Stereospecific Dearomatising Cyclisation of Tertiary α-Amidoorganolithiums

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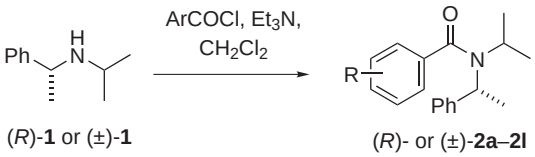
Abstract: Lithiation of benzamides derived from a chiral and enantiomerically pure α-methylbenzylamine leads to diastereoselective and regioselective dearomatising cyclisations with overall conservation of the stereochemistry of the starting stereogenic centre.

Key words: amide;, lithiation, cyclisation, stereospecificity, dearomatisation

α-Heterosubstituted benzyllithiums commonly exhibit configurational stability,[1] and tertiary α-heterosubstituted benzyllithiums are often configurationally stable on the macroscopic (i.e. laboratory) timescale.[2,3] Several examples exist of chiral benzylic esters,[4] carbamates[2,5,6] and thiocarbamates[7–9] which may be deprotonated to yield enantiomerically pure organolithiums. These organolithiums may go on to react stereospecifically, with either retention or inversion or a mixture, depending on their structure.[10,11]

In this paper we show that the same is true for simple chiral amides. Various *N*-benzoyl derivatives of α-methylbenzylamine may be deprotonated at their single stereogenic centre to form chiral organolithiums.[12] These organolithiums cannot be quenched with external electrophiles because they undergo a dearomatising cyclisation.[13–15] We show that the overall deprotonation-cyclisation sequence is stereospecific,[16] indicating that the chiral organolithium is configurationally stable on the timescale of the cyclisation.

The amides **2a**–**2l** shown in Table 1 were made in both racemic and enantiomerically pure form by acylation of *N*-isopropyl (±)- and (*R*)-α-methylbenzylamine (>99% ee) **1** using a range of substituted benzoyl chlorides (Scheme 1). In general these compounds had complex NMR spectra due to interconversion of conformers about the C–N bond. They were treated with *t*-BuLi in THF at –78 °C to yield deeply coloured solutions of benzyllithiums **3** which were allowed to warm to 20 °C over a period of a few hours, generating enolates **4** (Scheme 2). In some cases DMPU was added to facilitate the cyclisation. The reactions were quenched with ammonium chloride and products **5**–**15** were isolated as shown in Schemes 3–5 below.



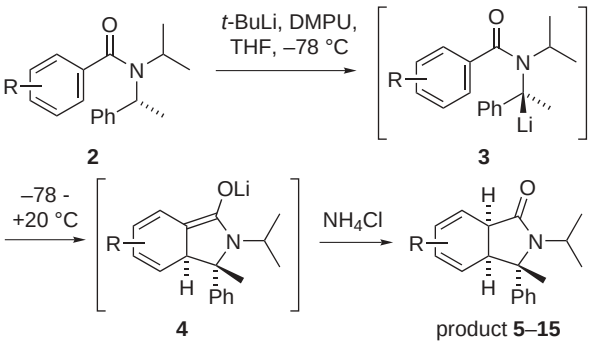
(*R*)-**1** or (±)-**1** (*R*)- or (±)-**2a**–**2l**

Scheme 1 Synthesis of the amides.

Table 1 Starting Benzamides

Entry	Compound	Substituents R
1	**2a**	–
2	**2b**	4-Me
3	**2c**	4-MeO
4	**2d**	2-Me
5	**2e**	2-MeO
6	**2f**	2,4-di-MeO
7	**2g**	3-Me
8	**2h**	3-MeO
9	**2i**	3,4-di-MeO
10	**2j**	3,5-di-MeO
11	**2k**	2,3-di-MeO
12	**2l**	2,6-di-MeO

Under these conditions unsubstituted benzamide **2a** underwent a dearomatising cyclisation[13–15] to give a single diastereoisomer of the cyclohexadiene **5** in 70% yield plus a small amount (10%) of a mixture of other diene regio-



Scheme 2 Lithiation and cyclisation.

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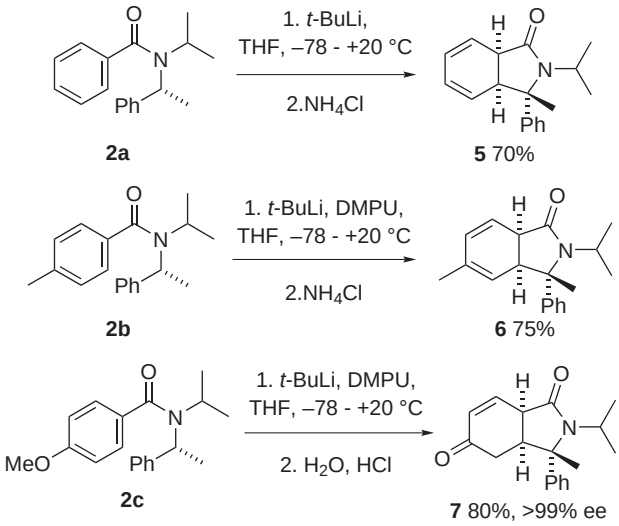
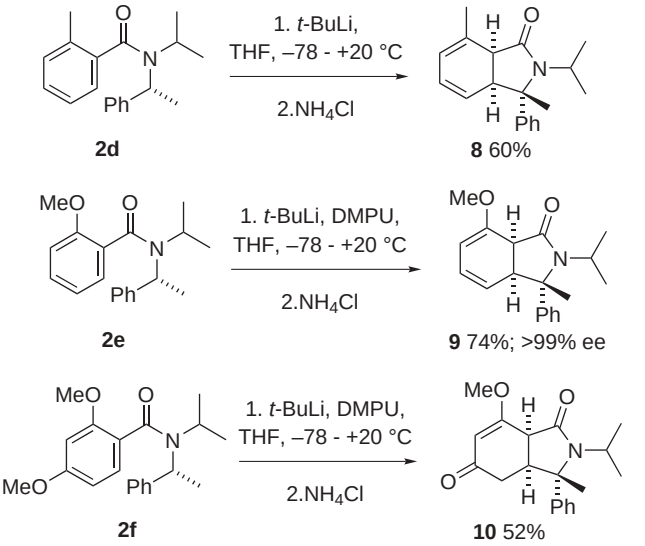
isomers. Benzamides **2b** and **2c**, both substituted in the *para* position, cyclised with similar complete diastereoselectivity. A single regioisomer of diene **6** was isolated; the cyclisation product from **2c** was quenched with aqueous acid and generated the enone **7** with no trace of other regioisomers. To the extent of NMR detection, a single diastereoisomer was formed in every case. Comparison of the HPLC trace on chiral stationary phase of the products **7** derived from the racemic and the enantiomerically pure amide **2c** indicated that the deprotonation and cyclisation, at least in this case, is fully stereospecific.[17]



Scheme 3 Cyclisation of unsubstituted and *para*-substituted amides.

With amides **2d**, **2e** and **2f** bearing an *ortho* substituent, cyclisation onto the unsubstituted carbon atom was observed exclusively in each case, and again single regioisomers, diastereoisomers and (where measured) enantiomers of the products **8**, **9** and **10** were formed (Scheme 4). When **2f** was cyclised, the presumed initial bis-alkoxydiene product hydrolysed during work-up to generate the alkoxyenone **10**. A single regioisomer forms, to which we assign the regiochemistry shown on the basis of precedent.[14]

Benzamides with a *meta* substituent have the choice of cyclisation onto either of two unsubstituted carbon atoms (Scheme 5). The cyclisations of **2g**, **2h** and **2i**, along with the results of attempted cyclisation of **2j** and **2k**, reveal the factors controlling the regioselectivity of the cyclisation. With a *meta* methyl substituent (**2g**), the cyclisation exhibits no selectivity: a mixture of regioisomers **11** and **12** is formed. With a *meta* methoxy group (**2h**), cyclisation gives a single enantiomerically pure regioisomer **13** in which the organolithium has attacked the position *ortho* to the methoxy group. A preference for cyclisation *ortho*, rather than *para*, to a methoxy group has been noted before.[15] Presumably, although π-donation deactivates the positions *ortho* and *para* to the methoxy group, with methoxy *ortho*, inductive electron withdrawal counteracts



Scheme 4 Cyclisation of *ortho*-substituted amides.

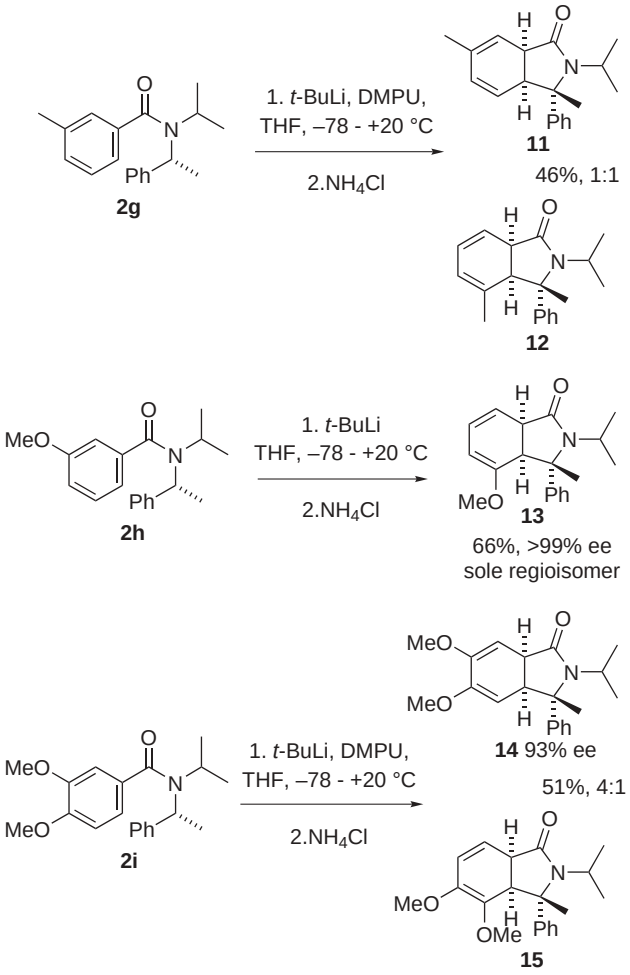
this effect, making this the favourable position for cyclisation.[18] This preference in the 3,4-dimethoxy substituted amide **2i** is overridden by the unfavourability of a 1,2,3,4-tetrasubstituted arrangement in the transition state, and **14** is the major product, though some of the regioisomer **15** is also formed. The reluctance of **2i** to cyclise erodes the ee of **14**, the only cyclisation product in which we could detect the formation of a second enantiomer from an enantiomerically pure starting amide. Presumably, slow cyclisation onto the electron-rich ring permits partial racemisation of the intervening organolithium.

The 3,4- and 2,3-dimethoxy amides **2j** and **2k** fail to cyclise. Attempted intramolecular nucleophilic substitution[19] in **2l** also failed.

Notably, in all cases where ee's were measured, except **14**, complete stereospecificity was observed, indicating that both lithiation and cyclisation are fully stereospecific and that the chiral lithioamide intermediate **3** is configurationally stable on the timescale of its cyclisation. We have noted previous stereospecific cyclisation reactions in which stereochemistry was conserved in the chiral Ar-CO axis of the amide[20,21] – a form of chiral memory.[22] Symmetry dictates that benzamides **2a**–**c**, and precedent[23–25] that benzamides **2g**–**i**, cannot have a chiral axis, so stereospecificity in this current work must be ascribed simply to the kinetic configurational stability of the organolithium intermediate.

We are currently exploring the use of this class of stereospecific cyclisations in the introduction of quaternary chiral centres to a range of other ring systems.[26]

General procedure for the cyclisation: *t*-BuLi (1.3 equiv) was added to a solution of the amide (ca. 0.50 g) in THF (30 ml) at –78 °C with *t*-BuLi. The solution was allowed to warm to room temperature over 2 h. Saturated ammonium chloride solution was added and the THF was removed under reduced pressure. The residue was extracted



Scheme 5 Cyclisation of *meta*-substituted amides

with ether and the combined organic extracts were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography.

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