Anionic cyclisations of an *N*-benzyl naphthamide: a route to benzo[*e*]isoindolones

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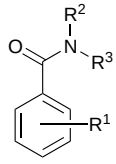
On treatment with Bu^{t}Li and HMPA, *N*-*tert*-butyl-*N*-benzyl-1-naphthamide undergoes cyclisation to a tricyclic enolate which reacts diastereoselectively with electrophiles to give substituted 2,3,3a,9b-tetrahydro-1*H*-benzo[*e*]-isoindol-1-ones, the first example of an anionic cyclisation onto an aromatic ring.

When tertiary aromatic amides **1** are treated with organolithium bases, they are usually *ortho*-lithiated.[1–3] Amides bearing 2-alkyl groups may be laterally lithiated[4,5] and, in exceptional cases (for example if the 2 and 6 positions are blocked,[6–9] if the nitrogen bears an activating group such as benzyl[10] or with a lithium amide base[1,11]), lithiation may take place α to nitrogen.[12,13] Alkylation of these dipole-stabilised anions is well known,[13] and both *ortho*-lithiation[14] and lateral lithiation[15] followed by electrophilic quench have been made enantioselective by the addition of (−)-sparteine.[16]



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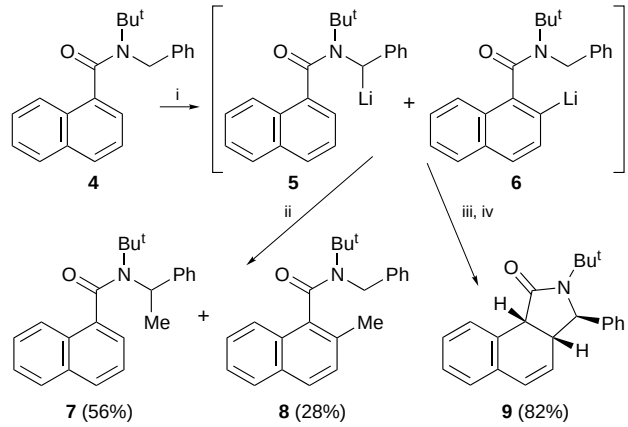
We have shown that both *ortho*-lithiated[17,18] and laterally lithiated[19] tertiary 1-naphthamides can react atroposelectively with electrophiles—frequently only one of two possible atropisomeric products (which arise from restricted rotation about the aryl–carbonyl bond) is formed.[19] For example, the 2-ethyl-*N*,*N*-diisopropylnaphthamide **2** reacts with Bu^{s}Li to give a single, configurationally stable (at both stereogenic axis and centre) organolithium[20] which reacts stereospecifically with many electrophiles to give a single atropisomer of the product **3** (Scheme 1).

In connection with this work, we lithiated *N*-*tert*-butyl-*N*-benzyl-1-naphthamide **4** with Bu^{t}Li and quenched the resulting red solution with MeI. We obtained two compounds, in a ratio of about 2 : 1: compound **7** results from methylation α to nitrogen, and **8** from methylation on the aromatic ring *ortho* to the amide group.† Lithiation of **4** therefore apparently gives a mixture of α- and *ortho*-lithiated compounds **5** and **6**.

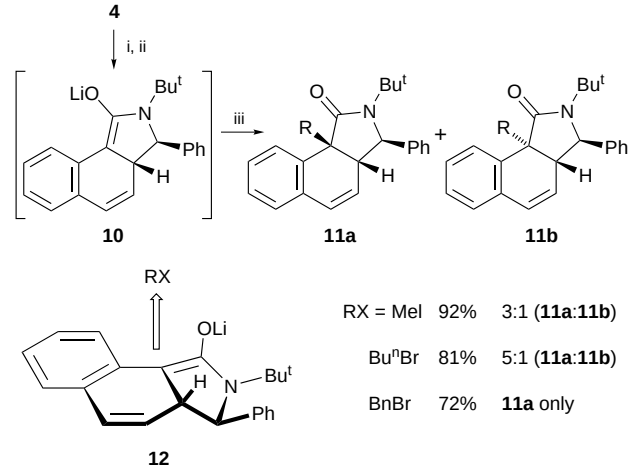
When we treated this mixture of organolithiums with HMPA (6 equiv.), it underwent a remarkable cyclisation reaction.‡ After an aqueous quench, we isolated the tricyclic 2,3,3a,9b-tetrahydro-1*H*-benzo[*e*]isoindol-1-one **9** as a single diastereoisomer in 82% yield (Scheme 2). Nuclear Overhauser enhancement (NOE) experiments showed that the 6,5-ring junction was *cis*, with the phenyl group on the *exo* face. This is the more stable of the two ring-junction isomers: **9** was recovered as a single unchanged diastereoisomer after stirring overnight with Bu^{t}OK in Bu^{t}OH at 40 °C.§



4 **5** **6** **7** (56%) **8** (28%) **9** (82%)

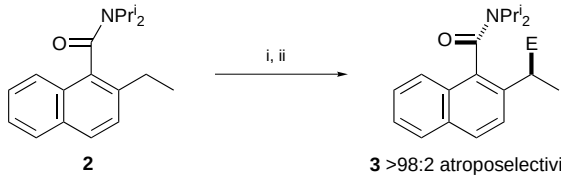
Scheme 2 *Reagents and conditions*: i, Bu^{t}Li (1.3 equiv.), THF, −78 °C, 2 h; ii, MeI, −78 °C; iii, HMPA (6 equiv.), −78 °C, 16 h; iv, NH_4Cl

The initial product of the cyclisation triggered by the HMPA is an enolate **10** which we could alkylate with MeI, Bu^{n}Br or BnBr, giving compounds **11** as shown in Scheme 3. Diastereoselectivity depended on the size of the electrophile, with BnBr being the most selective—**11** (R = Bn) was obtained as a single isomer **11a** (R = Bn) only. MeI gave a 3 : 1 ratio of **11a** and **11b**, and the same ratio of diastereoisomers is obtained by methylating the lithium enolate formed from **9** with LDA in the absence of HMPA: HMPA does not affect the diastereoselectivity of the



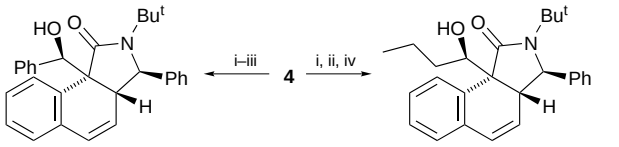
4 **10** **11a** **11b** **12**

Scheme 3 *Reagents and conditions*: i, Bu^{t}Li, −78 °C; ii, HMPA, −78 °C; iii, RX



2 **3** >98:2 atroposelectivity

Scheme 1 *Reagents and conditions*: i, Bu^{s}Li, −78 °C; ii, E^+ (EtI or R_3SiCl)



13 (81%)

14 (47%)
plus other diastereoisomers (37%)

Scheme 4 *Reagents and conditions*: i, Bu^{t}Li, −78 °C; ii, HMPA, −78 °C; iii, PhCHO; iv, Pr^{n}CHO

reaction. The identity of the diastereoisomers was determined by NOE experiments, and the major one in each case results from alkylation from the less hindered *exo* face of the enolate as shown (**12**), giving a *cis* 6,5-ring junction.

The cyclised enolate **10** also underwent clean aldol reactions (Scheme 4). A reaction with benzaldehyde gave the alcohol **13** as a single diastereoisomer in 81% yield. Tricycle **13** has four new adjacent chiral centres, and its relative stereochemistry was proved by X-ray crystallography (Fig. 1). An aldol reaction with *n*-butyraldehyde was somewhat less stereoselective, although NMR correlation indicated that again the major product **14** arose from attack of the aldehyde on the less hindered face of the enolate.

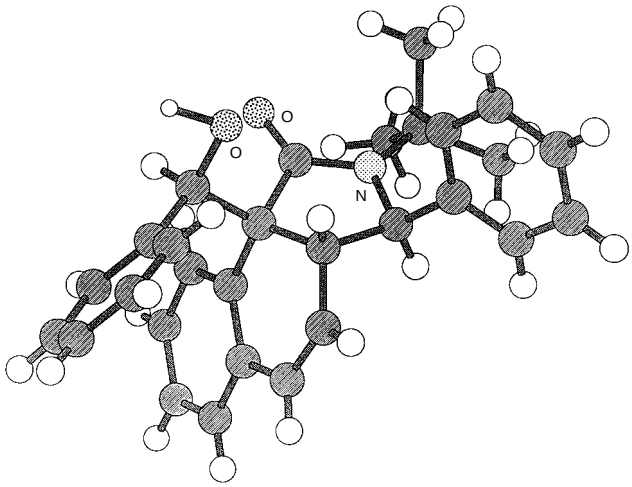


Fig. 1

While additions onto aromatic rings which result in loss of aromaticity are rare,[21] the addition of organometallic nucleophiles to electron-poor naphthalenes is precedented.[22] However, our cyclisation is, as far as we are aware, the first example of an *anionic cyclisation* onto an aromatic ring of any sort. Anionic cyclisation onto π systems is turning out to be a useful way of making rings, both carbocyclic[23,24] and heterocyclic,[25] but is invariably initiated by transmetallation and not deprotonation.[26] We are currently extending the scope and applicability of this new reaction as a promising method for the stereocontrolled synthesis of fused five-membered nitrogen heterocycles.[27]

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Notes and References

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† Later, we found that this reaction also gives a small amount (*ca.* 10%) of **11** (R = Me).

‡ For an example of an anionic cyclisation triggered by $Me_2NCH_2CH_2NMe_2$, see ref. 24.

§ A kinetic protonation of the enolate with Bu^{t}Br likewise gave a single diastereoisomer of **9**.

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