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Mechanistic interrogation of the asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine and pyrrolidine†

 Peter J. Rayner,^a Joshua C. Smith,^a Charline Denneval,^a Peter O'Brien,^{a*}
 Paul A. Clarke^a and Richard A. J. Horan^b

A fundamental mechanistic study of the *s*-BuLi/chiral diamine-mediated lithiation-trapping of *N*-thiopivaloyl azetidine and pyrrolidine is reported. We show that lithiated thiopivalamides are configurationally unstable at $-78\text{ }^{\circ}\text{C}$. Reaction then proceeds via a dynamic resolution of diastereomeric lithiated intermediates and this accounts for the variable sense and degree of asymmetric induction observed compared to *N*-Boc heterocycles.

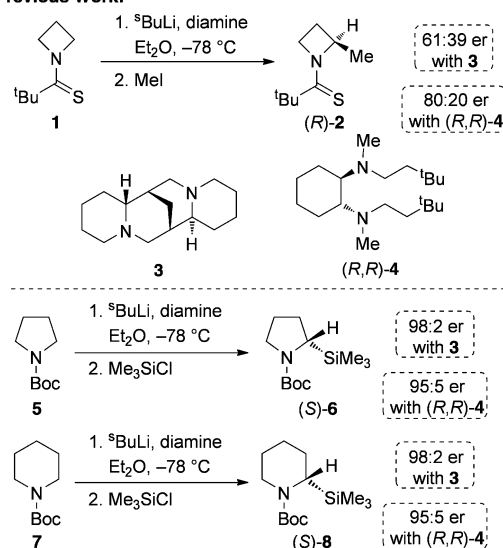
The development of methodology for the direct asymmetric α -functionalisation of saturated nitrogen heterocycles¹ continues to attract attention due to the prevalence of such motifs in potential pharmaceuticals.² The most successful, direct approach to enantioenriched α -substituted pyrrolidines, piperidines and piperazines is Beak's asymmetric lithiation-trapping of *N*-Boc heterocycles,³ with a number of noteworthy applications within the pharmaceutical industry.^{3c,4} In order to explore new areas of 3-D pharmaceutical space, extension of the *N*-Boc-mediated lithiation-trapping methodology to azetidines would be attractive. Unfortunately, however, Beak's approach is not suitable for the α -lithiation-trapping of azetidine.⁵ To solve this limitation, Hodgson and Kloesges⁵ reported the use of Seebach's⁶ *N*-thiopivaloyl activating group, culminating with the first example of asymmetric α -lithiation-trapping of azetidine using *s*-BuLi and chiral diamines. For example, lithiation of *N*-thiopivaloyl azetidine **1** using *s*-BuLi/($-$)-sparteine **3** or Alexakis' diamine (*R,R*)-**4**⁷ gave, after trapping with MeI, α -substituted azetidine (*R*)-**2** in 61 : 39 er and 80 : 20 er respectively (Scheme 1). These results piqued our interest as the sense of asymmetric induction was opposite to that obtained with *N*-Boc pyrrolidine and *N*-Boc piperidine. Some examples are shown in Scheme 1: use of ($-$)-sparteine **3** or (*R,R*)-**4** with *N*-Boc pyrrolidine **5** and

piperidine **7** delivered α -functionalised pyrrolidine (*S*)-**6**^{3a,8} and piperidine (*S*)-**8**.^{3b,9}

Comparing the thiopivaloyl and Boc results presented in Scheme 1, we wondered whether the cause of the difference was the four-membered ring, the *N*-thiopivaloyl group or the electrophile. To explore the reasons for the difference, we set out to determine the mechanism of asymmetric induction in the *s*-BuLi/chiral diamine-mediated α -lithiation-trapping of *N*-thiopivaloyl heterocycles **1/9** $\rightarrow$ **10** $\rightarrow$ **11** (Scheme 2).

Our study focused on both *N*-thiopivaloyl azetidine **1** and pyrrolidine **9** together with a range of electrophiles to allow comparison with the well-studied *N*-Boc pyrrolidine. Two limiting mechanisms are known: asymmetric deprotonation to give a configurationally stable organolithium species **10** (as is established for *N*-Boc pyrrolidine and piperidine at $-78\text{ }^{\circ}\text{C}$ ^{3a,b} and up to $-30\text{ }^{\circ}\text{C}$ ¹⁰) or dynamic resolution of a configurationally labile

Previous Work:



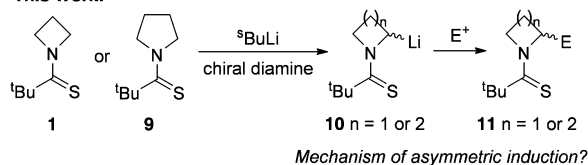
Scheme 1 Opposite sense of induction in asymmetric lithiation-trapping of *N*-substituted heterocycles.

^a Department of Chemistry, University of York, Heslington, York YO10 5DD, UK.
E-mail: peter.obrien@york.ac.uk

^b GlaxoSmithKline Research & Development Ltd., Medicines Research Centre,
Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

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This Work:

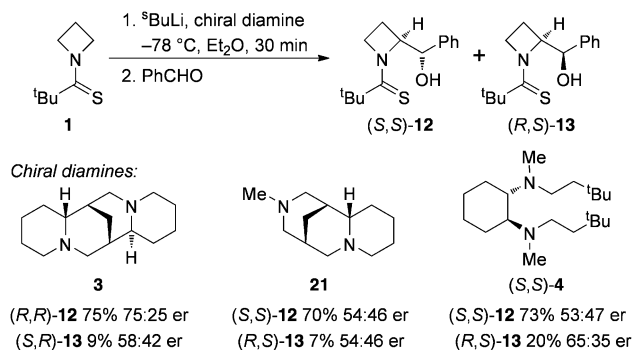


Scheme 2 Investigation of the mechanism of asymmetric induction in the lithiation-trapping of *N*-thiopivaloyl heterocycles.

organolithium species **10** (as reported for pyrrolidines and piperidines at temperatures above $-20\text{ }^{\circ}\text{C}^{11}$). Herein, we disclose that, unexpectedly, the α -lithiation-trapping of *N*-thiopivaloyl heterocycles **1** and **9** at $-78\text{ }^{\circ}\text{C}$ proceeds *via* a dynamic resolution mechanism. Our results show that the thiopivaloyl group is the source of the difference when compared to *N*-Boc heterocycles. This finding may have consequences for asymmetric efforts with the *N*-thiopivaloyl and the recently reported *t*-butoxythiocarbonyl group.¹²

The lithiation-trapping of *N*-thiopivaloyl azetidine **1** and pyrrolidine **9** was investigated using similar conditions to those originally described by Hodgson:⁵ lithiation of **1** or **9** was accomplished using *s*-BuLi (1.2–1.3 eq.) and (–)-sparteine **3** (1.2–1.3 eq.) in Et₂O at $-78\text{ }^{\circ}\text{C}$ for 30 min (for **1**) and 1 hour (for **9**). Then, trapping was carried out with four electrophiles (PhCHO, MeO₂CCl, CO₂ and MeI) at $-78\text{ }^{\circ}\text{C}$ for 1 hour before quenching with HCl_(aq) at this temperature. The results of this study are shown in Scheme 3. The relative and absolute configurations of **2** and **12–20** were established using X-ray crystallography and inter-conversions to/from known compounds (see ESI†).

The results in Scheme 3 immediately highlight the fact that the sense of induction in the lithiation-trapping of **1** and **9** depends on the electrophile employed. Indeed, when considering the newly formed stereogenic centre α to nitrogen, the products formed by trapping with PhCHO ($\rightarrow$ (*R,R*)-**12** + (*S,R*)-**13** and $\rightarrow$ (*R,R*)-**14** + (*S,R*)-**15**) or MeO₂CCl ($\rightarrow$ (*R*)-**16** and (*R*)-**17**) were of opposite configuration to those formed using CO₂ ($\rightarrow$ (*S*)-**18**



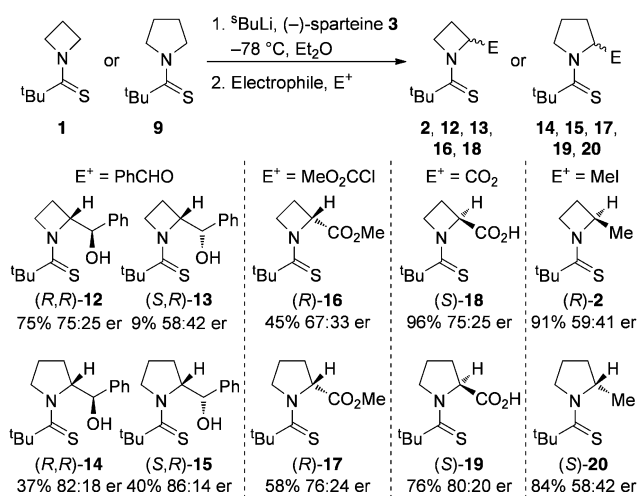
Scheme 4 Asymmetric lithiation-PhCHO trapping of *N*-thiopivaloyl azetidine **1** with different chiral diamines.

and (*S*)-**19**). Such a difference is unprecedented in the lithiation-trapping of non-benzylic sp³-hybridised C–Li systems.¹³ With MeI, products of opposite configuration were obtained with the azetidine and pyrrolidine systems ($\rightarrow$ (*R*)-**2**¹⁴ and (*S*)-**20**, albeit with low ers). All of these variable stereochemical outcomes appear to be at odds with the results obtained with configurationally stable lithiated *N*-Boc heterocycles.^{3,15,16}

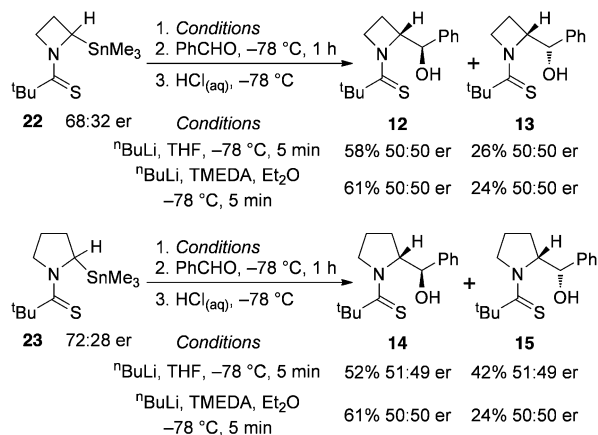
This unpredictability continued when different chiral diamines were employed. For example, lithiation of **1** using *s*-BuLi and the (+)-sparteine surrogate **21**¹⁷ or diamine (*S,S*)-**4**^{7,8} and subsequent trapping with PhCHO gave (*S,S*)-**12** and (*R,S*)-**13** in high total yields (77–93%) but moderate enantioselectivity (Scheme 4). The difference between (–)-sparteine **3** and (+)-sparteine surrogate **21** with azetidine **1** is particularly striking since the (+)-sparteine surrogate **21** was originally designed based on its “sparteine-like” structure¹⁷ and *both* diamines gave high er (in the expected opposite sense) in the lithiation-trapping of pyrrolidine **9** (see ESI†).

The wide variation in enantioselectivity and sense of induction under essentially the same reaction conditions appeared to preclude asymmetric deprotonation *via* a configurationally stable organolithium species as the mechanism that is operating with *N*-thiopivaloyl heterocycles. To prove this beyond doubt, we investigated the configurational stability¹⁸ of the intermediate lithiated *N*-thiopivaloyl azetidine and pyrrolidine **10** at $-78\text{ }^{\circ}\text{C}$.

Initially, stannanes **22** (68:32 er) and **23** (72:28 er) of unknown configuration were prepared by lithiation-trapping of *N*-thiopivaloyl azetidine **1** and pyrrolidine **9** respectively (using (–)-sparteine **3**) (see ESI†). Then, azetidine stannane **22** of 68:32 er was subjected to tin-lithium exchange using *n*-BuLi in THF at $-78\text{ }^{\circ}\text{C}$ for 5 min and trapped with PhCHO. This delivered racemic adducts **12** and **13** (84% total yield). Virtually the same outcome was observed with stannane **22** using tin-lithium exchange with *n*-BuLi/TMEDA in Et₂O at $-78\text{ }^{\circ}\text{C}$ for 5 min before PhCHO trapping (Scheme 5). A similar set of results was also obtained starting from pyrrolidine stannane **23** (72:28 er): essentially racemic adducts **14** and **15** were generated under both sets of tin-lithium exchange conditions (Scheme 5). These unexpected results establish that lithiated *N*-thiopivaloyl azetidine and pyrrolidine **10** are configurationally unstable at $-78\text{ }^{\circ}\text{C}$ in THF (no diamine) or in Et₂O (in the presence of TMEDA). This is in stark contrast to *N*-Boc pyrrolidine and other *N*-Boc



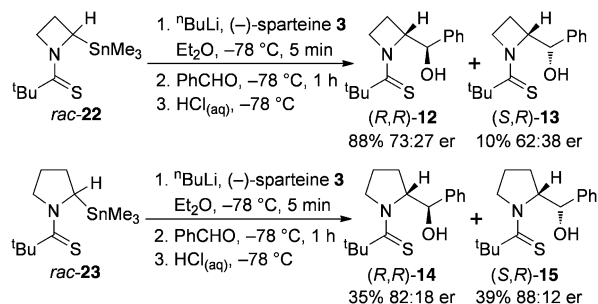
Scheme 3 Asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **1** and pyrrolidine **9** with different electrophiles.



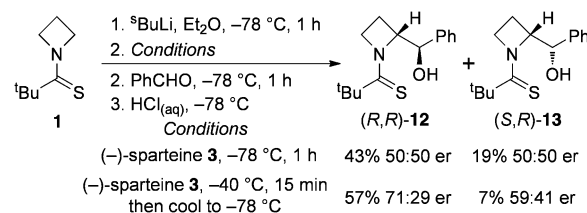
Scheme 5 Investigation of the configurational stability of lithiated *N*-thiopivaloyl azetidine and pyrrolidine **10** via tin-lithium exchange.

heterocycles. It appears that there is a fundamental difference between carbamates (C=O) and thioamides (C=S) in terms of the configurational stability of their lithiated intermediates. This difference may be due to the longer bond lengths in thioamides¹⁹ (compared to carbamates) leading to a weaker C–Li bond.

The results of the configurational stability study establish that a dynamic resolution mechanism must be occurring in the *s*-BuLi/diamine-mediated reactions of *N*-thiopivaloyl azetidine **1** and pyrrolidine **9** (see Schemes 3 and 4). If so, for a given *N*-thiopivaloyl heterocycle, chiral diamine and electrophile, it should be possible to start with a racemic lithiated species, add the chiral diamine and recreate the same level of enantioselectivity as that obtained in Schemes 3 and 4. To investigate this, tin-lithium exchange from racemic stannanes **22** and **23** was initially used (Scheme 6). Thus, azetidine stannane *rac*-**22** was subjected to tin-lithium exchange using *n*-BuLi and (–)-sparteine **3** in Et₂O at –78 °C for 5 min and then trapped with PhCHO. This gave (*R,R*)-**12** in 73:27 er (88% yield) and (*S,R*)-**13** in 62:38 er (10% yield) which was comparable to the *s*-BuLi/(–)-sparteine **3**-mediated lithiation-PhCHO trapping of azetidine **1** in Et₂O at –78 °C ((*R,R*)-**12** in 75:25 er and (*S,R*)-**13** in 58:42 er, Scheme 3). A similar result was obtained starting from pyrrolidine stannane *rac*-**23**: (*R,R*)-**14** in 82:18 er (35% yield) and (*S,R*)-**15** in 88:12 er (39% yield) were formed, results which match very well with the direct reaction ((*R,R*)-**14** in 82:18 er and (*S,R*)-**15** in 86:14 er, Scheme 3).



Scheme 6 Dynamic resolution of racemic lithiated *N*-thiopivaloyl azetidine and pyrrolidine via tin-lithium exchange.



Scheme 7 Dynamic resolution of racemic lithiated *N*-thiopivaloyl azetidine **1** via direct lithiation.

We also explored the generation of a racemic lithiated intermediate in the absence of any tin-based species. Thus, *N*-thiopivaloyl azetidine **1** was deprotonated using *s*-BuLi in Et₂O at –40 °C²⁰ and then, after cooling to –78 °C, (–)-sparteine **3** was added and incubated at –78 °C for 1 h before trapping with PhCHO. Under these conditions, adducts **12** and **13** were generated in 50:50 er (62% combined yield). To rationalise the lack of asymmetric induction, we speculated that the rate of complexation of (–)-sparteine **3** to the lithiated azetidine might be too slow at –78 °C. Thus, incubation of the racemic lithiated azetidine with (–)-sparteine **3** was carried out at a higher temperature (–40 °C) for 1 hour before cooling to –78 °C and trapping with PhCHO. This time, high enantioselectivity was restored and (*R,R*)-**12** in 71:29 er and (*S,R*)-**13** in 59:41 er were isolated (Scheme 7). This supports our conjecture that (–)-sparteine **3** was unable to coordinate to the lithiated azetidine at –78 °C due to the coordination kinetics. To our knowledge, this is the first documented example of such an effect.

In conclusion, the results from our mechanistic studies indicate that the lithiation-trapping of *N*-thiopivaloyl azetidine and pyrrolidine are very different to *N*-Boc heterocycles. Lithiated *N*-thiopivaloyl azetidine/pyrrolidine are not configurationally stable at –78 °C in THF or Et₂O (in the presence of a diamine). Thus, dynamic resolution of interconverting diastereomeric, lithiated species accounts for the enantioselectivity of the lithiation-trappings of the *N*-thiopivaloyl heterocycles shown in Schemes 3 and 4 and those previously reported by Hodgson.⁵ The range of enantioselectivities with different electrophiles (under otherwise identical conditions) presumably arises due to different rates of trapping and this can lead to a difference in the configuration of the major product. We conclude with three comments. First, given the variation in configuration that we have observed with the four electrophiles studied (PhCHO, MeO₂CCl, CO₂ and MeI), we recommend that attention is paid to establishing the sense of induction with all novel products formed from these types of reactions. Second, optimisation of enantioselectivity in the future should focus on chiral diamines that work well in dynamic resolutions.¹¹ Finally, our results could explain the stereoselective lithiation-trapping of *N*-thiopivaloylazetidin-3-ol²¹ and suggest that asymmetric lithiation-trapping of *N*-*t*-butoxythiocarbonyl azetidine¹² could proceed via dynamic resolution of a configurationally unstable lithiated intermediate.

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Notes and references

- 1 E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel and B. U. W. Maes, *Chem. – Eur. J.*, 2012, **18**, 10092.
- 2 (a) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845; (b) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- 3 (a) P. Beak, S. T. Kerrick, S. Wu and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231; (b) W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma and K. B. Wiberg, *J. Am. Chem. Soc.*, 2002, **124**, 1889; (c) B. P. McDermott, A. D. Campbell and A. Ertan, *Synlett*, 2008, 875.
- 4 (a) A. Klapars, K. R. Campos, J. H. Waldman, D. Zewge, P. G. Dormer and C.-y. Chen, *J. Org. Chem.*, 2008, **73**, 4986; (b) G. J. Tanoury, M. Chen, Y. Dong, R. Forslund, V. Jurkauskas, A. D. Jones and D. Belmont, *Org. Process Res. Dev.*, 2014, **18**, 1234.
- 5 D. M. Hodgson and J. Kloesges, *Angew. Chem., Int. Ed.*, 2010, **49**, 2900.
- 6 (a) D. Seebach and W. Lubosch, *Angew. Chem.*, 1976, **88**, 339; (b) W. Lubosch and D. Seebach, *Helv. Chim. Acta*, 1980, **63**, 102.
- 7 J.-C. Kizirian, J.-C. Caille and A. Alexakis, *Tetrahedron Lett.*, 2003, **44**, 8893.
- 8 D. Stead, P. O'Brien and A. Sanderson, *Org. Lett.*, 2008, **10**, 1409.
- 9 I. Coldham, P. O'Brien, J. J. Patel, S. Raimbault, A. J. Sanderson, D. Stead and D. T. E. Whittaker, *Tetrahedron: Asymmetry*, 2007, **18**, 2113.
- 10 G. Gelardi, G. Barker, P. O'Brien and D. C. Blakemore, *Org. Lett.*, 2013, **15**, 5424.
- 11 (a) I. Coldham, S. Dufour, T. F. N. Haxell, J. J. Patel and G. Sanchez-Jimenez, *J. Am. Chem. Soc.*, 2006, **128**, 10943; (b) I. Coldham, S. Raimbault, D. T. E. Whittaker, P. T. Chovatia, D. Leonori, J. J. Patel and N. S. Sheikh, *Chem. – Eur. J.*, 2010, **16**, 4082.
- 12 D. M. Hodgson, C. L. Mortimer and J. M. McKenna, *Org. Lett.*, 2015, **17**, 330.
- 13 (a) A. Carstens and D. Hoppe, *Tetrahedron*, 1994, **50**, 6097; (b) A. Carstens, D. Hoppe and T. Krämer, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1424; (c) C. Derwing and D. Hoppe, *Synthesis*, 1996, 149; (d) R. E. Gawley and Q. Zhang, *J. Org. Chem.*, 1995, **60**, 5763; (e) S. Thayumanavan, S. Lee, C. Liu and P. Beak, *J. Am. Chem. Soc.*, 1994, **116**, 9755; (f) Y. S. Park and P. Beak, *J. Org. Chem.*, 1997, **62**, 1574; (g) J. L. Stymiest, V. Bagutski, R. M. French and V. K. Aggarwal, *Nature*, 2008, **456**, 778; (h) R. E. Gawley, *Top. Stereochem.*, 2010, **26**, 93.
- 14 We have independently verified the sense and degree of asymmetric induction in the lithiation and MeI trapping of azetidine **1** with (–)-sparteine **3** and diamine (*S,S*)-**4**, as reported by Hodgson (ref. 5) (see ESI†).
- 15 J. L. Bilke, S. P. Moore, P. O'Brien and J. Gilday, *Org. Lett.*, 2009, **11**, 1935.
- 16 D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260.
- 17 (a) M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870; (b) P. O'Brien, *Chem. Commun.*, 2008, 655.
- 18 For a review on configurational stability of organolithium species, see: A. Basu and S. Thayumanavan, *Angew. Chem., Int. Ed.*, 2002, **41**, 716.
- 19 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.
- 20 In a control experiment, lithiation of *N*-thiopivaloyl azetidine **1** with *s*-BuLi in Et₂O at –40 °C for 1 h and trapping with PhCHO gave racemic **12** (42%) and **13** (21%), indicating that ~60% lithiation had occurred under these conditions.
- 21 D. M. Hodgson, C. I. Pearson and A. L. Thompson, *J. Org. Chem.*, 2013, **78**, 1098.