New symmetry-breaking deprotonation reactions of cyclic imides using a chiral lithium amide base

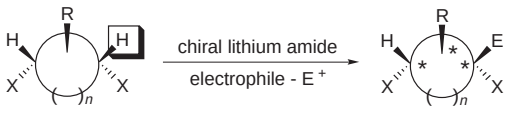
David J. Adams, Nigel S. Simpkins*† and Torben J. N. Smith

Department of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD

Treatment of various *N*-substituted succinimides, possessing additional three-, four- or five-membered ring-fusion, with a mixture of chiral lithium amide base and Me_3SiCl, enables enantioselective silylation to give products in up to 95% ee.

During the past few years there have been great developments in the application of chiral lithium amide base reactions to asymmetric synthesis.[1] Most of the enantioselective deprotonation reactions of these chiral bases described to date involve discrimination between enantiotopic hydrogens activated by a single common functional group. The best developed chemistry of this type is the asymmetric enolisation of cyclic ketones, although somewhat analogous situations involving metallation of sulfoxides and prochiral organometallics have also been described.[2]

We considered that a considerable broadening in the scope for applications of chiral lithium amides would be possible if *multifunctional* substrates could be employed. In a general sense this could involve desymmetrisation of a prochiral molecule having a number of functional groups deployed on a suitable conformationally constrained template (most likely a carbocyclic or saturated heterocyclic or polycyclic system). In this type of chiral base reaction the key step would involve kinetically controlled discrimination between hydrogens which are activated by *separate* functional groups. For a situation in which just two functional groups are involved (as the activating groups for two enantiotopic methine hydrogens), the transformation can be illustrated as the conversion of **1** into **2** (Scheme 1).[3]



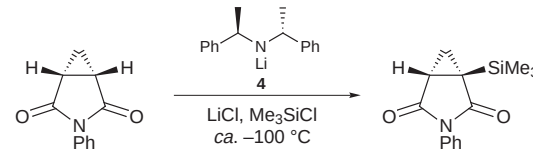
1 **2**

Scheme 1

The two activating groups X could be typical carbonyl types, including ketone, ester or amide, or other types such as sulfone. These two functions could be close together or somewhat remote (variation in *n*) and the overall framework could bear substituents R as long as the overall symmetry is retained in substrate **1**. As can be seen, the chiral base transformation, involving selective substitution at one activated position would be expected to generate chiral products having a number of asymmetric centres (marked *).

Herein we describe our initial results in this new area of chiral lithium amide base chemistry in which we have examined the desymmetrisation of a number of ring–fused imides, *i.e.* $n = 0$ and X = amide (X groups linked to form a five-membered ring imide).

Initial work showed that treatment of cyclopropane derivative **3** with chiral base **4** at low temperature in the presence of Me_3SiCl resulted in the formation of the desired product **5** in 80% yield and 95% ee (Scheme 2).[4]‡

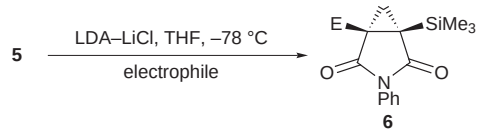


3 **5** 80% (95% ee)

Scheme 2

Imide **5** proved to be crystalline, which enabled us to determine the absolute configuration shown by single crystal X-ray structure determination.§ Our delight at this excellent result was tempered by the observation that only the use of Me_3SiCl as an *in situ* electrophile appears to enable clean substitution, with the attempted reaction with alkylating agents such as MeI resulting only in the destruction of starting material. Although this is a drawback, we were able to circumvent this apparent limitation by substitution of the remaining acidic hydrogen by conventional means (Table 1).

Table 1 Substitution of **5** using LDA

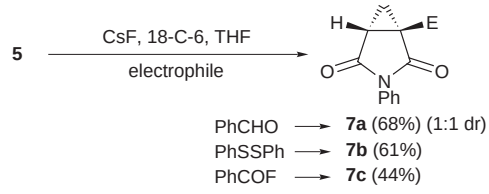


6

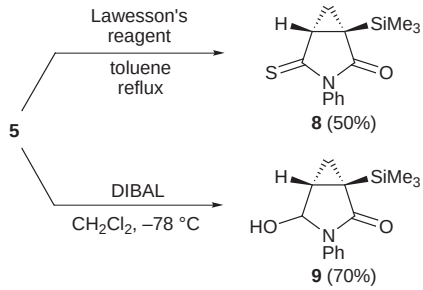
Compound	Electrophile	Yield of **6** (%)
6a	MeI	93
6b	AllylBr	73
6c	BnBr	67
6d	PhSSPh	71
6e	PhCHO[a]	61
6f	PhCOCl	57

[a] Formed as a *ca.* 1 : 1 ratio of diastereoisomers.

Thus, introduction of a range of different substituents was possible in good to excellent yield by use of LDA–LiCl as the base.[5] In the case of **6a** we have confirmed that removal of the silicon group is possible, to give the expected methylated imide. As an alternative approach to the problem we have found that fluoride-mediated substitution of the Me_3Si group of **5** is possible by a narrow range of electrophiles (PhCHO, PhSSPh and PhCOF), to give directly the imide products **7** (Scheme 3).[6] We expect that no loss of ee takes place in this process, although this has not been confirmed to date.



Scheme 3

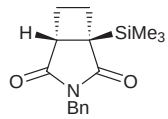


Scheme 4

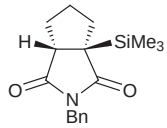
Since one of the main objectives of this new chiral base chemistry is to enable the synthesis of varied enantiomerically enriched products, it was important to establish if the initial enantioselective substitution to give **5** enabled subsequent regiocontrolled reactions of the imide. In line with our expectations, imide **5** undergoes highly regioselective thionation and reduction reactions, to give **8** and **9** respectively (Scheme 4).[7,8]

Taken in combination with the highly enantioselective access to compounds of type **6** and **7**, this chemistry begins to indicate some of the potential of our new approach for the synthesis of lactams, lactones, pyrrolidines, *etc*.

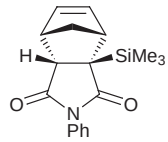
Finally, we were able to extend this new asymmetric process to several other imide systems, the silylated products **10–12**



10 (37%) (94% ee)



11 (72%) (91% ee)



12 (65%) (93% ee)

being isolated in excellent levels of ee from reaction of the appropriate symmetrical imide starting material with a mixture of **4** and Me_3SiCl at low temperature.[9]¶

These results show that the concept outlined in Scheme 1 can be realised, and the products clearly have some potential for target synthesis. However, these asymmetric transformations of ring-fused imides form but a small sub-group of the chemistry implicit in Scheme 1, and efforts to realise further examples of this diverse group of reactions are underway.

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Notes and References

† E-mail: nigel.simpkins@nottingham.ac.uk

‡ In a typical asymmetric silylation, a solution of the chiral lithium amide base **4** mixed with LiCl was added dropwise to a mixture of starting imide and Me_3SiCl (excess) in THF at *ca.* −100 °C (internal temperature). The mixture was then allowed to warm slowly (4 h) to ambient temperature before standard aqueous work-up and chromatography on silica gel. All products have been fully characterised by spectroscopic methods and give satisfactory elemental analysis and/or HRMS results. Enantiomeric excess values were established by HPLC (UV detection) using Pr^iOH–hexane as eluent, using a Chiralcel OD column for **5**, **11** and **12**, and a Chiralcel OJ column for **10**.

§ The absolute configuration of **5** was established by the collection of low temperature data, including Friedel equivalents, and by refinement of a Flack parameter, value 0.05(19), see H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876. The absolute stereochemistry of product **12** was likewise established; Flack parameter −0.12(14). We thank Dr A. J. Blake of this Department for these determinations; full details will be published elsewhere.

¶ These reactions have not been optimised; the absolute configurations shown for **10** and **11** are based on analogy with **5** and **12**.

1 For reviews, see P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439; P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1; N. S. Simpkins, *Advances in Asymmetric Synthesis*, ed. G. R. Stephenson, Blackie Academic, 1996; K. Koga, *Pure Appl. Chem.*, 1994, **66**, 1487.

2 For leading references in these two areas, see A. J. Blake, S. M. Westaway and N. S. Simpkins, *Synlett*, 1997, 919 (sulfoxides); R. A. Ewin, D. A. Price, N. S. Simpkins, A. M. MacLeod and A. P. Watt, *J. Chem. Soc., Perkin Trans. 1*, 1997, 401 (organometallics).

3 We have recently described an enantioselective elimination reaction akin to the process outlined in Scheme 1, see C. D. Jones, N. S. Simpkins and G. M. P. Giblin, *Tetrahedron Lett.*, 1998, **39**, 1023.

4 The starting imide **5** was prepared *via* reaction of the corresponding anhydride (J. J. Tufariello, A. S. Milowsky, M. Al-Nuri and S. Goldstein, *Tetrahedron Lett.*, 1987, **28**, 267) with aniline, see A. L. J. Beckwith and D. R. Boate, *J. Org. Chem.*, 1988, **53**, 4339. See also A. Mustafa, S. M. A. D. Zayed and S. Khattab, *J. Am. Chem. Soc.*, 1956, **78**, 145 for an alternative synthesis, and ref. 9.

5 In the past we have observed increased rates of metallation by addition of LiCl to lithium amides, see for example D. A. Price, N. S. Simpkins, A. M. MacLeod and A. P. Watt, *Tetrahedron Lett.*, 1994, **35**, 6159; B. J. Bunn, N. S. Simpkins, Z. Spavold and M. J. Crimmin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 3113. Recently, little effect of LiCl on the rate of deprotonation of a simple ketone by LDA was observed, see M. Majewski and P. Nowak, *Tetrahedron Lett.*, 1998, **39**, 1661.

6 These reactions were modelled on analogous substitutions of episulfones that we examined previously, see A. P. Dishington, R. E. Douthwaite, A. Mortlock, A. B. Muccioli and N. S. Simpkins, *J. Chem. Soc., Perkin Trans. 1*, 1997, 323.

7 M. J. Milewska, M. Gdaniec and T. M. Polonski, *J. Org. Chem.*, 1997, **62**, 1860.

8 T. Mukaiyama, H. Yamashita and M. Asami, *Chem. Lett.*, 1983, 385.

9 For details of the preparation and enantioselective reduction of these types of *meso*-imide, see M. Ostendorf, R. Romagnoli, I. C. Pereiro, E. C. Roos, M. J. Moolenaar and W. N. Speckamp and H. Hiemstra, *Tetrahedron: Asymmetry*, 1997, **8**, 1773.

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