Enantioselective synthesis of cyclopropylcarboxamides using s-BuLi–sparteine-mediated metallation†

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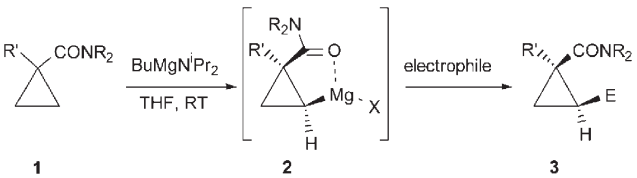
Enantioselective synthesis of cyclopropylcarboxamides is possible by asymmetric metallation of prochiral starting cyclopropanes using s-BuLi–sparteine.

Chiral cyclopropanes are important structures, which are commonly encountered in natural products, and in synthetic compounds with significant medicinal properties.[1,2] The consequent requirement for access to diverse functionalized and substituted cyclopropanes, in highly enantioenriched form, has acted as a driver for research into their asymmetric synthesis. Important established methods for the enantioselective synthesis of cyclopropanes include asymmetric variants of the Simmons–Smith procedure,[3] transition-metal catalysed diazoester cyclopropanation,[4] and organocatalysed approaches using ylide chemistry.[5] The area is one of intense current activity, and new approaches are emerging, such as asymmetric addition reactions of cyclopropenes.[6]

Through our ongoing interest in desymmetrisation reactions mediated by chiral bases, we became attracted to a new possibility for the asymmetric synthesis of cyclopropanes, based on a report from Eaton's group of the β-metallation of cyclopropylcarboxamide **1** (Scheme 1).[7]

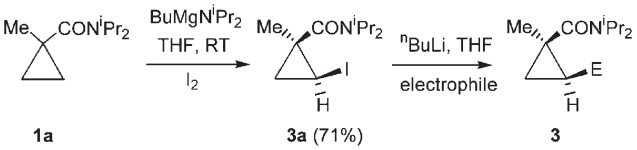
Efficient cyclopropane metallation *syn* to the directing amide substituent was achieved using $BuMgN^iPr_2$ as a base, giving an intermediate formulated as **2**, and subsequent electrophilic quenching enabled access to variously substituted products **3**. The metallation is remarkable in that predominant β-substitution is observed, even when an α-hydrogen is available (*i.e.* when R′ = H) that would enable competing formation of a metal enolate type intermediate. This was rationalised as the result of equilibration to give the more stable β-magnesium amide.

We conceived an asymmetric variant of this cyclopropane substitution using chiral metal amide bases derived from amines or diamines, *e.g.* **4** and **5**. These amine motifs, in the form of lithium amides or bis-lithium amides, have a good track record for asymmetric induction by deprotonation of various carbonyl-substituted systems.[8] Consequently, we expected to achieve asymmetric induction using either lithium amide bases or chiral analogues of the Eaton type of base highlighted in Scheme 1.



Scheme 1 Eaton's cyclopropane substitution using a magnesium base (R = Et, ^{i}Pr; R′ = H, Me, Ph).

As a prelude to chiral base studies, and in order to provide access to racemic cyclopropanes required for analytical work, we briefly re-examined the Eaton metallation illustrated in Scheme 1. We decided to employ systems substituted at the α-position in order to avoid possible equilibration pathways. Preparation of racemic iodides, such as **3a**, was very straightforward, although direct C–C bond formation by alkylation or aldol addition (which was described as requiring CuI)[7] was less satisfactory in our hands, Scheme 2.[9]



Scheme 2 Synthesis and lithium–iodine exchange of cyclopropane **3a**.

Significantly for our later studies we established that a wide range of substituted cyclopropanes could be accessed *via* lithium–iodine exchange reactions of **3a**, followed by addition of various types of electrophile. These compounds could also be prepared by metallation using s-BuLi–TMEDA in Et_2O at low temperature.

At this stage we probed for asymmetric induction in the synthesis of cyclopropanes, especially **3a**, by use of a range of basic reagents, including those which can be formulated as **4**–Li, **5**–Li, **5**–Li_2, BuMg–**4**, BuMg–**5**, *etc.*, but with no success.[10]

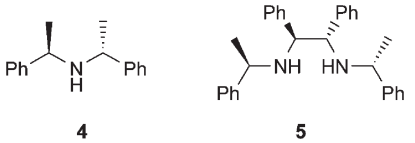


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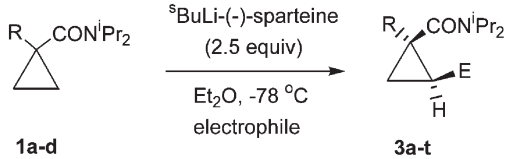
Table 1 Asymmetric metallation-substitution of cyclopropanes



1a-d **3a-t**

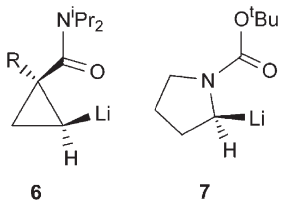
Entry	Cyclopropane	Electrophile	Product	Yield (%)	Ee (%)
1	**1a** R = Me	I_2	**3a**	58	88
2	**1a**	MeI	**3b**	29	90
3	**1a**	PhSSPh	**3c**	69	90
4	**1a**	PhCOCl	**3d**	52	90
5	**1a**	Prenyl bromide	**3e**	61	90
6	**1a**	PhCHO	**3f**	67[a]	80[b]
7	**1a**	Cyclohexanone	**3g**	56	88
8	**1a**	Acetone	**3h**	52	90
9	**1b** R = Ph	I_2	**3i**	66	85
10	**1b**	MeI	**3j**	31	88
11	**1b**	PSSPh	**3k**	89	90
12	**1b**	PhCOCl	**3l**	32	nd[c]
13	**1b**	Prenyl bromide	**3m**	83	nd[c]
14	**1b**	Cyclohexanone	**3n**	52	79
15	**1c** R = Bn	I_2	**3o**	75	nd[c]
16	**1c**	PhSSPh	**3p**	48	88
17	**1d** R = CF_3	I_2	**3q**	75	nd[c]
18	**1d**	PhSSPh	**3r**	75	77

[a] *ca.* 2:1 Mixture of diastereomers. [b] Average ee of two diastereomers (the individual ee values were 82% for the major product and 78% for the minor one). [c] Not determined.

At last we turned to the s-BuLi–(−)-sparteine combination for the asymmetric metallation,[11] using diethyl ether as solvent, and immediately found interesting levels of asymmetric induction. By optimizing the stoichiometry of the reaction process and other reaction parameters such as length of reaction time and dilution we were able to establish a general protocol for the asymmetric substitution of several prochiral cyclopropanes with good enantiomeric excess levels, usually in the 88–90% range, Table 1.§

Chemical yields are rather variable, which could be due to the known tendency of lithiated cyclopropanes to undergo decomposition and self-condensation.[12] However, we were able to demonstrate moderate to good yields with a range of carbon electrophiles, including additions to enolisable carbonyl partners, and also in iodination and sulfenylation reactions.

The sense of asymmetric induction is proposed to be as shown above for **3a–3r**, based on analogy with the well-known *N*-Boc pyrrolidine deprotonations—*i.e.* comparing **6** with **7**, Fig. 1.[13]



6 **7**

Fig. 1 Comparison of sense of asymmetric induction with pyrrolidine outcome.

In the case of the iodo-derivative **3i**, we were able to recrystallise the sample and obtain enantiomerically pure crystals suitable for X-ray analysis, Fig. 2.¶

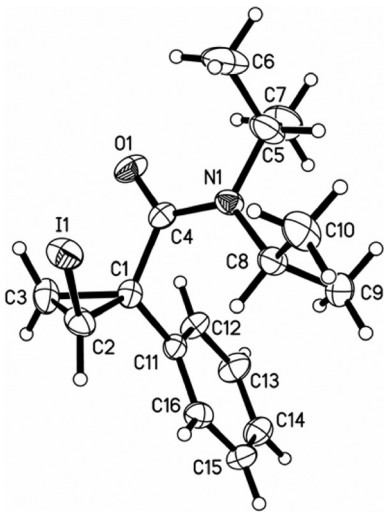
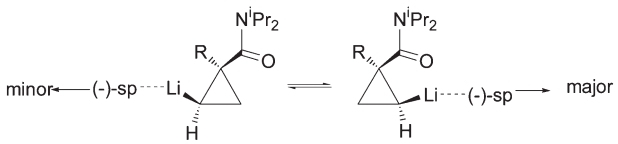


Fig. 2 A view of one of the two independent molecules of **3i** in the asymmetric unit. Displacement ellipsoids are drawn at the 50% probability level.

The structure shows the arrangement of the congested amide function with respect to the cyclopropane, and confirms both the relative configuration and the proposed sense of absolute asymmetric induction. We assume that all of the compounds generated using (−)-sparteine will be of the same enantiomeric series. It is not too surprising that the ee values for the different series of cyclopropanes should be similar, since the deprotonation event occurs *syn* to the same amide function in each case, and *anti* to the substituent which is varied.

We expected that this process would proceed by an asymmetric deprotonation mechanism, involving kinetically controlled selection between the two enantiotopic hydrogens orientated *syn* to the carboxamide. The above selectivity results support this proposal, but we also considered an alternative asymmetric substitution type of mechanism, which in our case would require equilibration between the diastereomeric organolithium–ligand pairs **8a** and **8b**, with the latter reacting faster to give the major enantiomeric product, Scheme 3.[11,14]



8a **8b**

Scheme 3 Alternative asymmetric substitution mechanism.

In order to eliminate this possibility we generated the lithiated cyclopropane, starting from **3a**, by lithium–iodine exchange, as mentioned above, followed by addition of sparteine and then quenching with various electrophiles. As expected, the products obtained in this way were racemic, which lends further support to the asymmetric deprotonation mechanism.

In summary, we have established a new asymmetric access to various cyclopropylcarboxamides, in synthetically useful yields and levels of stereoselectivity. Further work is in progress to explore the flexibility of this approach as a route to varied chiral cyclopropanes, cyclopropenes, and derived products.

We are grateful to the School of Chemistry, University of Nottingham, and to Pfizer Central Research, Sandwich, for joint support of the project through a studentship to SL.

Notes and references

§ Typical procedure for asymmetric lithiation–substitution: Under an atmosphere of argon, a solution of s-BuLi (1.4 M in cyclohexane 1.0 mL, 1.4 mmol, 2.5 eq.) was added dropwise to a stirred solution of (−)-sparteine (0.32 g, 1.4 mmol, 2.5 eq.) in dry Et_2O (4 mL) at −78 °C. Then a solution of cyclopropanecarboxamide (0.55 mmol, 1.0 eq.) in dry Et_2O (1 mL) was introduced slowly *via* syringe. The mixture was stirred for 2 h at −78 °C before addition of the electrophile (4.0 eq.), and then stirred for a further 1 h at −78 °C and 1 h at room temperature. It was then poured into an aqueous solution of 2 M HCl (3 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (2 × 2 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to give the product cyclopropane in the yields given in Table 1.

Data for iodo-cyclopropane **3a** (58% yield) colourless solid (mp 74–76 °C), $[\alpha]_D^{18}$ 117 (*c*, 0.97, $CHCl_3$); ee = 88% as determined by chiral HPLC, chiral support CHIRALPAK AD-H, ^{n}hexane : EtOH, 98 : 2, flow rate 1 mL min^{-1}, retention time: 5.5 min (major), 6.2 min (minor); Found C, 42.68; H, 6.54; N, 4.42%. $C_{11}H_{20}INO$ requires C, 42.73; H, 6.52; N, 4.53%. ν_{max} ($CDCl_3$)/cm^{-1} 2968, 2934, 2875, 1628, 1461, 1370, 1345, 1041; δ_H (400 MHz, $CDCl_3$) 1.18 (1H, dd, *J* 8.0, 6.2), 1.22 (3H, d, *J* 6.6), 1.37 (3H, s), 1.39 (6H, d, *J* 6.6), 1.40 (3H, d, *J* 6.6), 1.41 (1H, dd, *J* 6.2, 6.2), 2.55 (1H, dd, *J* 8.0, 6.2), 3.27 (1H, sept, *J* 6.6), 4.15 (1H, sept, *J* 6.6); δ_C (100 MHz, $CDCl_3$) −6.0 (CHI), 20.1 (CH_3), 20.5 (CH_3), 21.3 (CH_3), 21.7 (CH_3), 22.0 (CH_3), 24.3 (CH_2), 28.3 (C), 46.1 (CH), 48.7 (CH), 169.7 (C═O); HRMS (ESI+) $C_{11}H_{21}INO$ requires 310.0673; found 310.0671 $[MH]^+$.

¶ Crystal data for **3i**: $C_{16}H_{22}INO$, M = 371.25, monoclinic, space group $P2_1$, a = 8.5952(4), b = 23.5395(10), c = 8.7614(4) Å, β = 111.232(1)°, U = 1652.34(13) $Å^3$, Z = 4 D_c = 1.492 Mg m^{-3}, μ(Mo-Kα) = 1.932 mm^{-1}, T = 150(2) K, 7310 unique reflections (R_{int} = 0.011). Final R_1 [7265 $I > 2\sigma(I)$] = 0.0174, wR_2 (all data) = 0.0459. The absolute configuration was determined by refinement of the Flack parameter to a value of −0.022(10).

1 (*a*) For reviews covering many aspects of cyclopropane synthesis and chemistry see the special edition of *Chemical Reviews* 2003, **103**, 931, guest editor A. De Meijere, especially a review on stereoselective cyclopropanation; H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*b*) W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589.

2 For some leading references, see: (*a*) V. F. Ferreira, R. A. C. Leao, F. de C. da Silva, S. Pinheiro, P. Lhoste and D. Sinou, *Tetrahedron: Asymmetry*, 2007, **18**, 1217; (*b*) A. Reichelt and S. F. Martin, *Acc. Chem. Res.*, 2006, **39**, 433.

3 (*a*) A. B. Charette, *Org. React. (N. Y.)*, 2001, **58**, 1; (*b*) For a recent example, see: H. Shitama and T. Katsuki, *Angew. Chem., Int. Ed.*, 2008, **47**, 2450.

4 (*a*) M. P. Doyle, *J. Org. Chem.*, 2006, **71**, 9253, and references therein; (*b*) For a more recent example, see: J. R. Denton, K. Cheng and H. M. L. Davies, *Chem. Commun.*, 2008, 1238.

5 H. Xie, L. Zu, J. Wang and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 10886, and references therein.

6 (*a*) I. Marek, S. Simaan and A. Masarwa, *Angew. Chem., Int. Ed.*, 2008, **47**, 1982; (*b*) N. Yan, X. Liu and J. M. Fox, *J. Org. Chem.*, 2008, **73**, 563; (*c*) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117.

7 M.-X. Zhang and P. E. Eaton, *Angew. Chem., Int. Ed.*, 2002, **41**, 2169.

8 (*a*) For a review of chiral lithium amide base reactions, see: P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439. For our most recent papers, see: (*b*) V. Rodeschini, N. S. Simpkins and C. Wilson, *J. Org. Chem.*, 2007, **72**, 4265; (*c*) V. Rodeschini, N. S. Simpkins and F. Zhang, *Org. Synth.*, 2007, **84**, 306; (*d*) B. Butler, T. Schultz and N. S. Simpkins, *Chem. Commun.*, 2006, 3634.

9 We obtained good yields only on the cases of iodination, sulfenylation (using PhSSPh) and carboxylation (with CO_2). Eaton reported that the addition of 20% of a copper salt was needed to obtain "reasonable rates in the alkylations", which includes the addition to PhCHO. In ref. 7 the cyclopropane alkylations were done on cyclopropane **1** where either R′ = H, *or* R = Et, and the more hindered nature of our substrates (R′ = alkyl *and* R = ^{i}Pr) perhaps explains why our efforts at cyclopropane alkylation were ineffective.

10 Lithium amides were described as unsatisfactory for *α-metallation* of cyclopropylcarboxamides, due to the similar pK_a of the cyclopropane and typical secondary amines.[7] We hoped that the required *β-metallation* might still be possible, particularly through use of a bis-lithium amide, or by addition of LiCl, which had promoted similar problematic metallations in the past.[8] However, we were unable to achieve effective cyclopropane substitution with any lithium amides, with or without LiCl, at various temperatures in THF. Room temperature substitution, along the lines shown in Scheme 1, was possible with a magnesium base derived from amine **4**, but gave only very low yields (*ca.* 10%) of racemic product.

11 (*a*) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552; (*b*) See also: M. J. McGrath, J. L. Bilke and P. O'Brien, *Chem. Commun.*, 2006, 2607, and references therein.

12 This is usually a problem with α-metallated systems, see for example: (*a*) H. W. Pinnick, Y.-H. Chang, S. C. Foster and M. Govindan, *J. Org. Chem.*, 1980, **45**, 4505; (*b*) We have observed similar problems in chiral base reactions in the absence of an *in situ* quench, see: D. J. Adams, A. J. Blake, P. A. Cooke, C. D. Gill and N. S. Simpkins, *Tetrahedron*, 2002, **58**, 4603.

13 S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708.

14 The organolithium interconversion considered here is distinct from the enantiomerization of systems in which the C–Li bond is the sole stereogenic feature, see: T. I. Yousaf, R. L. Williams, I. Coldham and R. E. Gawley, *Chem. Commun.*, 2008, 97.

