Highly Enantioselective Synthesis of Substituted Piperidines using the Chiral Lithium Amide Base Approach

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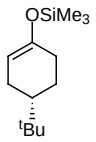
Abstract: The symmetry-breaking enolisation reaction of a *meso*-piperidine diester using a chiral *bis*-lithium amide base allows access to alkylated derivatives in highly diastereo- and enantioselective fashion (≥ 98% ee).

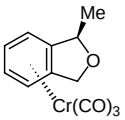
Key words: chiral lithium amide, asymmetric synthesis

Introduction

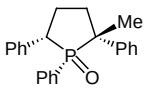
Over recent years there have been significant developments in the application of chiral lithium amide base reactions to asymmetric synthesis.[1] Typically, such reactions involve a symmetry-breaking enolisation or metallation process to give an enantiomerically enriched nucleophilic intermediate, which can then be reacted with electrophiles to give useful non-racemic products. Most of this chemistry involves enolisation of cyclic ketones, e.g. the synthesis of enol silane **1**,[2] but more recently we have applied the same principle to other systems, for example to generate chiral organometallics such as **2**,[3] or the chiral phospholane oxide **3**.[4]



1 (*ca.* 90% ee)



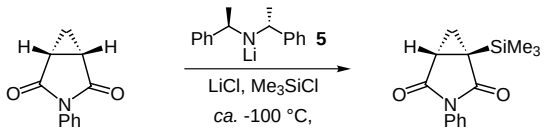
2 (99% ee)



3 (*ca.* 90% ee)

Most such enantioselective deprotonation reactions described to date involve discrimination between enantiotopic hydrogens activated by a *single* common functional group. We expected that a considerable broadening in the scope for applications of chiral lithium amides would be possible if *multifunctional* substrates could be employed. In this type of chiral base reaction the acidic hydrogens would be activated by *separate* functional groups.

We recently described a specific example of this concept, involving the symmetry-breaking reactions of various carbocyclic systems having a ring-fused imide, e.g. conversion of the cyclopropane **4** into silylated product **6**, mediated by chiral lithium amide **5**, Scheme 1.[5]

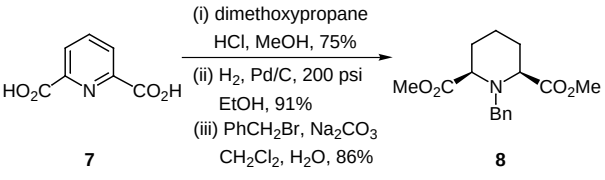


4 **6** 80% (95% ee)

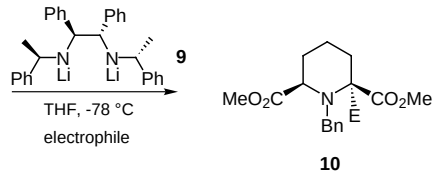
Scheme 1

Here we describe the application of this symmetry-breaking concept to a very different situation, which has exciting implications for the synthesis of chiral heterocyclic systems.

Since a number of symmetrical heteroaromatic compounds are readily available it is a simple matter to access the corresponding saturated *meso* derivatives via highly stereoselective hydrogenation. In our initial studies, we have applied this approach to dipicolinic acid **7**, as shown in Scheme 2.



7 **8**



10

Scheme 2

Transformation of diacid **7** into a suitable symmetrical diester **8** was carried out very straightforwardly as shown.[6] Several related derivatives were prepared, having different nitrogen protecting groups, but since the *N*–benzyl compound **8** behaved well in initial deprotonation reactions, all subsequent work was carried out with this series.

Initial chiral base studies with the simple lithium amide base **5** gave rather poor results, and it was not until we turned to the use of the *bis*-lithium amide base **9** that we

achieved useful results. To our delight, treatment of **8** with this base, followed by alkylation with benzyl bromide, furnished product **10a** in good yield as a single diastereomer, and in ≥98% ee.[7,8] Similar excellent levels of diastereocontrol and enantiocontrol were seen with a number of other electrophiles, as indicated in the Table.[9]

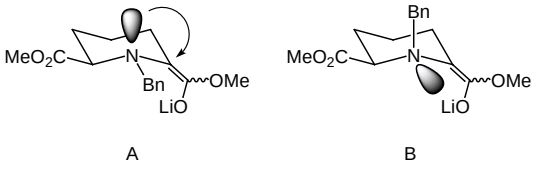
Table Asymmetric Alkylations of Diester 8

product	alkylating agent	yield (%)
10a	$PhCH_2Br$	78
10b	$ArCH_2Br$*	73
10c	MeI	75
10d	allylbromide	61
10e	$PhCH{=}CHCH_2Cl$	67
10f	$HC{\equiv}CCH_2Br$	64

* Ar = p-bromophenyl

Aldol reactions with various carbonyl compounds have also been attempted, but give less consistent results, and to date we have not secured the stereochemical assignments.[10]

Although the sense of enantioselectivity in the reaction of diester **8** with *bis*-lithium amide **9** is not readily rationalised, we can propose several explanations for the high degree of diastereoselectivity in the alkylations of the intermediate enolate, Figure.

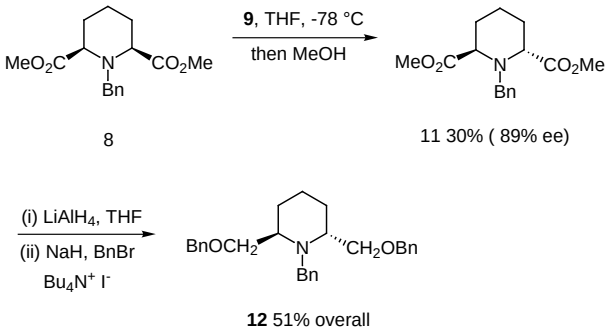


Figure

If the exocyclic enolate has an equatorial disposition of both the neutral amine group and the *N*-benzyl group then selectivity may be determined mainly by the stereoelectronic effect of the ring nitrogen as shown in structure A (i.e. alkylation anti to the lone pair).[11] Alternatively, if A[1,3] strain considerations resulted in population of the *N*-invertomer B, then the axial benzyl group provides an obvious source of facial shielding.[12]

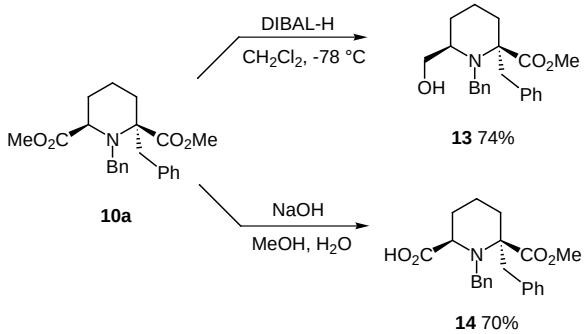
During the course of the alkylation studies we found that enolisation of **8**, followed simply by re-protonation by addition of MeOH, returned *meso* diester **8**, along with the corresponding C_2-symmetric diastereomer **11**, Scheme 3.[13]

The latter compound, although recovered in only 30 % yield from this process, proved to have an ee of 89%. Conversion of this diester into the known *bis*-benzyl ether **12** served to confirm the absolute configuration of this material.[14] Clearly, this finding has implications for the synthesis of this type of *trans*-substituted piperidine (and perhaps other types of heterocycle), which have important applications as chiral auxiliaries,[15] as well as being components of natural products.[16] To date, we have not yet explored the use of alternative protonating sources, which might allow a more stereoselective access to **11**, but this is clearly an attractive possibility.



Scheme 3

A key aspect of the new enantioselective substitution chemistry of **8** is that it should allow further regioselective modification of the product ester groups. We anticipated that this would be possible in simple examples by subsequent reaction at the unsubstituted, and therefore less hindered, ester position. Starting with compound **10a**, Scheme 4 illustrates how this is possible for reduction using DIBAL-H, and for hydrolysis under typical basic conditions.



Scheme 4

Clearly, further transformation of these systems is plausible, including the formation of additional rings, making them attractive starting points for natural product synthesis.

The new chiral base chemistry described above opens up new opportunities for the synthesis of chiral piperidines in a highly stereocontrolled fashion. We expect that analogous possibilities exist for other ring sizes and for rings incorporating different heteroatoms and substitution patterns, and we are actively pursuing these avenues.

Acknowledgement

We are grateful to The University of Nottingham and to AgrEvo UK Limited for support of N.J.G.

References and Notes

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(7) A solution of *bis*-lithium amide **9** was prepared by dropwiseaddition of a solution of BuLi (0.79 mmol) to the appropriatediamine (173 mg, 0.41 mmol) in THF (4 ml) at -78 °C. Theresulting red coloured solution was warmed briefly to r.t. (20 min) before cooling to -78 °C and addition of a solution of **8** (100 mg, 0.34 mmol) in THF (4 mL). The mixturewas stirred at -78 °C for 1 h before addition of benzyl bromide (1mL). After a further 1h at -78 °C the mixture was allowed to warm to r.t. overnight, before quenching with $NaHCO_3$ (5 mL) and extraction of the product into Et_2O (3 x 10 mL). Theorganic extract was dried ($MgSO_4$), and evaporation of the solvent under reduced pressure gave the crude product, which waspurified by flash column chromatography on silica-gel (10% Et_2O in petroleum ether) to give the product **10a** as an off-white solid.Recrystallisation from petroleum ether then gave colourlesscrystals of **10a** (101 mg, 78%), mp 122–123 °C. Data for **10a** $[\alpha]_D$ +27 (*c* 1.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.41–1.53 (2H,m), 1.68–1.76 (2H, m), 1.90–1.98 (2H, m), 2.66 (1H, d, *J*12.5, C*H*HPh), 3.58 (1H, m, CHN), 3.63 (3H, CO_2Me), 3.72(1H, d, *J* 12.5, CH*H*Ph), 3.77 (3H, s, CO_2Me), 3.80 (1H, d,*J* 16.2, NC*H*HPh), 4.90 (1H, d, *J* 16.2, NCH*H*Ph), 7.11(2H, d, J 8.1), 7.18–7.28 (4H, m) and 7.32–7.39 (4H, m); δ_C(67.5 MHz; $CDCl_3$) 18.0 (CH_2), 28.2 (CH_2), 33.5 (CH_2), 46.8(CH_2), 50.8 (CH_3), 51.1 (CH_3), 52.5 (CH_2), 58.2 (CH), 63.0(C), 126.6 (CH), 126.7 (CH), 127.7 (CH), 128.0 (CH), 128.3(CH), 130.3 (CH), 136.1 (C), 140.8 (C), 173.9 (C=O) and 174.0 (C=O); *m/z* (Found: $M+H^+$ 382.2011.$C_{23}H_{27}NO_4$ requires *M+H*, 382.2019).
The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column with 1% *i*-PrOH in hexane as eluant, using UV detection at 254 nm. Retention times were 15.1 min (minor) and 16.5 min (major).

(8) The relative and absolute configuration shown for **10** has been proved by X-ray crystallography for **10b**, full details will be published elsewhere.

(9) The enantiomeric excess has been measured for **10a**, **10c** and **10e**, the other examples are expected to have the same ee.

(10) Reaction with benzaldehyde gave three aldol products in a roughly 2:1:2 ratio, whereas the corresponding reactions involving either acetaldehyde or isobutyraldehyde gave single diastereomeric aldolproducts (after chromatography) in modest yield (*ca*. 40%). Thestereochemistry of these aldol products has not been assigned.

(11) See Nagumo, S.; Mizukami, M.; Akutso, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209, and references therein.

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(16) For a recent review, see Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem Comm.* **1998**, 633.

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