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# Asymmetric deprotonation and dearomatising cyclisation of *N*-benzyl benzamides using chiral lithium amides: formal synthesis of (–)-kainic acid

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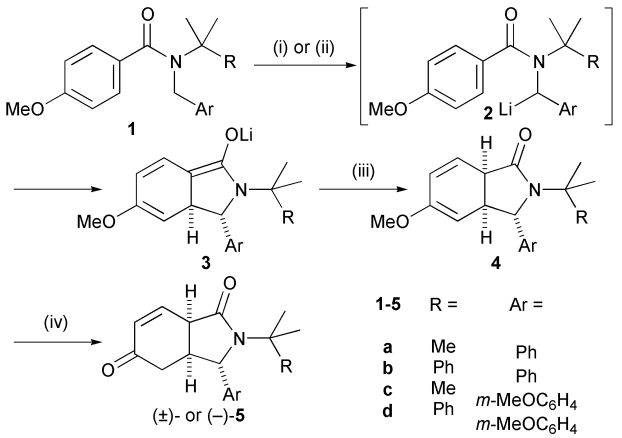
**Chiral lithium amides deprotonate *N*-benzyl benzamides enantioselectively, initiating an asymmetric dearomatising cyclisation to enantiomerically enriched isoindolinones.**

We have previously reported[1] that lithiated *N*-benzyl amides cyclise at temperatures approaching 0 °C (−78 °C in the presence of HMPA[2,3]) to yield dearomatised products which take the form of partially saturated isoindolinones (Scheme 1).

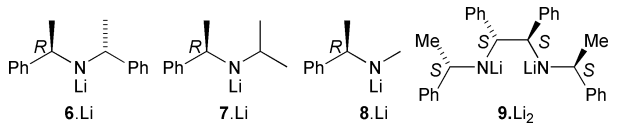



**Scheme 1** Dearomatising cyclisation of lithiated *N*-benzyl benzamides. (i) [for (±)-**5**] LDA, −78–+25 °C, 1.5 h; (ii) [for (−)-**5**] chiral lithium amide, −78–+25 °C, 1.5 h; (iii) $NH_4Cl$; (iv) HCl, $H_2O$.

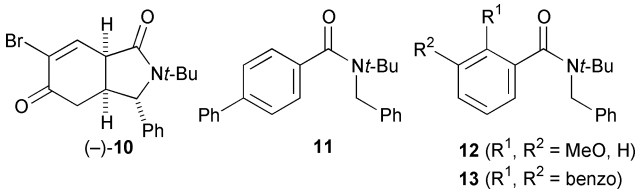
These heterocycles, with their three new stereogenic centres and versatile functional groups, are versatile synthetic intermediates, and we have published a synthesis of (±)-kainic acid using the cyclisation of **1b** as a key step.[4] In this paper we report an asymmetric cyclisation achieved† by means of chiral lithium amide bases which proceeds *via* an asymmetric benzylic deprotonation.

α-Amido benzyllithiums related to **2** may be generated enantioselectively with s-BuLi–(−)-sparteine and are configurationally stable over a period of 10 h at −78 °C.[5,6] However, while treatment of **1a** with s-BuLi–(−)-sparteine[7] in THF gave the cyclised product **5a**, it turned to be racemic. Insufficient solubility prevented the use of $Et_2O$ or *t*-BuOMe; toluene turned out to be too acidic, becoming lithiated itself and leading to benzyl ketones; no reactions took place in cumene.

As we knew that LDA deprotonates **1a** at temperatures approaching −40 °C,[1] we turned to chiral versions of LDA, namely the lithium amides **6**·Li, **7**·Li, **8**·Li and **9**·$Li_2$.[8] Each base was used with the amide **1a**, and the crude product was hydrolysed to the enone with aqueous hydrochloric acid. The products **5a–d** were purified by flash chromatography, and the yields and enantiomeric excesses obtained are shown in Table 1. The best results were with **7**·Li: not only did it give the highest enantiomeric excesses, but it was also the easiest to remove from the product mixture by a simple acid wash.‡ A single recrystallisation was enough to return the products **1a** and **1b** in >99% ee. Attempts to improve enantioselectivity by changing the temperature régime (entries 2, 10) were unsuccessful. The absolute stereochemistry of the products (which were all laevorotatory with **6**·Li–**8**·Li and dextrorotatory with **9**·$Li_2$) was determined by X-ray crystallography of the enone (−)-**10** obtained by bromination ($Br_2$, $Et_3N$, $CH_2Cl_2$: 80%) of enantiomerically pure (−)-**5a**.




Enantioselective cyclisation of the *para*-substituted amide **11** was also successful under these conditions, though unfortunately it was impossible to improve the enantiomeric excess of the product by recrystallisation. However, amides bearing *ortho* substituents such as **12** or **13** gave either low yields or low enantioselectivities, probably because such *ortho*-substituted tertiary aromatic amides are chiral compounds at low temperatures.§




As for the origin of the enantioselectivity, two limiting possibilities present themselves. The first is that the reaction proceeds *via* an asymmetric deprotonation of the achiral starting material **1**, generating an enantiomerically enriched organolithium which is configurationally stable on the timescale of the reaction and which cyclises *stereospecifically*. The second is that the reaction is a *stereoselective* cyclisation of an intermediate organolithium (which may or may not be configura-

**Table 1** Asymmetric cyclisation of *N*-benzyl benzamides

| Entry | Starting material | Base | (−)-**5** yield (%) | (−)-**5** ee[a] (%) | (−)-**5** ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | **6**·Li | 73 | 80 | >99 |
| 2 | **1a** | **6**·Li[c] | 65 | 50 | — |
| 3 | **1a** | **7**·Li | 72 | 80 | >99 |
| 4 | **1a** | **8**·Li | 72 | 17 | — |
| 5 | **1a** | **9**·$Li_2$ | 38 | −75[d] | — |
| 6 | **1b** | **6**·Li | 64 | 75 | >99 |
| 7 | **1b** | **7**·Li | 72 | 81 | >99 |
| 8 | **1b** | **9**·$Li_2$ | 23 | −30[d] | — |
| 9 | **1c** | **6**·Li | 59 | 73 | – |
| 10 | **1c** | **6**·Li[e] | 67 | 60 | — |
| 11 | **1d** | **7**·Li | 87 | 84 | — |
| 12 | **11** | **7**·Li | 70 | 60 | 0 |

[a] Ee after flash chromatography.[b] Ee after recrystallisation.[c] Reaction carried out −78–−60 °C, 16 h.[d] (+)-**5** is the major enantiomer.[e] Reaction carried out −50 °C–+25 °C.

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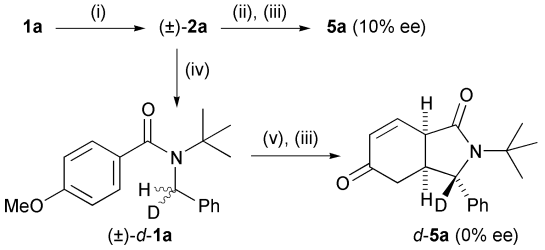
tionally stable) under the asymmetric influence of the amine such as **7**·H regenerated after deprotonation. The known configurational stability of lithio amides similar to **2**[5,6] at least does not rule out the first mechanism. To distinguish between these two possibilities, we carried out two experiments.[9]

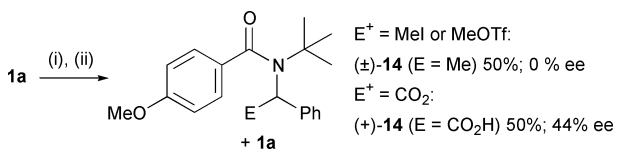
In the first experiment, we treated **1a** with *t*-BuLi to generate organolithium (±)-**2a**, and then added chiral amine **7**·H, recreating the conditions of the asymmetric cyclisation but with a starting organolithium that must, at least initially, be racemic (Scheme 2). After an aqueous quench and acidic work-up, the product **5a** of this reaction was nearly racemic, proving that the enantioselectivity in the asymmetric reaction is determined before the cyclisation step.




**Scheme 2** Mechanism of the cyclisation (i) *t*-BuLi, THF, −78 °C; (ii) **6**·H, −78 °C–+25 °C; (iii) $NH_4Cl$ then HCl, $H_2O$; (iv) $CD_3OD$; (v) **6**.Li, THF, −78–+25 °C.

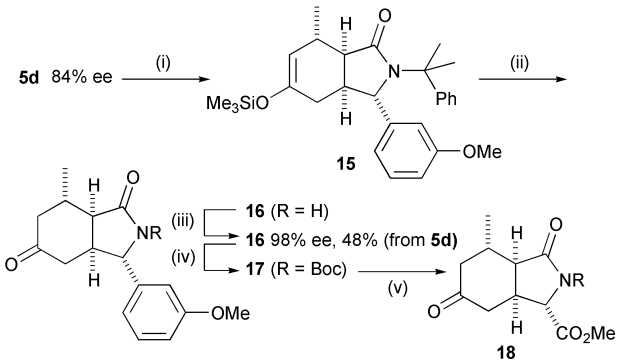
In the second experiment, we used racemic, deuterium-labelled (±)-*d*-**1a** (obtained by deuteration of (±)-**2a**, Scheme 2) as the starting material for the asymmetric cyclisation. Cyclisation of (±)-*d*-**1a** with **6**·Li gave racemic material **5a** which was >99% deuterated — a result consistent only with a primary kinetic isotope effect $k_H/k_D$ of at least 100 which has completely overturned the enantioselectivity of the chiral base.[10,11] This in turn implies the enantioselective step must be a step subject to a primary kinetic isotope effect, *i.e.* the deprotonation.

While the *s*-BuLi–(−)-sparteine has commonly been used for the enantioselective removal of one of a pair of enantiotopic geminal H atoms to give a chiral organolithium,[7] the less basic chiral lithium amide bases are much more frequently employed to generate chiral planar anions, such as enolates, by selecting between enantiotopic enolisation sites of prochiral carbonyl compounds.[8] By carrying out the asymmetric deprotonation at temperatures too low for cyclisation to occur (< −40 °C), we hoped to observe the asymmetric formation and external quench of a chiral, non-planar organolithium generated with a chiral lithium amide, a reaction observed before only with $Cr(CO)_3$-complexed benzyl groups.[12,13] When we treated the amide **1a** with **7**·Li at −78 °C, warmed to −40 °C over 1 h to ensure deprotonation, and then added an electrophile, the ee of the product was dependent on the electrophile used (Scheme 3). Presumably the rate of racemisation of the organolithium **2a** is similar to the rate of reaction with an electrophile, and racemisation outpaces attack on MeI but not on $CO_2$.¶ We conclude that asymmetric deprotonation of one of the pair of enantiotopic protons of **1** gives a benzylic organolithium with sufficient configurational stability to cyclise stereospecifically but insufficient configurational stability to prevent partial or complete racemisation on the timescale of its addition to an external electrophile.




**Scheme 3** External electrophiles (i) **7**·Li, −78–−40 °C, 1 h; (ii) $E^+$.

Our published route to (±)-kainic acid[4] uses **18** as an intermediate. As a demonstration of the utility of the asymmetric cyclisation, we therefore converted **5d** (which was produced in 84% ee by the most enantioselective cyclisation we could find, Table 1, entry 11) to **18** in four steps (Scheme 4). **5d** could not be recrystallised to enantiomeric purity, but after addition of $Me_2CuLi$ and deprotection/hydrolysis of the enol ether **15**, recrystallisation of pyrrolidinone **16** gave enantiomerically pure material in an overall yield of 48% from **5d**. Boc protection of **16** and oxidation of the *m*-$MeOC_6H_4$ ring of **18** gave the enantiomerically pure ester **18**, which we have converted to kainic acid in five steps.[4]




**Scheme 4** Formal synthesis of (−)-kainic acid (i) $Me_2CuLi$, $Me_3SiCl$; (ii) $CF_3CO_2H$; (iii) recrystallise; (iv) $Boc_2O$, DMAP, $Et_3N$, $CH_2Cl_2$; (v) $RuCl_3$, $NaIO_4$, $H_2O$, MeCN then $CH_2N_2$.

We are grateful to the EPSRC for a studentship (to CJM), to Dr C. S. Frampton for determining the absolute stereochemistry of **10**, and to Miss K. Hebditch for studying the cyclisation of **12**.

## Notes and references

† Related cyclisations of *N*-benzyl-1-naphthamides[14,15] have been made asymmetric by the use of a chiral auxiliary[16] or chiral starting material.[17]
‡ **7**·H was made in 61% yield by stirring (*S*)-α-methylbenzylamine with isopropyl bromide.[18]
§ Tertiary 1-naphthamides and *ortho*-substituted benzamides exhibit atropisomerism at low temperature,[19] and hence **12** and **13** must be viewed as racemic compounds under the conditions of the deprotonation. This feature has a governing role in the cyclisation of chiral 1-naphthamides.[20]
¶ The absolute stereochemistry of (+)-**14** (E = $CO_2H$) is unknown.

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