Evaluation of sparteine-like chiral diamines in the enantioselective lithiation–electrophilic trapping of an *O*-alkyl carbamate†

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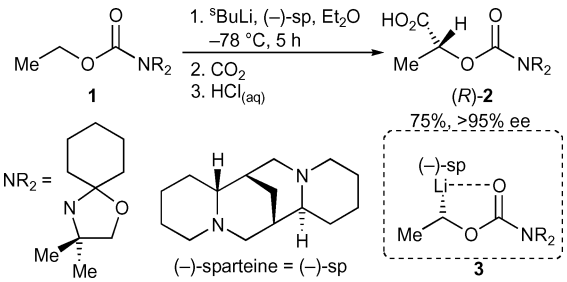
Seven (+)-sparteine-like diamines and (−)-sparteine were evaluated in the diamine-mediated asymmetric lithiation–trapping of an *O*-alkyl carbamate. The (+)-sparteine-like diamines (≥98 : 2 er by chiral shift NMR spectroscopy) were prepared from (−)-cytisine (>99 : 1 er by chiral HPLC of *N*-benzyl cytisine) and two new (+)-sparteine-like diamines containing *N*-CD_3 substituents were included as part of this study. The following results from the ligand evaluation study were obtained: (−)-sparteine is unrivalled in its ability to induce near-perfect enantioselectivity (99 : 1 er); *N*-methyl diamine and the two *N*-CD_3-substituted diamines are the optimal (+)-sparteine surrogates (up to 96 : 4 er); sterically more hindered *N*-alkyl substituents gave reduced enantioselectivity (*N*-*iso*-propyl: 86 : 14 er; *N*-$CH_2{}^t$Bu: 54 : 46 er). From a synthetic point of view, these results show that either enantiomer of α-substituted *O*-alkyl carbamates can be obtained by enantioselective lithiation–trapping using (−)-sparteine and the *N*-methyl (+)-sparteine surrogate.

Introduction

In 1990, Hoppe and co-workers reported the conversion of *O*-alkyl carbamates into α-substituted *O*-alkyl carbamates of high %ee *via* enantioselective lithiation with *sec*-butyllithium and (−)-sparteine followed by reaction with a range of electrophiles.[1] This was the first example of high enantioselectivity in *sec*-butyllithium/(−)-sparteine-mediated asymmetric deprotonation.[2] A typical example is shown in Scheme 1. Thus, treatment of *O*-alkyl carbamate **1** with 1.4 equivalents of *sec*-butyllithium/(−)-sparteine in diethyl ether at −78 °C for five hours followed by electrophilic trapping with carbon dioxide and work-up gave acid (*R*)-**2** of >95% ee (75% isolated yield). The reaction was shown to proceed *via* a highly enantioselective lithiation process to give configurationally stable organolithium intermediate **3** which was subsequently trapped with retention of configuration. In a recent report,[3] Würthwein and Hoppe studied *O*-alkyl carbamate lithiation using quantum chemical DFT calculations at the B3LYP/6-31G(d) level and found good agreement between experiment and theory for the preferred abstraction of the *pro-S* proton of *O*-alkyl carbamates such as **1** using alkyllithiums/(−)-sparteine.

Since Hoppe's disclosure of the asymmetric deprotonation of *O*-alkyl carbamates using *sec*-butyllithium/(−)-sparteine, its generality and synthetic utility have been amply demonstrated (Fig. 1). For example, Hoppe and co-workers reported a concise synthesis of (*S*)-1-methyldodecyl acetate **4**,[4] a pheromone of *Drosophila mulleri*, as well as developing routes to (*R*)-pantolactone **5**[5] and protected cyclopropanols such as **6**.[5,6] Over the years, the Hoppe group has comprehensively studied many aspects of selectivity (*e.g.* match/mismatch effects) in a wide range of *O*-alkyl carbamates.[2]



Scheme 1

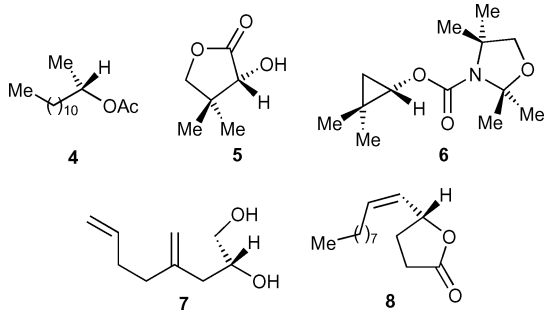


Fig. 1 Synthetic applications of Hoppe's *O*-alkyl carbamate methodology.

These studies have included new routes to chiral amino alcohols[7] and the asymmetric deprotonation reactions have been combined with intramolecular carbolithiation onto alkenes and alkynes.[8] Not surprisingly, other groups have also utilised the methodology. As a representative example, Menges and Brückner reported the preparation of diol **7** as a key building block in a projected synthesis of an algae nonaether from *Tolypothrix conglutinata*.[9] Most recently, there have been several reports of transmetallating the organolithium (*e.g.* **3**) to other metals thus opening up new electrophilic trapping opportunities. For example, transmetallation of organolithiums to the corresponding organocopper reagents

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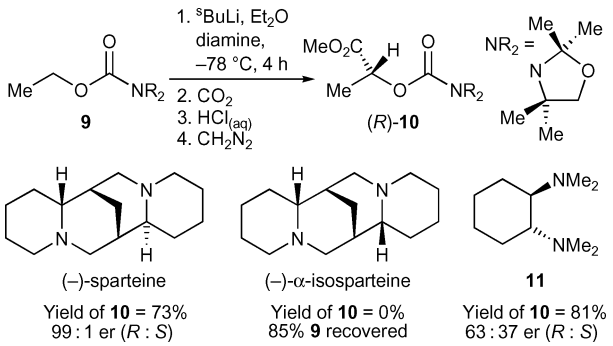
was independently developed by Taylor,[10] Dieter,[11] Nakai[12] and Kocienski[13] and, using such an approach, Papillon and Taylor developed an asymmetric synthesis of (*R*)-japonilure **8** in which an enantioenriched organocopper reagent was trapped with decynyl bromide.[10] In a further significant development, Hoppe *et al.* reported an elegant route to secondary alcohols *via* initial boronate trapping and subsequent homologation of the intermediate alkylboranates with Grignard reagents.[14]

To date, there has been limited investigation of other chiral ligands in the asymmetric lithiation of *O*-alkyl carbamates. This presumably reflects the commercial availability of (−)-sparteine and the fact that *sec*-butyllithium/(−)-sparteine induces such high enantioselectivity in these reactions. Indeed, as far as we are aware, there has been only one report of ligand variation in the asymmetric deprotonation of *O*-alkyl carbamates (Scheme 2).[15] Würthwein, Behrens and Hoppe investigated lithiation–trapping of *O*-alkyl carbamate **9** using *sec*-butyllithium and each of (−)-sparteine, (−)-α-isosparteine and cyclohexane diamine **11**. (−)-Sparteine gave adduct (*R*)-**10** with the highest enantioselectivity (99 : 1 er). Diamine **11** promoted lithiation such that a high yield (81%) of adduct (*R*)-**10** was obtained but the enantioselectivity was modest (63 : 37 er). In contrast, use of the sterically more hindered (−)-α-isosparteine did not generate any of adduct **10**. The reduced reactivity of *sec*-butyllithium/(−)-α-isosparteine compared to (−)-sparteine has been noted with other related deprotonation reactions (*e.g. N*-Boc pyrrolidine).[16] Furthermore, if the methyl substituent of the *O*-alkyl carbamate in **9** was changed to a more sterically demanding group (*e.g. iso*-propyl or *tert*-butyl), the yield of the α-substituted adduct decreased significantly using (−)-sparteine. With these more sterically hindered *O*-alkyl carbamates, the "slimmer" diamine **11** gave much higher yields of the adducts (and improved ers up to 89.5 : 10.5) compared to (−)-sparteine.



Scheme 2

One limitation of Hoppe's *O*-alkyl carbamate methodology is the fact that sparteine is only commercially available as its (−)-antipode. Although it is possible to change the order in which substituents are introduced using the (−)-sparteine-mediated reactions as a way of accessing each enantiomer of a product, we have focused our attention on developing a (+)-sparteine surrogate. Thus, over the last few years, our group has been active in the development and evaluation of a series of (+)-sparteine surrogates **12**–**16** (Fig. 2).[17–22]

Diamines **12**–**16** can be readily prepared in three steps from (−)-cytisine, itself extracted from *Laburnum anagyroides* seeds.[23]

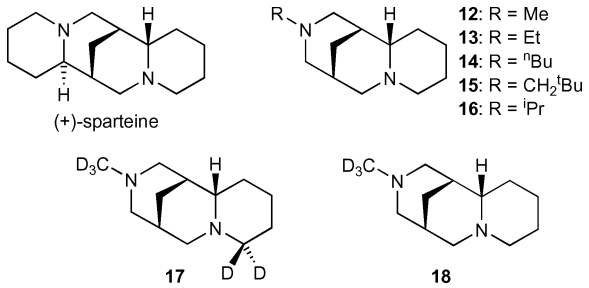


Fig. 2 The (+)-sparteine surrogates.

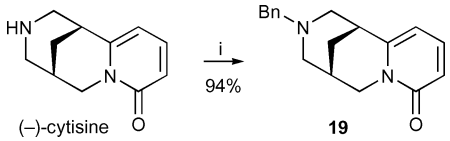
Results from our group indicate that, in three different reactions, diamines **12** (*N*-methyl) and **13** (*N*-ethyl) are comparable and they each behave in an enantiocomplementary fashion to (−)-sparteine.[20,21] Similar results have been reported by Kann *et al.* for lithiation of phosphine boranes[24,25] and by Wilkinson *et al.* for some benzylic functionalisation reactions.[26] However, as the steric hindrance of the *N*-alkyl group in the diamines was increased (*e.g.* **14**–**16**), the yield and enantioselectivity generally decreased. This was particularly pronounced in the asymmetric lithiation of *N*-Boc pyrrolidine where use of *sec*-butyllithium/diamine **16** (*N*-*iso*-propyl) gave no product after electrophilic trapping.[21]

To show that either enantiomer of α-substituted *O*-alkyl carbamates could be accessed using Hoppe's methodology simply by switching the ligand from (−)-sparteine to one of the (+)-sparteine surrogates and to provide additional ligand variation results for comparison with the one previous study,[15] we decided to investigate a representative *O*-alkyl carbamate asymmetric lithiation reaction using *sec*-butyllithium and diamines **12**–**16**. As part of this study, we included new deuterated diamines **17** and **18**. In our previous study on *N*-Boc pyrrolidine,[21] it appeared that the sterically small *N*-methyl group in diamine **12** was optimal for high enantioselectivity. Since a CD_3 group is even smaller in size, we speculated that the *N*-CD_3-substituted diamines **17** and **18** might show improved enantioselectivity to that obtained with the other diamines. Herein, we report the results of this study.

Results and discussion

Synthesis of (+)-sparteine surrogates

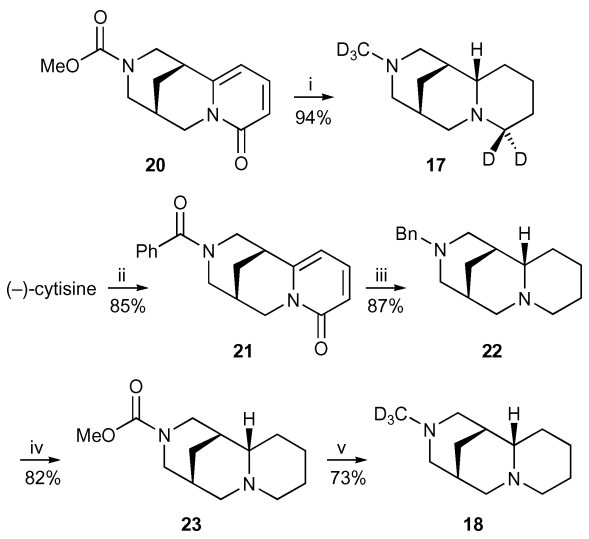
Diamines **12**–**16** were prepared starting from extracted (−)-cytisine using the procedures previously described.[19–21,25] We also report here an accurate determination of the %ee of (−)-cytisine *via* chiral HPLC of *N*-benzyl cytisine **19** (prepared in 94% yield from (−)-cytisine, Scheme 3). Thus, racemic *N*-benzyl cytisine **19**, prepared using our new route,[27] showed two well-resolved peaks on a Chiralcel OD column. In contrast, *N*-benzyl cytisine **19** synthesied from (−)-cytisine (obtained by extraction form *Laburnum anagyroides* seeds) showed only one peak under identical HPLC conditions (see Experimental). This



Scheme 3 Reagents and conditions: (i) K_2CO_3, BnBr, MeCN, reflux, 5 h.

establishes that extracted (−)-cytisine is of >99 : 1 er. Previously, we have shown that diamine **12** was of high %ee using ^{1}H NMR spectroscopy in the presence of a chiral shift reagent ((*R*)- and (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol)).[18,19] As detailed in the Experimental section, quantitative chiral shift NMR experiments have been carried out to demonstrate that diamine **12** is of ≥98 : 2 er. Taking the chiral HPLC and chiral shift NMR experiments together with the fact that all (−)-cytisine-derived diamines are obtained as single diastereomers, we conclude that all (+)-sparteine surrogates synthesised from extracted (−)-cytisine are of ≥98 : 2 er.

Next, we synthesised the two new deuterated diamines **17** and **18**. For **17**, a simple modification of the published route to the *N*-methyl diamine **12** was all that was required. Hence, methyl carbamate **20** (prepared from the reaction of (−)-cytisine with methyl chloroformate) was hydrogenated and then reduced using lithium aluminium deuteride to directly give pentadeuterated diamine **17** in 94% yield over the two steps (Scheme 4). Successful incorporation of the expected CD_2 and CD_3 groups was established by HRMS and ^{13}C NMR spectroscopy: δ_C 56.6 (quin, *J* 21.0, CD_2N) and 46.8–45.8 (m, NCD_3). The synthesis of trideuterated diamine **18** required a modified strategy and a more convoluted synthetic sequence (Scheme 4). Firstly, *N*-benzyl diamine **22**[25] was prepared in good yield using the standard three-step route (benzoylation of (−)-cytisine followed by hydrogenation–lithium aluminium hydride reduction). Then, *N*-benzyl hydrogenolysis was achieved using transfer hydrogenation, a method we have found particularly successful for *N*-benzyl amines that are resistant to other typical hydrogenolysis conditions, and subsequent reaction with methyl chloroformate gave methyl carbamate **23** (82% over two steps). A final lithium aluminium deuteride reduction furnished us with the desired diamine **18** in 73% yield. In this case, the presence of only a CD_3 group was verified by HRMS and ^{13}C NMR spectroscopy: δ_C 46.8–45.8 (m, NCD_3). With a range of diamines in hand, we were now ready to evaluate them in comparison with (−)-sparteine

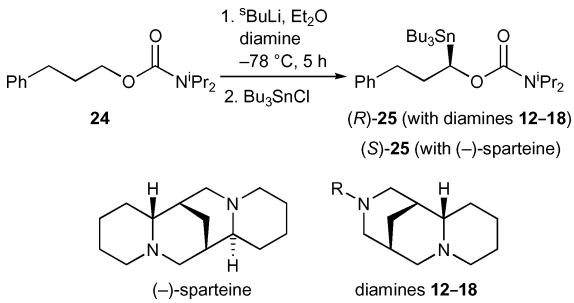


Scheme 4 Reagents and conditions: (i) (a) PtO_2, H_2, MeOH, rt, 12 h; (b) $LiAlD_4$, THF, reflux, 16 h; (ii) Et_3N, PhCOCl, CH_2Cl_2, rt, 5 h; (iii) (a) PtO_2, H_2, MeOH, rt, 12 h; (b) $LiAlH_4$, THF, reflux, 16 h.; (iv) (a) $Pd(OH)_2/C$, $NH_4^+HCO_2^-$, EtOH, reflux, 2 h; (b) Et_3N, MeO_2CCl, CH_2Cl_2, rt, 16 h; (v) $LiAlD_4$, THF, reflux, 16 h.

in the asymmetric lithiation-electrophilic trapping of an *O*-alkyl carbamate.

Evaluation of diamines in lithiation of an *O*-alkyl carbamate

To evaluate (−)-sparteine and diamines **12**–**18** in the lithiation–trapping of an *O*-alkyl carbamate, we selected the conversion of *O*-alkyl carbamate **24** (obtained from 3-phenylpropanol[28]) into α-stannylated carbamate **25**[29] since analysis of the product by chiral HPLC was well-described. In addition, α-stannylated carbamate **25** is a useful synthetic building block since tin–lithium exchange (with or without subsequent transmetallation) allows further elaboration. The conversion of *O*-alkyl carbamate **24** into **25** was originally reported by Nakai *et al.* and was used by us to demonstrate the effectiveness of diamine **12** as a (+)-sparteine surrogate.[18] The results obtained for the evaluation of (−)-sparteine and diamines **12**–**18** are summarised in Table 1 (Scheme 5).



Scheme 5

Typical reaction conditions for the lithiation–electrophilic trapping involve deprotonation using 1.4 equiv. of *sec*-butyllithium/diamine in diethyl ether for 5 h followed by trapping with tributyltin chloride. Subsequent work-up and chromatography afforded adduct (*R*)- or (*S*)-**25** in 17–84% yields with different enantioselectivity (Table 1). When the reaction was conducted with *sec*-butyllithium (no diamine ligand), a 17% yield of *racemic* adduct **25** (Entry 1) was obtained showing that uncomplexed *sec*-butyllithium does lead to some lithiation of *O*-alkyl carbamate **24**. As expected, reaction in the presence of (−)-sparteine gave adduct (*S*)-**25** in high yield (73%) and an impressive 99 : 1 er (Entry 2). This clearly demonstrates that (−)-sparteine complexes the

Table 1 Lithiation–trapping of *O*-alkyl carbamate **24** using (−)-sparteine and diamines **12**–**18**

Entry	Diamine	R	Yield (%)[a]	Er (*R* : *S*)[b]
1	—	—	17	—
2	(−)-sp	—	73	1 : 99
3	(−)-sp[c]	—	17	15 : 85
4	**12**	Me	84[d]	95 : 5
5	**17**	CD_3[e]	82	96 : 4
6	**18**	CD_3	68	96 : 4
7	**13**	Et	64	95 : 5
8	**14**	^{n}Bu	72	91 : 9
9	**15**	^{i}Pr	55[f]	86 : 14
10	**16**	^{t}BuCH$_2$	18	54 : 46

[a] Isolated yield after chromatography. [b] Er determined by chiral HPLC. [c] Reaction carried out using 0.2 equiv. (−)-sparteine only. [d] Reference 18. [e] Diamine also contains a CD_2 group. [f] 36% starting material also isolated.

sec-butyllithium and activates it for lithiation of **24**. An attempt at asymmetric catalysis using sub-stoichiometric (−)-sparteine (0.2 equiv.) was not successful (Entry 3): adduct (*S*)-**25** was obtained in only 17% yield with reduced er (85 : 15). The yield suggests that after the initial lithiation, (−)-sparteine does not dissociate from the lithiated carbamate complex (analogous to **3** in Scheme 1) and is therefore not available to activate more *sec*-butyllithium for deprotonation. Instead, some unselective deprotonation by uncomplexed *sec*-butyllithium presumably occurs to account for the reduced enantioselectivity. A similar effect has been noted by Hoppe with other *O*-alkyl carbamates[30] and by Beak and co-workers in the asymmetric deprotonation of *N*-Boc pyrrolidine.[31]

When the same reaction was carried out with (+)-sparteine surrogates **12** (*N*-methyl), **13** (*N*-ethyl) and **14** (*N*-*n*-butyl), as well as the new deuterated diamines **17** and **18**, good yields (64–84%) and high enantioselectivity (>90 : 10 er) in the opposite sense to that obtained with (−)-sparteine were obtained (entries 4–7). There was essentially no difference between the *N*-methyl diamine **12** (entry 4) and the deuterated diamines **17** and **18** (entries 5 and 6). The most sterically hindered *N*-alkyl substituents gave the worst results in terms of yield and enantioselectivity (entries 9 and 10). Although this is the same general trend that we had previously observed in the lithiation–trapping of *N*-Boc pyrrolidine,[21] there are some important differences. The *N*-*iso*-propyl diamine **15** behaved far better than expected in the lithiation of *O*-alkyl carbamate **24**: adduct (*R*)-**25** of 86 : 14 er was generated in 55% yield. In contrast, lithiation trapping of *N*-Boc pyrrolidine using *sec*-butyllithium/diamine **15** gave no product whatsoever. For the *N*-$CH_2{}^t$Bu diamine **16**, enantioselectivity was similarly poor for the *O*-alkyl carbamate reaction (54 : 46 er, entry 1) and the *N*-Boc pyrrolidine reaction (51 : 49 er) but the yield was higher with *N*-Boc pyrrolidine. To date, we have been unable to rationalise the subtle differences between the *N*-Boc pyrrolidine and *O*-alkyl carbamate results even on inspection of the calculated transition state models that have recently been disclosed.[3,21,32]

Conclusion

Using the diamine-mediated enantioselective lithiation-trapping of *O*-alkyl carbamate **24** as a representative example, some important conclusions can be drawn. First of all, (−)-sparteine remains unrivalled in its ability to induce near-perfect enantioselectivity (Table 1, entry 2). Secondly, the *O*-alkyl carbamate lithiation is far more tolerant of ligand structure than the corresponding *N*-Boc pyrrolidine lithiation, with a range of diamines (**12**, **13**, **14**, **17** and **18**) producing >90 : 10 er. Thirdly, the readily accessible *N*-methyl diamine **12** and *N*-CD_3-substituted diamine **17** are the optimum (+)-sparteine surrogate producing the highest yields and enantioselectivity (Table 1, entries 4 and 5). Finally, as the steric hindrance of the *N*-alkyl substituent increased, the enantioselectivity was lowered (Entries 9–10). This is the same broad trend as previously noted in our *N*-Boc pyrrolidine study[21] although the results are not perfectly in line. Indeed, the *O*-alkyl carabamate results presented here are more reminiscent of those observed by Kann *et al.* for the lithiation–trapping of phosphine–boranes[25] in that the sterically hindered *N*-*iso*-propyl diamine **15** gives satisfactory yield and high enantioselectivity. Thus, it appears that lithiation of *N*-Boc pyrrolidine is far more sensitive to ligand structure than lithiation of *O*-alkyl carbamates. In summary, this ligand variation study emphasises that either enantiomer of α-substituted *O*-alkyl carbamates can be obtained by asymmetric deprotonation using (−)-sparteine and (+)-sparteine surrogate **12**.

Experimental

General

General details have been described previously.[19] (−)-Cytisine was extracted from *Cytisus* (*Laburnum anagyroides*) seeds (from Vilmorin, France) using the published procedure[23] and as described elsewhere.[18,19] Methyl carbamate **20**,[19] diamines **12**,[19] **13**,[20] **14**,[20] **15**[20] and **16**[21,25] and *N*,*N*-diisopropylcarbamoyl-3-phenylpropanol **24**[28] were synthesised using the published procedures. For Kugelrohr distillation, the temperatures quoted correspond to the oven temperatures. Chiral stationary phase HPLC was performed on a Gilson system with 712 controller software and a 118 UV/Vis diode array detector.

(1*R*,9*R*)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one (19). A stirred suspension of (−)-cytisine (100 mg, 0.52 mmol), benzyl bromide (0.14 cm^3, 1.04 mmol) and K_2CO_3 (380 mg, 2.60 mmol) in MeCN (3 cm^3) was heated at reflux under N_2 for 5 h. After cooling to rt, the solvent was evaporated under reduced pressure and CH_2Cl_2 (10 cm^3) was added to the residue. The solids were removed by filtration through Celite and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash chromatography with CH_2Cl_2–MeOH (97 : 3) as eluent gave *N*-benzyl cytisine **19** (137 mg, 94%, >99 : 1 er by chiral HPLC) as a white solid, mp 139–141 °C (lit.,[33] 143–145); R_F (9 : 1 CH_2Cl_2–MeOH) 0.6; $[\alpha]_D$ −302 (*c* 0.5 in $CHCl_3$) (lit.,[33] +216 (*c* 0.42 in $CHCl_3$) for (1*S*,9*S*)-**19**). Spectroscopic data identical to that reported in the literature.[33] HPLC: Chiralcel OD, 20% ^{i}PrOH in heptane containing 0.1% Et_2NH, 0.5 cm^3 min^{-1}, 254 nm, 18 min [(1*R*,9*R*)-**19**]. Under the same conditions, a sample of *rac*-**19**[27] showed two peaks: 18 min [(1*R*,9*R*)-**19**] and 23 min [(1*S*,9*S*)-**19**].

Analysis of enantiomer ratio (er) of diamine 12 using ^{1}H NMR spectroscopy in the presence of (*R*)- and (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a chiral shift reagent. The enantiomer ratio (er) was determined by ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 3 equiv. of (*R*)- or (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol). A 0.12 M solution of diamine **12** in $CDCl_3$ was prepared by dissolving diamine **12** (46 mg, 0.24 mmol) in $CDCl_3$ (2 cm^3); a 0.06 M solution of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) was prepared by dissolving (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) (33 mg, 0.12 mmol) in $CDCl_3$ (2 cm^3). The sample for ^{1}H NMR spectroscopy analysis was then prepared using 0.05 cm^3 of the 0.12 M of the diamine in $CDCl_3$ (0.006 mmol), 0.30 cm^3 of the 0.06 M solution of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) in $CDCl_3$ (0.018 mmol, 3 equiv.) and 0.15 cm^3 of $CDCl_3$ (total volume of NMR sample = 0.5 cm^3). Key signals: δ_H(400 MHz; $CDCl_3$) 2.95 (1 H, br d, *J* 11.0), 2.85 (1 H, br d, *J* 11.0), 2.64 (1 H, br s), 2.50 (1 H, br s) and 2.11 (3 H, s). In a similar way, a sample for ^{1}H NMR spectroscopy analysis was prepared using 0.05 cm^3 of the 0.12 M of the diamine in $CDCl_3$ (0006 mmol), 0.30 cm^3 of a 0.06 M solution of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) in $CDCl_3$ (0.018 mmol, 3 equiv.) and 0.15 cm^3 of $CDCl_3$ (total volume of NMR sample = 0.5 cm^3).

Key signals: δ_H (400 MHz; $CDCl_3$) 2.93 (1 H, br d, *J* 11.0), 2.85–2.62 (2 H, m) and 1.96 (3 H, s). The absence of any signals due to the other diastereomeric complex in each of these ^{1}H NMR spectra indicates that diamine **12** is ≥98 : 2 er.

(1*R*,2*S*,9*S*)-*d*^{5}-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (17). A suspension of methyl carbamate **20** (1.37 g, 5.5 mmol) and PtO_2 (150 mg, 0.66 mmol) in MeOH (20 cm^3) was stirred at rt under a H_2 atmosphere (balloon) for 12 h. The solids were removed by filtration through Celite and the filter cake was washed with CH_2Cl_2 (100 cm^3). The filtrate was evaporated under reduced pressure to give the crude product as a white solid. A solution of this crude product in THF (20 cm^3) was added dropwise to a stirred suspension of $LiAlD_4$ (1.30 g, 31.0 mmol) in THF (40 cm^3) at 0 °C under N_2. The resulting suspension was stirred and heated at reflux for 16 h. After cooling to 0 °C, Et_2O (10 cm^3) was added followed by the portionwise addition (CARE) of solid hydrated Na_2SO_4 until effervescence ceased. The solids were removed by filtration through Celite and the filter cake was washed with CH_2Cl_2 (100 cm^3). The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave pentadeuterated diamine **17** (927 mg, 84%) as a colourless oil, bp 170–175 °C/3.5 mmHg; $[\alpha]_D$ +26.7 (*c* 1.1 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2220 (C–D), 2170 (C–D) and 2015 (C–D); δ_H(400 MHz; $CDCl_3$) 3.02–2.90 (2 H, m), 2.86 (1 H, d, *J* 11.0), 2.22 (1 H, ddd, *J* 11.0, 3.5 and 2.5), 2.12 (1 H, ddd, *J* 11.0, 3.5 and 2.5), 1.94 (1 H, dd, *J* 11.5, 3.0), 1.88 (1 H, d, *J* 11.0), 1.83–1.77 (1 H, m), 1.76–1.58 (3 H, m), 1.58–1.41 (4 H, m) and 1.34–1.18 (2 H, m); δ_C(100.6 MHz; $CDCl_3$) 66.2 (CHN), 60.2 (CH_2N), 60.1 (CH_2N), 56.6 (quin, *J* 21.0, CD_2N), 56.0 (CH_2N), 46.8–45.8 (m, NCD_3), 35.0 (CH), 33.8 (CH_2), 30.6 (CH_2), 30.4 (CH), 25.2 (CH_2) and 24.9 (CH_2); *m*/*z* (CI; NH_3) 200 [100%, $(M + H)^+$][Found: $(M + H)^+$, 200.2169. $C_{12}H_{17}D_5N_2$ requires *M* + H, 200.2175].

(1*S*,9*S*)-11-Benzoyl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one (21). Benzoyl chloride (4.3 cm^3, 36.8 mmol) was added dropwise over 10 min to a stirred solution of (−)-cytisine (700 mg, 3.68 mmol) and Et_3N (5.1 cm^3, 36.8 mmol) in CH_2Cl_2 (15 cm^3) at 0 °C under N_2. After stirring for 5 h at rt, the solvent was evaporated under reduced pressure. EtOAc (10 cm^3) was added to the residue and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2–MeOH (9 : 1) as eluent gave *N*-benzoyl pyridone **21** (919 mg, 85%) as a white solid, mp 184–188 °C (lit.,[34] 193); $[\alpha]_D$ −277.0 (*c* 1.0 in $CHCl_3$)(lit.,[34] −277.9 (*c* 1.0 in $CHCl_3$)). Spectroscopic data were identical to that reported in the literature.[34]

(1*R*,2*S*,9*S*)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (22). A suspension of *N*-benzoyl pyridone **21** (3.60 g, 12.2 mmol) and PtO_2 (250 mg, 1.1 mmol) in MeOH (30 cm^3) was stirred at rt under a H_2 atmosphere (balloon) for 12 h. The solids were removed by filtration through Celite and the filter cake was washed with CH_2Cl_2 (100 cm^3). The filtrate was evaporated under reduced pressure to give the crude product as a yellow oil. A solution of this crude product in THF (50 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (2.60 g, 67.0 mmol) in THF (100 cm^3) at 0 °C under N_2. The resulting suspension was stirred and heated at reflux for 16 h. After cooling to 0 °C, Et_2O (20 cm^3) was added followed by the portionwise addition (CARE) of solid hydrated Na_2SO_4 until effervescence ceased. The solids were removed by filtration through Celite and the filter cake was washed with CH_2Cl_2 (150 cm^3). The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave *N*-benzyl diamine **22** (2.70 g, 87%) as a colourless oil, bp 210–220 °C/2.5 mmHg (lit.,[25] 180–190 °C/6 mmHg); $[\alpha]_D$ +38.0 (*c* 1.1 in $CHCl_3$)(lit.,[25] +44.6 (*c* 2.79 in $CHCl_3$)). Spectroscopic data were identical to that reported in the literature.[25]

(1*R*,2*S*,9*R*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane 11-carboxylate (23). A stirred solution of *N*-benzyl diamine **22** (1.80 g, 6.65 mmol) and $NH_4^+HCO_2^-$ (1.30 g, 20.0 mmol) in EtOH (25 cm^3) under N_2 was heated at reflux. Then, 10 mol % $Pd(OH)_2$ on C (500 mg, 4.0 mmol) was added in one portion and the resulting suspension was heated at reflux for 2 h. After cooling to rt, the solids were removed by filtration through Celite and the filter cake was washed with Et_2O (50 cm^3). 2 M $NH_4OH_{(aq)}$ (30 cm^3) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 cm^3) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. To a stirred solution of this crude product in CH_2Cl_2 (25 cm^3) at 0 °C under N_2 was added Et_3N (1.0 cm^3, 7.3 mmol) and then methyl chloroformate (0.6 cm^3, 7.3 mmol). After stirring for 16 h at rt, the solvent was evaporated under reduced pressure. EtOAc (10 cm^3) was added to the residue and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane–EtOAc (1 : 1) as eluent gave methyl carbamate **23** (1.32 g, 82%) as a yellow oil, R_F (9 : 1 CH_2Cl_2–MeOH) 0.9; $[\alpha]_D$ +21.2 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (C=O); δ_H(400 MHz; $CDCl_3$) approx. 60 : 40 mixture of rotamers: 4.44 (0.6 H, br d, *J* 13.5), 4.33–4.24 (1 H, m), 4.10 (0.4 H, br d, *J* 13.5), 3.70 (1.8 H, s, MeO), 3.66 (1.2 H, s, MeO), 3.06 (0.4 H, br d, *J* 13.0), 2.98 (0.6 H, br d, *J* 13.0), 2.88 (1.2 H, br d, *J* 12.5), 2.81 (0.8 H, br d, *J* 12.5), 2.68 (0.6 H, br d, *J* 11.0), 2.62 (0.4 H, br d, *J* 11.0), 2.29–2.18 (1 H, m) and 1.98–1.13 (12 H, m); δ_C(100.6 MHz; $CDCl_3$) approx. 60 : 40 mixture of rotamers: 156.4 (C=O), 65.5 (CHN), 61.1 and 60.8 (CH_2N), 57.2 and 57.0 (CH_2N), 52.3 and 52.1 (OMe), 48.9 and 48.8 (CH_2N), 44.9 and 44.6 (CH_2N), 34.5 (CH), 34.1 (CH_2), 30.5 (CH_2), 29.6 and 29.4 (CH), 25.9 and 25.7 (CH_2) and 24.9 (CH_2); *m*/*z* (CI; NH_3) 239 [100%, $(M + H)^+$][Found: $(M + H)^+$, 239.1760. $C_{13}H_{22}N_2O_2$ requires *M* + H, 239.1760].

(1*R*,2*S*,9*S*)-*d*^{3}-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (18). A solution of methyl carbamate **23** (1.30 g, 5.8 mmol) in THF (20 cm^3) was added dropwise to a stirred suspension of $LiAlD_4$ (1.30 g, 31.0 mmol) in THF (30 cm^3) at 0 °C under N_2. The resulting suspension was stirred and heated at reflux for 16 h. After cooling to 0 °C, Et_2O (10 cm^3) was added followed by the portionwise addition (CARE) of solid hydrated Na_2SO_4 until effervescence ceased. The solids were removed by filtration through Celite and the filter cake was washed with CH_2Cl_2 (100 cm^3). The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave trideuterated diamine **18** (800 mg, 73%) as a colourless oil, bp 170–180 °C/3 mmHg; $[\alpha]_D$ +27.7

(*c* 1.1 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2220 (C–D), 2170 (C–D) and 2015 (C–D); δ_H(400 MHz; $CDCl_3$) 3.00 (2 H, t, *J* 11.0), 2.90 (1 H, br d, *J* 11.5), 2.86 (1 H, br d, *J* 11.5), 2.25 (1 H, ddd, *J* 11.0, 3.5 and 2.0), 2.16 (1 H, ddd, *J* 11.0, 3.5 and 2.0), 1.98 (1 H, dd, *J* 11.5, 3.0), 1.90 (1 H, d, *J* 11.0), 1.87–1.82 (1 H, m), 1.81–1.63 (3 H, m), 1.62–1.47 (5 H, m) and 1.38–1.19 (2 H, m); δ_C(100.6 MHz; $CDCl_3$) 66.2 (CHN), 60.3 (CH_2N), 60.2 (CH_2N), 57.5 (CH_2N), 56.0 (CH_2N), 46.8–45.8 (m, NCD_3), 35.0 (CH), 33.9 (CH_2), 30.7 (CH_2), 30.5 (CH), 25.5 (CH_2) and 25.0 (CH_2); *m*/*z* (CI; NH_3) 198 [100%, $(M + H)^+$][Found: $(M + H)^+$, 198.2046. $C_{12}H_{19}D_3N_2$ requires *M* + H, 198.2050].

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane (*rac*-25) (Table 1, entry 1). A solution of *O*-alkyl carbamate **24** (400 mg, 1.52 mmol) in Et_2O (2.0 cm^3) was added dropwise *via* a cannula to a stirred solution of *sec*-butyllithium (1.8 cm^3 of a 1.1 M solution in cyclohexane, 2.0 mmol) in Et_2O (4.0 cm^3) at −78 °C under Ar. After stirring for 5 h at −78 °C, Bu_3SnCl (0.54 cm^3, 2.0 mmol) was added and the solution was allowed to warm to rt over 16 h. Then, 2 M $HCl_{(aq)}$ (10 cm^3) was added, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were washed with saturated $KF_{(aq)}$ (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by flash chromatography using 40 : 1 petrol–Et_2O gave adduct *rac*-**25** (148 mg, 17%) as a colourless oil and starting *O*-alkyl carbamate **24** (230 mg, 58%) as a colourless oil. Spectroscopic data were identical to that reported in the literature.[29]

General procedure for asymmetric lithiation–trapping of *O*-alkyl carbamate (24). A solution of (−)-sparteine or diamine **12**–**18** (1.4 or 0.2 equiv.) in Et_2O (4.0 cm^3) was added dropwise *via* a cannula to a stirred solution of *sec*-butyllithium (1.2 M solution in cyclohexane, 1.4 equiv.) in Et_2O (4.0 cm^3) at −78 °C under Ar. After stirring for 10 min at −78 °C, a solution of *O*-alkyl carbamate **24** (503 mg, 1.8 mmol) in Et_2O (3.0 cm^3) was added dropwise over 10 min *via* a cannula and the resulting solution was stirred at −78 °C for 5 h. Then, Bu_3SnCl (1.4 equiv.) was added dropwise and the solution was allowed to warm to rt over 16 h. 2 M $HCl_{(aq)}$ (10 cm^3) and Et_2O (10 cm^3) were added, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 (10 cm^3)). The combined Et_2O extracts were washed with saturated $KF_{(aq)}$ (10 (10 cm^3)), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. The er was determined by chiral HPLC: Daicel Chiralcel OD, 600 : 1 *v*/*v* hexane–^{i}PrOH, 0.5 cm^3 min^{-1}, 226 nm, 6.5 min [(*S*)-**25**] 7.1 min [(*R*)-**25**].

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*S*)-25) (Table 1, entry 2). Using the general procedure, (−)-sparteine (576 mg, 2.46 mmol), *sec*-butyllithium (2.5 cm^3 of a 1.0 M solution in cyclohexane, 2.5 mmol), *O*-alkyl carbamate **24** (462 mg, 1.75 mmol) and Bu_3SnCl (0.68 cm^3, 2.5 mmol) in Et_2O (11 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*S*)-**25** (710 mg, 73%, 99 : 1 er by chiral HPLC) as a colourless oil, $[a]_D$ +22 (*c* 1.0 in $CHCl_3$)(lit.,[29] $[a]_D$ +21.9 (*c* 1.0 in $CHCl_3$) for (*S*)-**25** of 98.5 : 1.5 er). Spectroscopic data were consistent with that reported in the literature.[29]

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*S*)-25) (Table 1, entry 3). Using the general procedure, (−)-sparteine (184 mg, 0.786 mmol), *sec*-butyllithium (5.0 cm^3 of a 1.0 M solution in cyclohexane, 5.0 mmol), *O*-alkyl carbamate **24** (1.03 g, 3.9 mmol) and Bu_3SnCl (1.2 cm^3, 5.1 mmol) in Et_2O (11 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*S*)-**25** (365 mg, 17%, 85 : 15 er by chiral HPLC) as a colourless oil, $[a]_D$ +10.0 (*c* 1.0 in $CHCl_3$).

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane (*R*)-25 (Table 1, entry 5). Using the general procedure, diamine **17** (501 mg, 2.5 mmol), *sec*-butyllithium (2.5 cm^3 of a 1.0 M solution in cyclohexane, 2.5 mmol), *O*-alkyl carbamate **24** (487 mg, 1.8 mmol) and Bu_3SnCl (0.6 cm^3, 2.2 mmol) in Et_2O (9 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*R*)-**25** (820 mg, 82%, 96 : 4 er by chiral HPLC) as a colourless oil, $[a]_D$ −22.9 (*c* 1.0 in $CHCl_3$).

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*R*)-25) (Table 1, entry 6). Using the general procedure, diamine **18** (408 mg, 2.1 mmol), *sec*-butyllithium (1.7 cm^3 of a 1.2 M solution in cyclohexane, 2.1 mmol), *O*-alkyl carbamate **24** (407 mg, 1.5 mmol) and Bu_3SnCl (0.5 cm^3, 1.8 mmol) in Et_2O (9 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*R*)-**25** (630 mg, 68%, 96 : 4 er by chiral HPLC) as a colourless oil, $[a]_D$ −21.4 (*c* 1.3 in $CHCl_3$).

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*R*)-25) (Table 1, entry 7). Using the general procedure, diamine **13** (634 mg, 3.0 mmol), *sec*-butyllithium (2.9 cm^3 of a 1.0 M solution in cyclohexane, 2.9 mmol), *O*-alkyl carbamate **24** (572 mg, 2.2 mmol) and Bu_3SnCl (0.8 cm^3, 3.0 mmol) in Et_2O (10 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*R*)-**25** (768 mg, 64%, 95 : 5 er by chiral HPLC) as a colourless oil, $[a]_D$ −20.3 (*c* 0.8 in $CHCl_3$).

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*R*)-25) (Table 1, entry 8). Using the general procedure, diamine **14** (272 mg, 1.15 mmol), *sec*-butyllithium (1.0 cm^3 of a 1.15 M solution in cyclohexane, 1.15 mmol), *O*-alkyl carbamate **24** (218 mg, 0.8 mmol) and Bu_3SnCl (0.3 cm^3, 1.2 mmol) in Et_2O (9 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*R*)-**25** (332 mg, 72%, 91 : 9 er by chiral HPLC) as a colourless oil, $[a]_D$ −20.9 (*c* 1.0 in $CHCl_3$).

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*R*)-25) (Table 1, entry 9). Using the general procedure, diamine **15** (530 mg, 2.4 mmol), *sec*-butyllithium (2.4 cm^3 of a 1.0 M solution in cyclohexane, 2.4 mmol), *O*-alkyl carbamate **24** (442 mg, 1.7 mmol) and Bu_3SnCl (0.65 cm^3, 2.4 mmol) in Et_2O (10 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*R*)-**25** (513 mg, 55%, 86 : 14 er by chiral HPLC) as a colourless oil, $[a]_D$ −20.0 (*c* 1.1 in $CHCl_3$) and recovered *O*-alkyl carbamate **24** (160 mg, 36%) as a colourless oil.

3-Phenyl-1-tributyltin-1-*N*,*N*-diisopropylcarbamoyloxypropane ((*R*)-25) (Table 1, entry 10). Using the general procedure, diamine **16** (463 mg, 1.8 mmol), *sec*-butyllithium (1.8 cm^3 of a 1.0 M

solution in cyclohexane, 1.8 mmol), *O*-alkyl carbamate **24** (345 mg, 1.3 mmol) and Bu_3SnCl (0.4 cm^3, 1.5 mmol) in Et_2O (9 cm^3) gave the crude product. Purification by flash column chromatography using 40 : 1 petrol–Et_2O as eluent gave adduct (*R*)-**25** (135 mg, 18%, 54 : 46 er by chiral HPLC) as a colourless oil, $[\alpha]_D$ −2.6 (*c* 1.0 in $CHCl_3$).

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