2** which reacts with electrophiles to give **3**.

## Acknowledgements

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## References

1. Bragg, R. A.; Clayden, J., preceding paper.
2. For a discussion of configurational stability in α-amino organolithiums, see: Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. For examples of retention and inversion in the reactions of chiral organolithiums, see: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.
3. Relative stereochemistry is assigned from the fact that the major conformer cyclises with retention (see Ref. 1), and the *syn/anti* nomenclature arbitrarily describes the relationship between the naphthalene ring and the benzylic substituent (as drawn).
4. Compound **1b** can also epimerise by C–N rotation, a process with a similar activation barrier (see Ref. 5).
5. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.

6. Since this reaction gave 32% cyclised product even without DMPU, cyclisation of α-methylbenzyl amides must be much faster than the cyclisation of simple benzylic amides, which do not cyclise in the absence of DMPU as a promoter. This explains why the first reaction of this kind (Ref. 1, **3**→**4**) was successful.
7. Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103.
8. The enantiomeric purity of **6** (E=D) shows that if **4** and **5** are in equilibrium, then either their interconversion must be fully stereospecific and **5** is configurationally stable, or the deuteration is stereoselective. It seems to us more likely that **5** never reverts to **4**.
9. By its nature, ortholithiation can rarely be diastereoselective: this is the first example. For examples of diastereoselective reactions of ortholithiated amides and diastereoselective lateral lithiations, see: Clayden, J. *Synlett* **1998**, 810.
10. For examples of 'memory of chirality' mediated by rotational restriction, see: Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694; Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809; Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373; Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1761; Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949.