HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 1288 - 1303. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 15th March, 2018, Accepted, 22nd May, 2018, Published online, 20th June, 2018
DOI: 10.3987/COM-18-S(T)87

A SYNTHETIC AND SPECTROSCOPIC INVESTIGATION OF THE ASYMMETRIC α-LITHIATION-TRAPPING OF SIX-MEMBERED *N*-BOC HETEROCYCLES USING ALEXAKIS DIAMINES

James D. Firth, Giacomo Gelardi, Peter J. Rayner, Darren Stead, and Peter O'Brien*

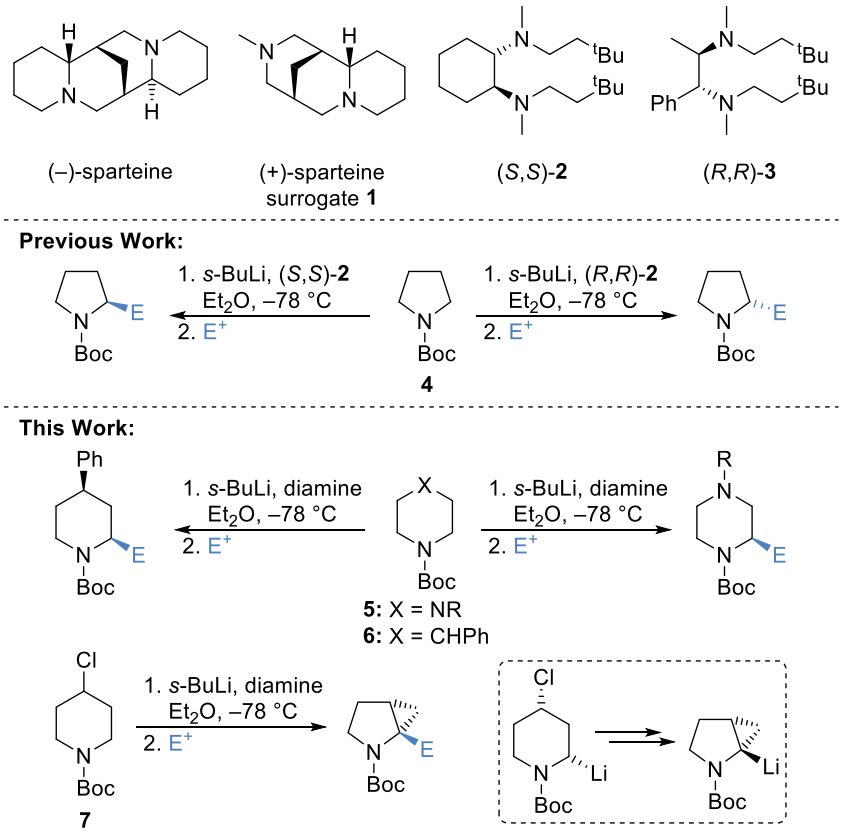
Department of Chemistry, University of York, Heslington, York YO10 5DD, U. K. E-mail: peter.obrien@york.ac.uk

This paper is dedicated to Professor Kiyoshi Tomioka, Doshisha Women's College, on the occasion of his 70th birthday.

Abstract – The asymmetric lithiation-trapping of six-membered *N*-Boc heterocycles using *s*-BuLi and two different Alexakis diamines is reported. These readily available ligands outperform the current 'best-in-class' sparteine-type diamines in the lithiation and benzophenone trapping of *N*-Boc piperazines and the lithiation-cyclisation-trapping of *N*-Boc-4-chloropiperidine. *In situ* IR spectroscopy has been used to optimise lithiation times and to discover previously unknown subtleties regarding the lithiation step.

The enantioselective α-functionalisation of *N*-Boc activated nitrogen heterocycles *via* lithiation-trapping methodology has become a mainstay of asymmetric heterocycle synthesis[1] since its inception by Beak in 1991.[2] The alkaloid (–)-sparteine and the (+)-sparteine surrogate **1**, developed in our laboratory,[3] have become the most useful ligands for such *s*-BuLi-mediated transformations (Scheme 1). Whilst (–)-sparteine and its antipode are naturally occurring,[4] the commercial availability has varied dramatically over the past 20 years.[5] Additionally, (+)-sparteine surrogate **1**, although commercially available, is prohibitively expensive and is more commonly synthesised from (–)-cytisine.[6] Recent developments from ourselves and Maulide have addressed the supply issues relating to these important diamines,[7] but since **1** is only a pseudo-enantiomer of (–)-sparteine, it exhibits significant differences in rates of organolithium-mediated transformations and it can also have different enantioselectivities.[8] Given that the use of enantiomeric ligands is preferred in asymmetric synthesis, and the supply of sparteine is unreliable, we chose to revisit chiral diamines that are readily available as both enantiomers. In this regard, the

C_2-symmetric diamine **2**,[9] and pseudoephedrine-derived diamine **3**,[10] devised by Alexakis, seemed highly suitable and both can be easily synthesised in multi-gram quantities from readily available enantiopure precursors.[11a]

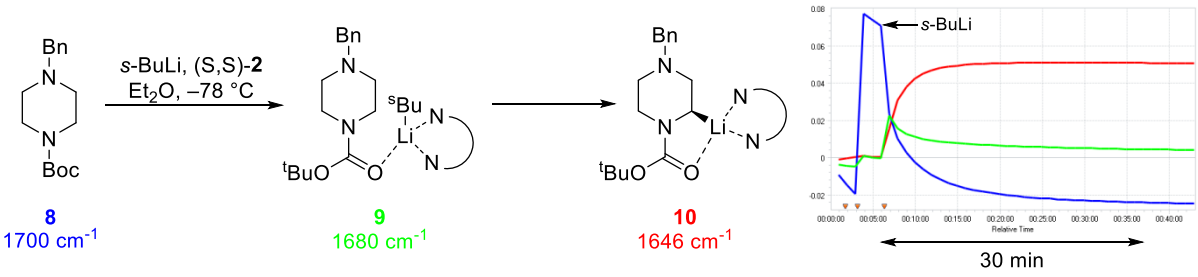


Scheme 1. Structure of diamine ligands and an overview of the lithiation-trapping of *N*-Boc heterocycles

Although diamines **2** and **3** were originally developed for the addition of MeLi to aromatic imines, both enantiomers of **2** have been used successfully in the lithiation-trapping of *N*-Boc pyrrolidine **4**,[11] giving comparable results to (–)-sparteine and the (+)-sparteine surrogate **1** (Scheme 1). Additionally, diamine **2** has found some utility in the asymmetric lithiation-trapping of other *N*-containing heterocyles,[12] aryl bromides[13] and paracyclophanes[14] as well as the dynamic resolution of lithiated *N*-thiopivaloyl azetidine.[15] Since diamine **2** can be considered the diamine of choice for the lithiation of *N*-Boc pyrrolidine **4**, we decided to investigate the use of diamine (*S*,*S*)-**2**, and the structurally related diamine (*R*,*R*)-**3**, in the asymmetric lithiation-trapping of six-membered *N*-Boc piperazines **5**[16] and *N*-Boc-4-phenylpiperidine **6** (Scheme 1).[12a] As part of this study, we also included the lithiation-cyclisation-trapping of *N*-Boc-4-chloropiperidine **7**. Lithiation of **7** is followed by internal substitution of the chloride to give a cyclopropane which then undergoes regioselective lithiation *via* removal of the more acidic α-*N*-Boc cyclopropyl proton.[12d,17] Herein, we present our results.

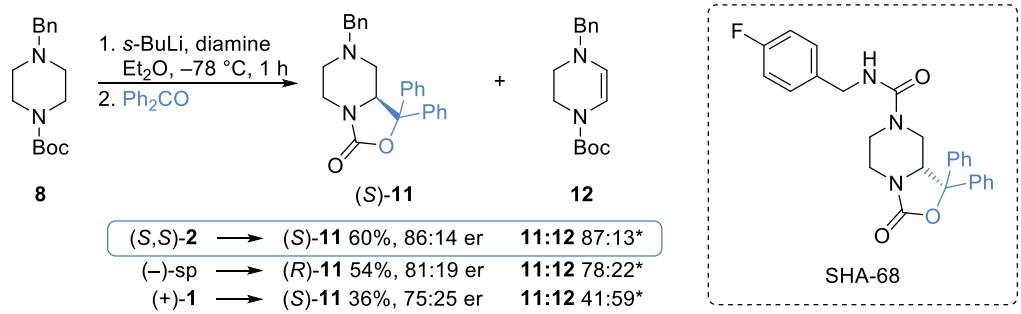
First, the asymmetric lithiation-trapping of *N*-Boc-*N*'-benzylpiperazine **8** using *s*-BuLi and diamine

(*S*,*S*)-**2** was explored. In order to determine the time required for lithiation of *N*-Boc piperazine **8**, *in situ* IR spectroscopy, which has become a popular technique in this context,[8b,16a,18] was employed. A solution of *N*-Boc piperazine **8** (1.0 mmol) in Et_2O (14 mL) at –78 °C (in the presence of diamine (*S*,*S*)-**2**) exhibited a $\nu_{C=O}$ peak at 1700 cm^{-1}. On addition of *s*-BuLi, lithiation proceeded to give the organolithium **10** ($\nu_{C=O}$ peak at 1646 cm^{-1}); formation of a pre-lithiation complex **9**, assigned to a peak at 1680 cm^{-1}, was also observed throughout the lithiation (Scheme 2, 2-D plot of absorbance versus time). As the reaction progressed, the proportion of both *N*-Boc piperazine **8** and pre-lithiation complex **9** decreased whereas that of the lithiated species **10** steadily increased, with lithiation taking ~30 min. For comparison, using *s*-BuLi and (–)-sparteine or the (+)-sparteine surrogate **1**, the lithiation time for *N*-Boc piperazine **8** is ~60 min and ~2 min respectively.[16a] Thus, *s*-BuLi/diamine (*S*,*S*)-**2** shows intermediate reactivity compared to *s*-BuLi/(–)-sparteine and *s*-BuLi/(+)-sparteine surrogate **1**.



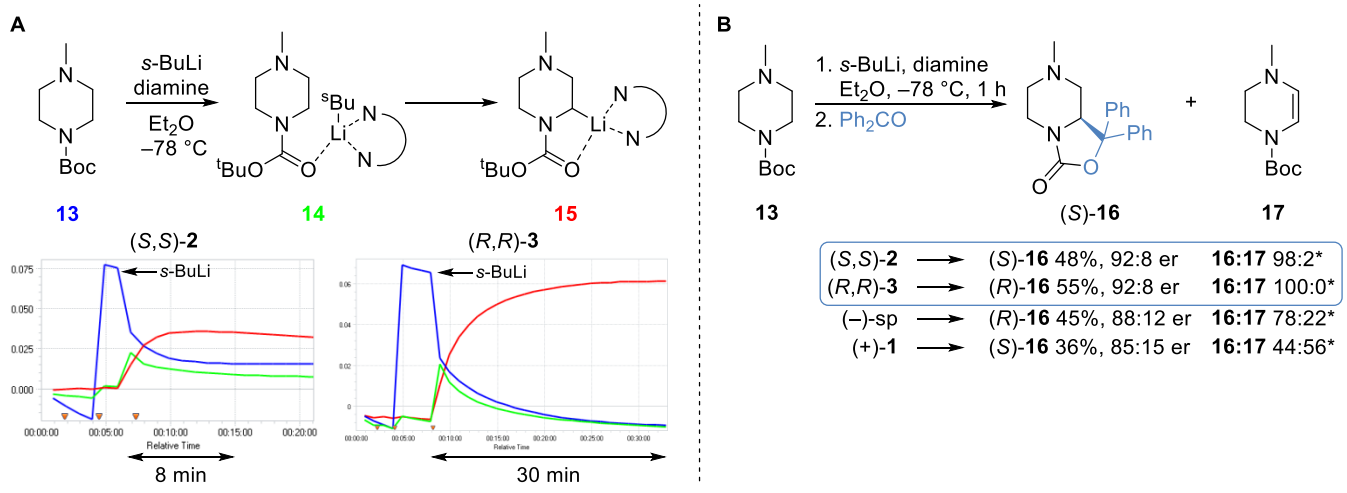
Scheme 2. *In situ* IR spectroscopic monitoring of the asymmetric lithiation of *N*-Boc piperazine **8** with *s*-BuLi/diamine (*S*,*S*)-**2**

With an idea of the lithiation time established, we treated *N*-Boc-*N*'-benzylpiperazine **8** with *s*-BuLi and (*S*,*S*)-**2** (Et_2O, –78 °C, 1 h) followed by trapping with benzophenone. This gave adduct (*S*)-**11** (in an 87:13 ratio with alkene by-product **12**), which was isolated in 60% yield and 86:14 er (Scheme 3). Alkene by-product **12** is believed to have formed through a single electron transfer (SET) mechanism;[19] one electron oxidation of lithiated *N*-Boc piperazine **8** by Ph_2CO would give an α-amino radical which could lose a β-hydrogen atom to give **12**. In comparison with lithiation employing either (–)-sparteine or the (+)-sparteine surrogate **1**,[16a] the reaction mediated by *s*-BuLi/diamine (*S*,*S*)-**2** gives higher yields and enantiomeric ratios and a lower proportion of alkene **12**, due to a decrease in SET side-reactions. With (–)-sparteine, (*R*)-**11** was isolated in 54% yield and 89:11 er; with (+)-sparteine surrogate **1**, the yield and er of (*S*)-**11** were 36% and 75:25 respectively. Employment of enantiomeric diamine (*R*,*R*)-**2** would allow an efficient synthesis of (*R*)-**11**, an advanced intermediate in the synthesis of SHA-68, a neuropeptide S receptor antagonist.[20]



Scheme 3. Lithiation-trapping of *N*-Boc piperazine **8**. *ratio determined by ^{1}H NMR spectroscopy of the crude product.

Next, we explored the lithiation-trapping of *N*-Boc-*N*'-methylpiperazine **13** using *s*-BuLi and diamines (*S*,*S*)-**2** and (*R*,*R*)-**3**. Initial *in situ* IR spectroscopic studies showed that a solution of piperazine **13** and diamine (*S*,*S*)-**2** in Et_2O at –78 °C exhibited a $\nu_{C=O}$ peak at 1703 cm^{-1} (Scheme 4A). Treatment with *s*-BuLi gave organolithium **15** ($\nu_{C=O}$ peak at 1646 cm^{-1}) *via* pre-lithiation complex **14** ($\nu_{C=O}$ peak at 1680 cm^{-1}). Interestingly, although lithiation of **13** initially proceeded rapidly, the reaction stalled at approximately 50% conversion within 8 min. This could account for the poor yield in the *s*-BuLi/diamine (*S*,*S*)-**2**-mediated lithiation-trapping of **13** (*vide infra*). Conversely, analogous *in situ* IR spectroscopic analysis of the lithiation of *N*-Boc-*N*'-methylpiperazine **13** with *s*-BuLi/diamine (*R*,*R*)-**3** showed rapid and full conversion of **13** ($\nu_{C=O}$ peak at 1702 cm^{-1}) to the lithiated intermediate **15** ($\nu_{C=O}$ peak at 1646 cm^{-1}) *via* pre-lithiation complex **14** ($\nu_{C=O}$ peak at 1680 cm^{-1}). Lithiation was complete within 30 min.[21]

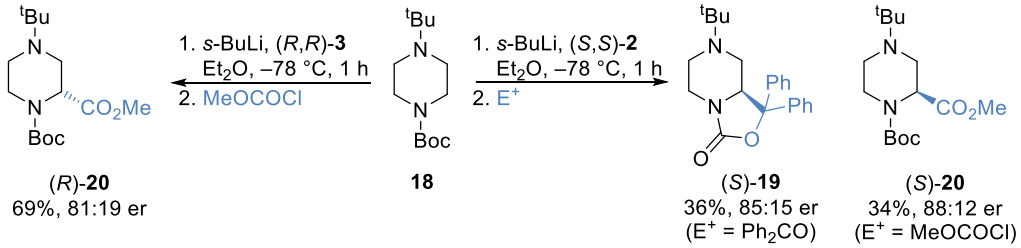


Scheme 4. Panel A: *In situ* IR spectroscopic monitoring of the asymmetric lithiation of *N*-Boc piperazine **13**; Panel B: Lithiation-trapping of *N*-Boc piperazine **13**. *ratio determined by ^{1}H NMR spectroscopy of the crude product.

Next, lithiation of *N*-Boc-*N*'-methylpiperazine **13** followed by trapping with benzophenone was investigated (Scheme 4B). In the presence of diamine (*S*,*S*)-**2**, oxazolidinone (*S*)-**16** was obtained in 48% yield and 92:8 er. Interestingly, only a trace of alkene side-product **17** was observed. It is thought that the modest yield is due to only partial lithiation of *N*-Boc piperazine **13** as indicated by *in situ* IR spectroscopy. Lithiation-trapping in the presence of *s*-BuLi and pseudoephedrine-derived diamine (*R*,*R*)-**3** resulted in oxazolidinone (*R*)-**16** being isolated in 55% yield and 92:8 er, without the formation of any alkene side-product **17**. In comparison, the more commonly employed diamines for lithiation-trapping of *N*-Boc heterocycles, (–)-sparteine and the (+)-sparteine surrogate **1**, performed worse in terms of yield and enantioselectivity. With (–)-sparteine, oxazolidinone (*R*)-**16** was isolated in 45% yield and 88:12 er; with (+)-sparteine surrogate **1**, the yield and er of (*S*)-**16** were 36% and 85:15 er respectively. This is believed to be due to an increase in SET side-reactions. Although it is currently unknown how the Alexakis diamines **2** and **3** suppress SET processes, they appear well-suited for use in the lithiation-trapping of *N*-Boc piperazines with benzophenone.

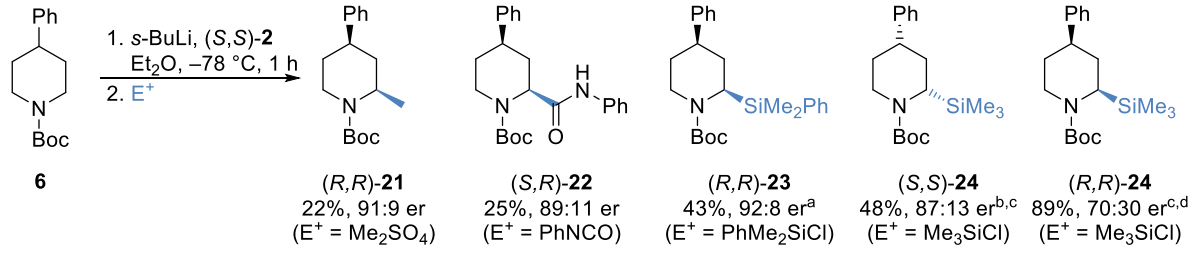
We then addressed the lithiation of *N*-Boc-*N*'-*tert*-butylpiperazine **18**. Previous *in situ* IR spectroscopic studies[16a] had shown that lithiation of *N*-Boc piperazine **18** with *s*-BuLi and (–)-sparteine in Et_2O at –78 °C took over 5 h to reach completion, which is significantly slower than either *N*-Boc-*N*'-benzylpiperazine **8** (~60 min)[16a] or *N*-Boc-*N*'-methylpiperazine **13** (~90 min) (for full details see SI). With (+)-sparteine surrogate **1**, the same trend was observed: lithiation of *N*-Boc-*N*'-*tert*-butylpiperazine **18** took longer (5 min) than either *N*-Boc-*N*'-benzylpiperazine **8** (2 min) or *N*-Boc-*N*'-methylpiperazine **13** (2 min). We were interested to see if this trend continued with the structurally distinct Alexakis diamines. As with *N*-Boc-*N*'-methylpiperazine **13**, lithiation of **18** with *s*-BuLi and diamine (*S*,*S*)-**2** resulted in rapid but incomplete lithiation (see SI for full details). However, using *s*-BuLi and diamine (*R*,*R*)-**3**, complete lithiation occurred within 30 min, which is in fact a similar rate of lithiation as that observed with *N*-Boc-*N*'-methylpiperazine **13** (c.f. 30 min, Scheme 4A). Interestingly, the sparteine-class ligands appear to result in more varied rates of lithiation of *N*-Boc piperazines than the Alexakis ligands, possibly due to the greater rigidity of the bispidine core.

Lithiation of *N*-Boc-*N*'-*tert*-butylpiperazine **18** using diamine (*S*,*S*)-**2** under standard conditions (*s*-BuLi, Et_2O, –78 °C, 1 h) and trapping with benzophenone gave adduct (*S*)-**19** in 36% yield and 85:15 er, without the formation of an alkene side-product (Scheme 5). Similarly, trapping with methyl chloroformate gave ester (*S*)-**20** in 34% yield and 88:12 er as the sole product. Here, the modest yields are likely to be caused by partial lithiation, as observed by *in situ* IR spectroscopy. Conversely, lithiation of **18** with *s*-BuLi/diamine (*R*,*R*)-**3** and trapping with methyl chloroformate gave ester (*R*)-**20** in a good 69% yield and 81:19 er.



Scheme 5. Lithiation-trapping of *N*-Boc-*N*'-*tert*-butylpiperazine **18**

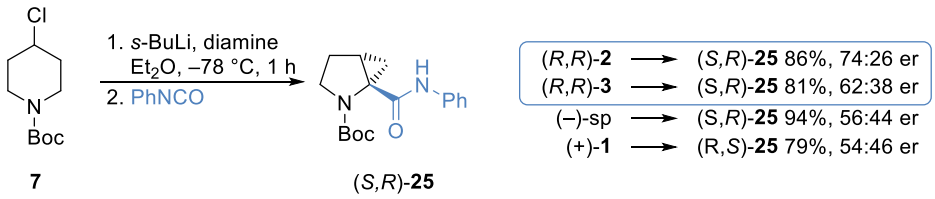
Next, we turned our attention to the lithiation-trapping of *N*-Boc-4-phenylpiperidine **6** using diamines (*S*,*S*)- and (*R*,*R*)-**2**. Treatment of *N*-Boc-4-phenylpiperidine **6** with *s*-BuLi and diamine (*S*,*S*)-**2** (Et_2O, –78 °C, 1 h) was followed by trapping with a range of electrophiles, giving *cis*-disubstituted piperidines **21**-**24** as single diastereomers in good er, but moderate yield (Scheme 6). Trapping with dimethyl sulfate gave (*R*,*R*)-**21** in 22% yield and 91:9 er (with 50% recovered starting material), phenyl isocyanate gave amide (*S*,*R*)-**22** in 25% yield and 89:11 er (with 49% recovered starting material) and $PhMe_2SiCl$ gave (*R*,*R*)-**23** in 43% yield and 92:8 er. Use of the enantiomeric ligand (*R*,*R*)-**2**, trapping with Me_3SiCl, gave (*S*,*S*)-**24** in 48% yield and 87:13 er.[12a] In comparison, lithiation with *s*-BuLi and (–)-sparteine or the (+)-sparteine surrogate **1** was much less successful. Use of (–)-sparteine resulted in a much poorer yield, with (*S*,*S*)-**24** being isolated in only 6% yield and 78:22 er.[12a] Conversely, the use of the (+)-sparteine surrogate **1** gave (*R*,*R*)-**24** in an excellent 89% yield but poorer 70:30 er. The *cis*-diastereomers are formed by equatorial lithiation of a conformation with an equatorial phenyl group and retentive trapping.[22] The moderate yields with the Alexakis diamines can be explained by stalling in the lithiation step, as observed by *in situ* IR spectroscopy (see SI for full details).



Scheme 6. Lithiation-trapping of *N*-Boc-4-phenylpiperidine **6**. [a]lithiation time 3 h; [b]using (*R*,*R*)-**2**; [c]lithiation time 6 h; [d]using **1**

Finally, we re-visited the asymmetric lithiation-trapping of *N*-Boc-4-chloropiperidine **7**.[12d] Treatment of *N*-Boc-4-chloropiperidine **7** with 2.2 eq. of *s*-BuLi and diamine (*R*,*R*)-**2** (–78 °C, 1 h) followed by trapping with phenyl isocyanate gave amide (*S*,*R*)-**25** in 86% yield and 74:26 er (Scheme 7). In comparison, use of pseudoephedrine derived (*R*,*R*)-**3** gave (*S*,*R*)-**25** in 81% yield and a poorer 62:38 er. In

contrast, use of the more established diamines, (–)-sparteine and (+)-sparteine surrogate **1**, resulted in near-racemic **25** being isolated (56:44 er and 46:54 er respectively).[12d]



Scheme 7. Lithiation-trapping of *N*-Boc-4-phenyl piperidine **7**

In conclusion, we describe the first spectroscopic and synthetic investigation of the asymmetric lithiation-trapping of six-membered *N*-Boc-activated nitrogen heterocycles using the Alexakis diamines **2** and **3** as ligands. Indeed, this is the first report of pseudoephedrine-derived **3** being used for the asymmetric lithiation of any *N*-Boc heterocycle. In comparison with the established diamines, (–)-sparteine and (+)-sparteine surrogate **1**, these readily available ligands give superior results in the lithiation of *N*-Boc piperazines, followed by trapping with benzophenone and the lithiation-trapping of *N*-Boc-4-chloropiperidine **7**. Furthermore, we have demonstrated the asymmetric synthesis of single diastereomers of 2,4-*cis*-disubstituted piperidines from *N*-Boc-4-phenylpiperidine **6**. The use of *in situ* IR spectroscopy has provided information on lithiation times and revealed the subtle effect of the lithiation of **6**, **13** and **18** stalling at ~50% in the presence of diamine (*S*,*S*)-**2**. Additionally, this technique revealed the fact that the lithiation of differentially protected *N*-Boc piperazines using *s*-BuLi and (*R*,*R*)-**3** occur at similar rates, unlike the analogous reactions using the sparteine class of ligands.

EXPERIMENTAL

For full details of the synthesis of starting materials and diamines as well as *in situ* IR experiments and NMR and CSP-HPLC data, see the supporting information.

General procedure A: Lithiation-trapping of *N*-Boc piperazines and *N*-Boc-4-phenylpiperidine 6. *s*-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc heterocycle (1.0–1.95 mmol, 1.0 eq.) and diamine (1.3 eq.) in Et_2O (3.5-10.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, the electrophile (2.0 eq.) was added dropwise, as a solution in Et_2O (1 mL) if necessary. The reaction mixture was allowed to warm slowly to rt overnight. Then, saturated $NH_4Cl_{(aq)}$ (10 mL), 20% $NaOH_{(aq)}$ (10 mL), and Et_2O (10 mL) were added, and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product.

General procedure B: Lithiation-trapping of *N*-Boc-4-chloropiperidine 7. *s*-BuLi (1.3 M solution in hexanes, 2.2 eq.) was added dropwise to a stirred solution of *N*-Boc-4-chloropiperidine **7** (0.75–1.09 mmol, 1.0 eq.) and diamine (2.2 eq.) in Et_2O (5.5-8.0 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, phenyl isocyanate (2.2 eq.) was added dropwise. The reaction mixture was allowed to warm slowly to rt overnight. Then, saturated $NH_4Cl_{(aq)}$ (10 mL), and Et_2O (10 mL) were added, and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product.

(8a*S*)-7-Benzyl-1,1-diphenyl-hexahydro-1*H*-[1,3]oxazolo[3,4-*a*]-piperazin-3-one (*S*)-11: Using general procedure A, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), (*S*,*S*)-**2** (606 mg, 1.95 mmol, 1.3 eq.), and *N*-Boc-*N*'-benzylpiperazine **8** (415 mg, 1.5 mmol, 1.0 eq.) in Et_2O (10.5 mL) and a solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product which contained an 87:13 mixture of (*S*)-**11** and alkene **12** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave oxazolidinone (*S*)-**11** (345 mg, 60%, 86:14 er by CSP-HPLC) as a white solid, mp 146–149 °C; R_F (7:3 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H, Ph), 7.40–7.21 (m, 13H, Ph), 4.54 (dd, J = 11.0, 3.5 Hz, 1H, NCH), 3.80 (ddd, J = 13.0, 3.5, 1.5 Hz, 1H, NCH), 3.50 (d, J = 13.0 Hz, 1H, CH_2Ph), 3.31 (d, J = 13.0 Hz, 1H, CH_2Ph), 3.09 (ddd, J = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.70–2.66 (m, 1H, NCH), 2.55 (ddd, J = 11.0, 3.5, 1.5 Hz, 1H, NCH), 1.93 (td, J = 12.0, 3.5 Hz, 1H, NCH), 1.57 (t, J = 11.0 Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5 (C=O), 142.7 (*ipso*-Ph), 139.1 (*ipso*-Ph), 137.6 (*ipso*-Ph), 129.1 (Ph), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.6 (Ph), 126.2 (Ph), 126.0 (Ph), 85.3 (Ph$_2$*C*O), 62.9 (NCH$_2$), 61.1 (NCH), 55.7 (NCH$_2$), 50.7 (NCH$_2$), 41.5 (NCH$_2$); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{25}N_2O_2$ $(M + H)^+$ 385.1911, found 385.1899 (–3.1 ppm error); $[\alpha]_D$ –157.7 (*c* 1.0 in $CHCl_3$) (lit.[16a] $[\alpha]_D$ –114.9 (*c* 1.0 in $CHCl_3$) for (*S*)-**11** of 75:25 er); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**11** 12.9 min, (*R*)-**11** 17.4 min. Spectroscopic data consistent with those reported in the literature.[16a]

Diagnostic signals for alkene **12**: ^{1}H NMR (400 MHz, $CDCl_3$) (67:33 mixture of rotamers) δ 6.03 (d, J = 6.5 Hz, 0.33H, CH=C*H*NBoc), 5.88 (d, J = 6.5 Hz, 0.67H, CH=C*H*NBoc), 5.49 (d, J = 6.5 Hz, 0.33H, C*H*=CHNBoc), 5.38 (d, J = 6.5 Hz, 0.67H, C*H*=CHNBoc), 3.94 (s, 2H, CH_2Ph).

(8a*S*)-7-Methyl-1,1-diphenyl-hexahydro-1*H*-[1,3]oxazolo[3,4-*a*]pyrazin-3-one (*S*)-16: Using general procedure A, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), (*S*,*S*)-**2** (606 mg, 1.95 mmol, 1.3 eq.) and *N*-Boc-*N*'-methylpiperazine **13** (300 mg, 1.5 mmol, 1.0 eq.) in Et_2O (10.5 mL) and a

solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product which contained a 98:2 mixture of (*S*)-**16** and alkene **17** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1 to 96:4 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*S*)-**16** (221 mg, 48%, 92:8 er by CSP-HPLC) as a white solid, mp 96–98 °C; R_F (19:1 CH_2Cl_2-MeOH) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) 7.52–7.47 (m, 2H, Ph), 7.37–7.23 (m, 8H, Ph), 4.50 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.83 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.12 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.68–2.64 (m, 1H, NCH), 2.43 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.18 (s, 3H, NMe), 1.93 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.43 (t, *J* = 11.0 Hz, 1H, NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8 (C=O), 142.2 (*ipso*-Ph), 138.6 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 125.8 (Ph), 125.6 (Ph), 85.1 (Ph_2CO), 60.9 (NCH), 56.9 (NCH_2), 53.2 (NCH_2), 46.3 (NMe), 41.5 (NCH_2); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}N_2O_2$ $(M+H)^+$ 309.1598, found 309.1599 (+0.1 ppm error); $[\alpha]_D$ –221.7 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel AD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**16** 11.7 min, (*R*)-**16** 17.4 min. Spectroscopic data consistent with those reported in the literature.[18c]

Diagnostic signals for alkene **17**: ^{1}H NMR (400 MHz, $CDCl_3$) (67:33 mixture of rotamers) δ 6.04 (d, *J* = 6.5 Hz, 0.33H, CH=C*H*NBoc), 5.88 (d, *J* = 6.5 Hz, 0.67H, CH=C*H*NBoc), 5.28 (d, *J* = 6.5 Hz, 0.33H, C*H*=CHNBoc), 5.18 (d, *J* = 6.5 Hz, 0.67H, C*H*=CHNBoc), 2.57, (s, 2H, NMe), 2.56, (s, 1H, NMe).

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-**1** (252 mg, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-methylpiperazine **13** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product which contained a 44:56 mixture of (*S*)-**16** and alkene **17** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1 to 96:4 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*S*)-**16** (120 mg, 39%, 85:15 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**16** 12.2 min, (*R*)-**16** 18.0 min.

(8a*R*)-7-Methyl-1,1-diphenyl-hexahydro-1*H*-[1,3]oxazolo[3,4-*a*]pyrazin-3-one (*R*)-16: Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (*R*,*R*)-**3** (450 mg, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-methylpiperazine **13** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 96:4 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*R*)-**16** (170 mg, 55%, 92:8 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +235.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiralcel AD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**16** 11.9 min, (*R*)-**16** 15.5 min.

Using general procedure A, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), (–)-sparteine (448 μL, 1.95 mmol, 1.3 eq.) and *N*-Boc-*N*'-methylpiperazine **13** (300 mg, 1.5 mmol, 1.0 eq.) in Et_2O (10.5 mL) and a solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product which contained a 78:22 mixture of (*R*)-**16** and alkene **17** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1 to 96:4 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*R*)-**16** (210 mg, 45%, 88:12 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralcel AD (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*S*)-**16** 12.2 min, (*R*)-**16** 16.7 min.

(8a*S*)-7-*tert*-Butyl-1,1-diphenyl-hexahydro-1*H*-[1,3]oxazolo[3,4-*a*]pyrazin-3-one (*S*)-19: Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (*S*,*S*)-**2** (403 mg, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-*tert*-butylpiperazine **18** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 97:3 CH_2Cl_2-MeOH as eluent gave oxazolidinone (*S*)-**19** (125 mg, 36%, 85:15 er by CSP-HPLC) as a white solid, mp 193–195 °C; R_F (99:1 CH_2Cl_2-MeOH) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H, Ph), 7.39–7.24 (m, 8H, Ph), 4.43 (dd, J = 11.0, 3.5 Hz, 1H, NCH), 3.85 (ddd, J = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.08 (ddd, J = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.92–2.88 (m, 1H, NCH), 2.62 (ddd, J = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.06 (td, J = 12.0, 3.5 Hz, 1H, NCH), 1.51 (t, J = 11.0 Hz, 1H, NCH), 0.93 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1 (C=O), 142.4 (*ipso*-Ph), 138.8 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.2 (Ph), 127.8 (Ph), 126.0 (Ph), 125.7 (Ph), 85.4 (Ph_2CO), 61.9 (NCH), 54.3 (CMe_3), 48.8 (NCH_2), 44.8 (NCH_2), 42.6 (NCH_2), 26.0 (CMe_3); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{27}N_2O_2$ $(M + H)^+$ 351.2067, found 351.2062 (–1.4 ppm error); $[\alpha]_D$ –144.6 (*c* 1.0 in $CHCl_3$) (lit.[16a] $[\alpha]_D$ +184.1 (*c* 1.0 in $CHCl_3$) for (*R*)-**19** of 90:10 er); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**19** 13.4 min, (*R*)-**19** 17.3 min. Spectroscopic data consistent with those reported in the literature.[16a]

1-*tert*-Butyl 2-methyl (2*S*)-4-*tert*-butylpiperazine-1,2-dicarboxylate (*S*)-20: Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (*S*,*S*)-**2** (403 mg, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-*tert*-butylpiperazine **18** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) and methyl chloroformate (155 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave ester (*S*)-**20** (103 mg, 34%, 88:12 er by CSP-HPLC) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.70 (br s, 0.5H, NCH), 4.53 (br s, 0.5H, NCH), 3.83 (br d, J = 12.5 Hz, 0.5H, NCH), 3.75–3.73 (m, 0.5H, NCH), 3.73 (s, 1.5H, OMe), 3.72 (s, 1.5H, OMe), 3.52–3.45 (m, 1H, NCH), 3.13 (td, J = 12.5, 3.5 Hz, 0.5H, NCH), 3.03 (td, J = 12.5, 3.5 Hz, 0.5H, NCH), 2.92 (br d, J = 11.0 Hz, 0.5H,

NCH), 2.84 (br d, J = 11.0 Hz, 0.5H, NCH), 2.28–2.23 (m, 1H, NCH), 2.11 (td, J = 11.0, 3.5 Hz, 1H, NCH), 1.46 (s, 4.5H, $OCMe_3$), 1.42 (s, 4.5H, $OCMe_3$), 0.96 (s, 9H, $NCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 171.6 (CO_2Me), 171.3 (CO_2Me), 155.8 (NC=O), 155.4 (NC=O), 80.0 ($OCMe_3$), 56.3 (NCH), 55.0 (NCH), 53.3 ($NCMe_3$), 51.9 (OMe), 47.6 (NCH_2), 45.2 (NCH_2), 42.9 (NCH_2), 42.0 (NCH_2), 28.3 (CMe_3), 25.8 (CMe_3); HRMS (ESI) m/z calcd for $C_{15}H_{29}N_2O_4$ $(M + H)^+$ 301.2122, found 301.2122 (0.0 ppm error); $[\alpha]_D$ –21.2 (c 1.0 in $CHCl_3$); (lit.[16a] $[\alpha]_D$ +22.2 (c 1.0 in $CHCl_3$) for (*R*)-**20** of 89:11 er); CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**20** 13.4 min, (*S*)-**20** 19.5 min. Spectroscopic data consistent with those reported in the literature.[16a]

1-*tert*-Butyl 2-methyl (2*R*)-4-*tert*-butylpiperazine-1,2-dicarboxylate (*R*)-20: Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (*R*,*R*)-**3** (404 mg, 1.3 mmol, 1.3 eq.) and *N*-Boc-*N*'-*tert*-butylpiperazine **18** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) and methyl chloroformate (155 μL, 2.0 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave ester (*R*)-**20** (206 mg, 69%, 81:19 er by CSP-HPLC) as a pale yellow oil, CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**20** 13.9min, (*S*)-**20** 23.7 min.

***tert*-Butyl (2*R*,4*R*)-2-methyl-4-phenylpiperidine-1-carboxylate (*R*,*R*)-21:** Using general procedure A, *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), (*S*,*S*)-**2** (465 mg, 1.5 mmol, 1.3 eq.) and *N*-Boc-4-phenylpiperidine **6** (300 mg, 1.15 mmol, 1.0 eq.) in Et_2O (3.8 mL) and Me_2SO_4 (210 μL, 2.3 mmol, 2.0 eq.) gave the crude product containing a single diastereomer of (*R*,*R*)-**21**. Purification by flash column chromatography on silica with 97:3 hexane-EtOAc as eluent gave piperidine (*R*,*R*)-**21** (70 mg, 22%, 91:9 er by CSP-HPLC) as a colourless oil, R_F (95:5 hexane-EtOAc) 0.2; IR ($CHCl_3$) 2973, 2932, 1692 (C=O), 1478, 1453, 1413, 1365, 1250, 1171, 1142, 759, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H, Ph), 7.25–7.17 (m, 3H, Ph), 4.02–3.90 (m, 1H, NCH), 3.81 (ddd, J = 14.0, 7.5, 3.0 Hz, 1H, NCH), 3.25 (ddd, J = 14.0, 10.0, 6.5 Hz, 1H, NCH), 2.81–2-71 (m, 1H, CHPh), 2.22–2.10 (m, 1H, CH), 1.91 (dddd, J = 13.5, 6.5, 3.0, 1.5 Hz, 1H, CH), 1.68–1.56 (m, 2H, CH), 1.49 (s, 9H, CMe_3), 1.20 (d, J = 6.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8 (C=O), 146.4 (*ipso*-Ph), 128.7 (Ph), 127.1 (Ph), 126.5 (Ph), 79.2 (CMe_3), 49.9 (NCH), 37.7 (CHPh), 37.4 (NCH_2), 36.9 (CH_2), 31.0 (CH_2), 28.3 (CMe_3), 19.5 (Me); HRMS (ESI) m/z calcd for $C_{17}H_{25}NO_2$ $(M + H)^+$ 276.1958, found 276.1953 (–1.8 ppm error); $[\alpha]_D$ –68.8 (c 0.55 in $CHCl_3$) (lit.,[23] $[\alpha]_D$ –72.1 (c 0.6 in $CHCl_3$) for (*R*,*R*)-**21**); CSP-HPLC: Chiralcel OD (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (*S*,*S*)-**21** 15.9 min, (*R*,*R*)-**21** 17.3 min and starting material **6** (152 mg, 50%) as a colourless oil. Spectroscopic data consistent with those reported in the literature.[23]

***tert*-Butyl (2*S*,4*R*)-4-phenyl-2-(phenylcarbamoyl)piperidine-1-carboxylate (*S*,*R*)-22:** Using general procedure A, *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), (*S*,*S*)-**2** (465 mg, 1.5 mmol, 1.3 eq.) and *N*-Boc-4-phenylpiperidine **6** (300 mg, 1.15 mmol, 1.0 eq.) in Et_2O (3.8 mL) and phenyl isocyanate (250 μL, 2.3 mmol, 2.0 eq.) gave the crude product containing a single diastereomer of (*S*,*R*)-**22**. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-Et_2O as eluent gave piperidine (*S*,*R*)-**22** (110 mg, 25%, 89:11 er by CSP-HPLC) as a white solid, mp 222–224 °C (lit.,[22b] 225–226 °C); R_F (97:3 CH_2Cl_2-Et_2O) 0.2; IR ($CHCl_3$) 2982, 1692 (C=O), 1600, 1524, 1442, 1155, 905, 730, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H, NH), 7.53 (dd, J = 8.5, 1.0 Hz, 2H, Ph), 7.36–7.29 (m, 4H, Ph), 7.28–7.20 (m, 3H, Ph), 7.11 (tt, J = 7.5, 1.0 Hz, 1H, Ph), 4.38 (dd, J = 8.5, 8.5 Hz, 1H, NCH), 3.71–3.55 (m, 2H, NCH), 2.78 (dddd, J = 10.5, 10.5, 6.5, 6.5 Hz, 1H, CHPh), 2.31–2.19 (m, 2H, CH), 2.14 (dddd, J = 13.5, 6.5, 6.5, 6.5 Hz, 1H, CH), 1.75 (dddd, J = 13.5, 10.5, 6.0, 6.0 Hz, 1H, CH), 1.47 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.1 (C=O), 156.7 (C=O), 145.1 (*ipso*-Ph), 137.9 (*ipso*-Ph), 129.0 (Ph), 128.6 (Ph), 126.8 (Ph), 126.5 (Ph), 124.1 (Ph), 119.5 (Ph), 81.5 (CMe_3), 58.5 (NCH), 41.7 (NCH_2), 37.8 (CH), 31.7 (CH_2), 30.9 (CH_2), 28.3 (CMe_3); HRMS (ESI) m/z calcd for $C_{23}H_{29}N_2O_3$ $(M + H)^+$ 381.2173, found 381.2162 (–2.9 ppm error).; $[\alpha]_D$ –48.7 (c 1.0 in $CHCl_3$) CSP-HPLC: Chiralcel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*,*S*)-**22** 11.7 min, (*S*,*R*)-**22** 17.0 min and starting material **6** (148 mg, 49%) as a colourless oil. Spectroscopic data consistent with those reported in the literature.[22b]

***tert*-Butyl (2*R*,4*R*)-2-[dimethyl(phenyl)silyl]-4-phenylpiperidine-1-carboxylate (*R*,*R*)-23:** Using general procedure A, *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.5 mmol, 1.3 eq.), (*S*,*S*)-**2** (465 mg, 1.5 mmol, 1.3 eq.) and *N*-Boc-4-phenylpiperidine **6** (300 mg, 1.15 mmol, 1.0 eq.) in Et_2O (3.8 mL) for 3 h at –78 °C and $PhMe_2SiCl$ (386 μL, 2.3 mmol, 2.0 eq.) gave the crude product containing a single diastereomer of (*R*,*R*)-**23**. Purification by flash column chromatography on silica with 96:4 petrol-EtOAc as eluent gave piperidine (*R*,*R*)-**23** (170 mg, 43%, 92:8 er by CSP-HPLC) as a white solid, mp 144–145 °C; R_F (96:4 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3020, 1685 (C=O), 1425, 1218, 929, 782, 736, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.56 (m, 2H, Ph), 7.38–7.28 (m, 5H, Ph), 7.25–7.16 (m, 3H, Ph), 4.11 (br s, 1H, NCH), 3.09–2.91 (br m, 1H, NCH), 2.79–2.60 (br m, 1H, NCH), 2.67 (dddd, J = 12.0, 12.0, 4.0, 4.0 Hz, 1H, CHPh), 1.88–1.77 (m, 2H, CH), 1.73–1.54 (m, 2H, CH), 1.47 (s, 9H, CMe_3), 0.48 (s, 3H, SiMe), 0.44 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 146.4 (*ipso*-Ph), 142.1 (*ipso*-Ph), 134.3 (Ph), 128.7 (Ph), 128.5 (Ph), 127.7 (Ph), 127.1 (Ph), 126.5 (Ph), 79.3 (CMe_3), 50.1 (NCH), 47.0 (NCH_2), 44.4 (*C*HPh), 33.4 (CH_2), 28.1 (CMe_3), –2.7 (SiMe), –3.3 (SiMe); HRMS (ESI) m/z calcd for $C_{24}H_{34}NO_2Si$ $(M + H)^+$ 396.2353, found 396.2348 (–1.3 ppm error), $[\alpha]_D$ –44.0 (c 1.0 in $CHCl_3$) CSP-HPLC: Chiralcel OD (99.9:0.1 hexane-*i*-PrOH, 0.5 mL min^{-1}) (*S*,*S*)-**23** 12.0 min, (*R*,*R*)-**23** 13.2 min.

***tert*-Butyl (2*R*,4*R*)-4-phenyl-2-(trimethylsilyl)piperidine-1-carboxylate (*R*,*R*)-24:** Using general procedure A, *s*-BuLi (1.25 mL of 1.18 M solution in cyclohexane, 1.47 mmol, 1.3 eq.), (+)-**1** (286 mg, 1.47 mmol, 1.3 eq.) and *N*-Boc-4-phenylpiperidine **6** (289 mg, 1.11 mmol, 1.0 eq.) in Et_2O (3.8 mL) for 6 h at –78 °C and Me_3SiCl (352 μL, 2.77 mmol, 2.5 eq.) gave the crude product containing a single diastereomer of (*R*,*R*)-**24**. Purification by flash column chromatography on silica with 96:4 petrol-Et_2O as eluent gave piperidine (*R*,*R*)-**24** (329 mg, 89%, 70:30 er by CSP-GC) as a colourless oil, $[\alpha]_D$ –1.4 (*c* 1.0 in $CHCl_3$) (lit.,[12a] $[\alpha]_D$ +4.6 (c 1.1, $CHCl_3$) for (*S*,*S*)-**24** 87:13 er) Spectroscopic data consistent with that previously reported.[12a]

CSP-GC: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d. [20% permethylated β-cyclodextrin in SPB-35 poly (35% diphenyl/65% dimethyl)siloxane, hydrogen carrier at 14 psi], retention times 34.0 min and 34.6 min (isothermal at 140 °C).

***tert*-Butyl (1*S*,5*R*)-1-(phenylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (*S*,*R*)-25:** Using general procedure B, *s*-BuLi (1.85 mL of a 1.3 M solution in hexanes, 2.4 mmol, 2.2 eq.), (*R*,*R*)-**2** (745 mg, 2.4 mmol, 2.2 eq.) and *N*-Boc-4-chloropiperidine **7** (240 mg, 1.09 mmol, 1.0 eq.) in Et_2O (8 mL) and phenyl isocyanate (261 μL, 2.4 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**25** (282 mg, 86%, 74:26 er by CSP-HPLC) as a pale yellow solid, mp 102–103 °C; R_F (98:2 CH_2Cl_2-Et_2O) 0.2; IR ($CDCl_3$) 3408 (NH), 2979, 1689 (C=O), 1682 (C=O), 1529, 1444, 1368, 1164, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (br s, 1H, NH), 7.49 (d, *J* = 8.0 Hz, 2H, Ph), 7.30 (t, *J* = 8.0 Hz, 2H, Ph), 7.07 (d, *J* = 8.0 Hz, 1H, Ph), 3.75 (ddd, *J* = 11.5, 9.0, 6.5 Hz, 1H, NCH), 3.66 (ddd, *J* = 11.5, 8.5, 5.5 Hz, 1H, NCH), 2.24 (ddt, *J* = 13.0, 9.0, 6.5 Hz, 1H, CH), 2.17-2.12 (m, 1H,CH), 2.07 (dd, *J* = 9.0, 5.0 Hz, 1H, CH), 1.94 (dddd, *J* = 13.0, 8.5, 6.5, 1.5 Hz, 1H, CH), 1.42 (s, 9H, CMe_3), 1.02 (t, *J* = 5.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.6 (PhN*C*O) 156.9 (N*C*$O_2$$CMe_3$), 137.8 (*ipso*-Ph), 128.9 (Ph), 123.9 (Ph), 119.3 (Ph), 81.2 (*C*Me_3), 51.3 (NCH_2), 50.6 (NC), 31.1 (CH), 28.1 (C*Me*$_3$), 26.4 (CH_2), 24.8 (CH_2); HRMS *m/z* calcd for $C_{17}H_{22}N_2NaO_3$ $(M + Na)^+$ 325.1523, found 325.1523 (0.0 ppm error); CSP-HPLC: Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*,*S*)-**25** 7.4 min, (*S*,*R*)-**25** 14.5 min. Spectroscopic data consistent with those reported in the literature.[12d]

Using general procedure B, *s*-BuLi (1.27 mL of a 1.3 M solution in hexanes, 1.65 mmol, 2.2 eq.), (*R*,*R*)-**3** (572 mg, 1.65 mmol, 2.2 eq.) and *N*-Boc-4-chloropiperidine **7** (164 mg, 0.75 mmol, 1.0 eq.) in Et_2O (5 mL) and phenyl isocyanate (179 μL, 1.65 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**25** (182 mg, 81%, 62:38 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL

min^{-1}) (*R*,*S*)-**25** 7.4 min, (*S*,*R*)-**25** 14.8 min.

Using general procedure B, *s*-BuLi (1.69 mL of a 1.3 M solution in hexanes, 2.2 mmol, 2.2 eq.), (–)-sparteine (506 μL, 2.2 mmol, 2.2 eq.) and *N*-Boc-4-chloropiperidine **7** (219 mg, 1.0 mmol, 1.0 eq.) in Et_2O (8 mL) and phenyl isocyanate (239 μL, 2.2 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*S*,*R*)-**25** (283 mg, 94%, 56:44 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*,*S*)-**25** 7.2 min, (*S*,*R*)-**25** 13.6 min.

***tert*-Butyl (1*R*,5*S*)-1-(phenylcarbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (*R*,*S*)-25:** Using general procedure B, *s*-BuLi (1.51 mL of a 1.3 M solution in hexanes, 1.96 mmol, 2.2 eq.), (+)-**1** (381 mg, 1.96 mmol, 2.2 eq.) and *N*-Boc-4-chloropiperidine **7** (194 mg, 0.89 mmol, 1.0 eq.) in Et_2O (5.5 mL) and phenyl isocyanate (179 μL, 1.65 mmol, 2.2 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave amide (*R*,*S*)-**25** (212 mg, 79%, 54:46 er by CSP-HPLC) as a pale yellow solid, CSP-HPLC: Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1}) (*R*,*S*)-**25** 7.4 min, (*S*,*R*)-**25** 14.8 min.

ACKNOWLEDGEMENTS

This work was supported by EPSRC, GlaxoSmithKline, Pfizer and AstraZeneca. The University of York funded the Mettler Toledo ReactIR ic10 spectrometer and Si-probe, and the equipment has been supported in part by the EPSRC 'ENERGY' grant EP/K031589/1.

REFERENCES AND NOTES

1. E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, and B. U. W. Maes, *Chem. Eur. J.*, 2012, **18**, 10092.
2. (a) P. Beak, S. T. Kerrick, S. Wu, and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231; (b) S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 9708.
3. M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870.
4. P. M. Dewick, *Nat. Prod. Rep.*, 2002, **19**, 181.
5. S. K. Ritter, *Chem. Eng. Rev.*, 2017, **95**, 18.
6. A. J. Dixon, M. J. McGrath, and P. O'Brien, *Org. Synth.*, 2006, **83**, 141.
7. (a) J. D. Firth, P. O'Brien, and L. Ferris, *Org. Biomol. Chem.*, 2014, **12**, 9357; (b) J. D. Firth, S. J. Canipa, L. Ferris, and P. O'Brien, *Angew. Chem. Int. Ed.*, 2018, **57**, 223; (c) N. Maulide, B. Peng, A. C. A. Mateus, and F. R. F. Machado, (Studiengesellschaft Kohle mbH, Universidade de Lisboa),

EP2808326A1, 2014.

8. (a) G. Carbone, P. O'Brien, and G. Hilmersson, *J. Am. Chem. Soc.*, 2010, **132**, 15445; (b) D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260.
9. (a) J.-C. Kizirian, J.-C. Caille, and A. Alexakis, *Tetrahedron Lett.*, 2003, **44**, 8893; (b) J.-C. Kizirian, N. Cabello, L. Pinchard, J.-C. Caille, and A. Alexakis, *Tetrahedron*, 2005, **61**, 8939.
10. Q. Perron and A. Alexakis, *Tetrahedron: Asymmetry*, 2007, **18**, 2503.
11. (a) D. Stead, P. O'Brien, and A. Sanderson, *Org. Lett.*, 2008, **10**, 1409; (b) J. L. Bilke, S. P. Moore, P. O'Brien, and J. Gilday, *Org. Lett.*, 2009, **11**, 1935; (c) W.-Y. Zhang, C. Sun, D. Hunt, M. He, Y. Deng, Z. Zhu, C.-L. Chen, C. E. Katz, J. Niu, P. C. Hogan, X.-Y. Xiao, N. Dunwoody, and M. Ronn, *Org. Process Res. Dev.*, 2016, **20**, 284; (d) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, and P. O'Brien, *J. Org. Chem.*, 2011, **76**, 5936.
12. (a) 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; (b) M. A. Perry, M. D. Morin, B. W. Slafer, and S. D. Rychnovsky, *J. Org. Chem.*, 2012, **77**, 3390; (c) C. Metallinos and S. Xu, *Org. Lett.*, 2010, **12**, 76; (d) P. J. Rayner, P. O'Brien, and R. A. J. Horan, *J. Am. Chem. Soc.*, 2013, **135**, 8071.
13. J. Praz, J. Graff, L. Egger, L. Guenee, S. Wagschal, E. P. Kundig, and A. Alexakis, *Chem. Commun.*, 2015, **51**, 16912.
14. K. Kanda, K. Endo, and T. Shibata, *Org. Lett.*, 2010, **12**, 1980.
15. (a) D. M. Hodgson and J. Kloesges, *Angew. Chem. Int. Ed.*, 2010, **49**, 2900; (b) P. J. Rayner, J. C. Smith, C. Denneval, P. O'Brien, P. A. Clarke, and R. A. J. Horan, *Chem. Commun.*, 2016, **52**, 1354.
16. (a) J. D. Firth, P. O'Brien, and L. Ferris, *J. Am. Chem. Soc.*, 2016, **138**, 651; (b) B. P. McDermott, A. D. Campbell, and A. Ertan, *Synlett*, 2008, 875.
17. Y. S. Park and P. Beak, *Tetrahedron*, 1996, **52**, 12333.
18. (a) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, and P. O'Brien, *J. Org. Chem.*, 2011, **76**, 5936; (b) N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien, and I. Coldham, *J. Am. Chem. Soc.*, 2012, **134**, 5300; (c) J. D. Firth, P. O'Brien, and L. Ferris, *J. Org. Chem.*, 2017, **82**, 7023; (d) D. J. Pippel, G. A. Weisenburger, N. C. Faibish, and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 4919; (e) X. Li, D. Leonori, N. S. Sheikh, and I. Coldham, *Chem. Eur. J.*, 2013, **19**, 7724; (f) E. J. Cochrane, D. Leonori, L. A. Hassall, and I. Coldham, *Chem. Commun.*, 2014, **50**, 9910; (g) A. Millet, D. Dailler, P. Larini, and O. Baudoin, *Angew. Chem. Int. Ed.*, 2014, **53**, 2678.
19. (a) R. E. Gawley, E. Low, Q. Zhang, and R. Harris, *J. Am. Chem. Soc.*, 2000, **122**, 3344; (b) R. E. Gawley, D. B. Eddings, M. Santiago, and D. A. Vicic, *Org. Biomol. Chem.*, 2006, **4**, 4285.

20. (a) N. Okamura, S. A. Habay, J. Zeng, A. R. Chamberlin, and R. K. Reinscheid, *J. Pharmacol. Exp. Ther.*, 2008, **325**, 893; (b) C. Trapella, M. Pela, L. Del Zoppo, G. Calo, V. Camarda, C. Ruzza, A. Cavazzini, V. Costa, V. Bertolasi, R. K. Reinscheid, S. Salvadori, and R. Guerrini, *J. Med. Chem.*, 2011, **54**, 2738.
21. With (–)-sparteine, complete lithiation occurred within 90 min. With (+)-sparteine surrogate **1**, complete lithiation occurred within 8 min (see SI for full details)
22. (a) P. Beak and W. K. Lee, *J. Org. Chem.*, 1990, **55**, 2578; (b) P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109.
23. M. Amat, M. Pérez, A. T. Minaglia, and J. Bosch, *J. Org. Chem.*, 2008, **73**, 6920.