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Solution phase structures of enantiopure and racemic lithium *N*-benzyl-*N*-(α-methylbenzyl)amide in THF: low temperature ^{6}Li and ^{15}N NMR spectroscopic studies

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ABSTRACT

The antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide are highly efficient enantiopure ammonia equivalents for the asymmetric synthesis of β-amino acid derivatives via conjugate addition to α,β-unsaturated esters. ^{6}Li and ^{15}N NMR spectroscopic studies of doubly labelled ^{6}lithium (*S*)-^{15}*N*-benzyl-^{15}*N*-(α-methylbenzyl)amide in THF at low temperature reveal the presence of lithium amide dimers as the only observable species. Either a monomeric or dimeric lithium amide reactive species can be accommodated within the transition state mnemonic for this class of conjugate addition reaction. This enantiopure lithium amide offers unique opportunities over achiral (e.g., lithium dibenzylamide) and C_2-symmetric (e.g., lithium bis-*N*,*N*-α-methylbenzylamide) counterparts for further mechanistic study owing to the ready distinction of the various dimers formed.

1. Introduction

Achiral lithium amides such as lithium diisopropylamide (LDA),[1] lithium hexamethyldisilylazide (LiHMDS) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP)[2] are ubiquitous throughout organic chemistry as strong, non-nucleophilic bases. Chiral lithium amides, meanwhile, have been employed to promote a range of enantioselective reactions[3] including nucleophilic additions to prochiral carbonyl compounds,[4] aldol reactions,[5] rearrangements,[6] and desymmetrisations.[7] As a result of these applications, a considerable amount of research has been directed towards understanding the structures (and thence reactivities) of both achiral and chiral lithium amides both in solution and the solid state, with solvent, exchange of lithium for another alkali metal, lithium solvating additives and the presence of salts all having been shown to play a defining role in the structure and reactivity of lithium amides.[8] For example, LDA in THF has been shown to exist as a disolvated dimer over a range of concentrations.[9]

We have pioneered the use of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide as enantiopure ammonia equivalents for diastereoselective conjugate additions to α,β-unsaturated esters and amides.[10,11] Based upon molecular modelling calculations, we have proposed a transition state mnemonic to rationalise and reliably predict the stereochemical outcome for this class of reaction, with either a monomeric or dimeric lithium amide reactive species being accommodated within these calculations.[12] Henderson et al.[13] and Andrews et al.[14] have independently shown that enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide/THF complexes are dimeric in the solid state, whilst Koga et al. showed (by ^{6}Li and ^{15}N NMR spectroscopic analysis) that the related enantiopure (C_2-symmetric) lithium bis-*N*,*N*-α-methylbenzylamide is dimeric in solution in THF at low temperature.[15] In an effort to further facilitate understanding of the origin of asymmetric induction in our lithium amide conjugate addition reaction, we have examined the solution structure of both enantiopure and racemic lithium *N*-benzyl-*N*-(α-methylbenzyl)amide via ^{6}Li and ^{15}N NMR spectroscopic analyses of doubly labelled material,[16,17] and report the results of these studies herein.

2. Results and discussion

Initial studies were directed towards the development of an efficient asymmetric synthesis of enantiopure (*S*)-^{15}*N*-benzyl-^{15}*N*-(α-methylbenzyl)amine (*S*)-^{15}N-**7**. Following an established procedure,[18] acylation of L-valine derived SuperQuat **1**[19] with BnCOCl gave **2** in 97% yield. Treatment of **2** with LiHMDS followed by MeI gave **3** in 97:3 dr, which was isolated in 84% yield and >99:1 dr.[18] Hydrolysis of **3** was achieved using LiOH, which provided acid (*S*)-**4** in 98% yield and >98% ee. Addition of $^{15}NH_4Cl$ (98 atom % ^{15}N) to a solution of the acyl chloride derived from (*S*)-**4** under Schotten–Baumann conditions[20] gave amide (*S*)-^{15}N-**5** in 98% yield from (*S*)-**4** (or 94% yield from $^{15}NH_4Cl$).[21] Hoffman-type rearrangement of (*S*)-^{15}N-**5** upon treatment with $PhI(OCOCF_3)_2$ [prepared

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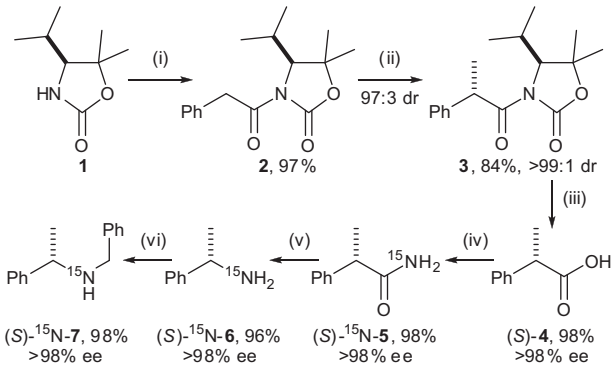
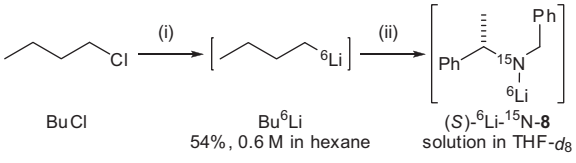


Scheme 1. *Reagents and conditions*: (i) BuLi, THF, −78 °C, 30 min, then BnCOCl, −78 °C to rt, 1 h; (ii) LiHMDS, THF, −78 °C, 30 min, then MeI, −78 °C to rt, 12 h; (iii) LiOH (2.0 M, aq), THF, rt, 12 h; (iv) $SOCl_2$, benzotriazole, CH_2Cl_2, 0 °C, 20 min, then $^{15}NH_4Cl$, Et_2O, NaOH (10 M, aq), 0 °C, 30 min; (v) $PhI(OCOCF_3)_2$, MeCN, H_2O, rt, 8 h; (vi) PhCHO, EtOH, reflux, 4 h, then $NaBH_4$, 0 °C to rt, 3 days.

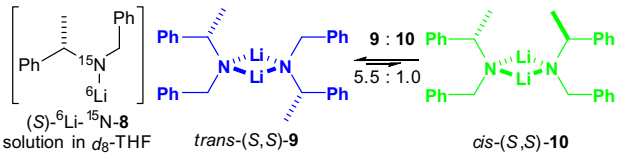
from $PhI(OAc)_2$ and F_3CCO_2H][22] gave (*S*)-^{15}N-**6** in 96% yield. Condensation of (*S*)-^{15}N-**6** with PhCHO in EtOH followed by treatment with $NaBH_4$ gave (*S*)-^{15}N-**7** in 98% yield, >98% ee,[23] and with >98% ^{15}N incorporation as determined by mass spectrometry (Scheme 1). The racemate (*RS*)-^{15}N-**7** was similarly prepared, in 93% overall yield and with >98% ^{15}N incorporation, starting from commercially available acid (*RS*)-**4**.

Bu^{6}Li was synthesised via sonication of BuCl and ^{6}Li chunks in hexane for 16 h; the resultant purple solution was then allowed to stand for two days at rt to allow precipitation of ^{6}LiCl. The clear solution was then decanted and filtered through flame-dried Celite® under an argon atmosphere.[24] Titration of the filtrate against diphenylacetic acid established the concentration of this solution of Bu^{6}Li as 0.6 M, indicating a 54% yield. Enantiopure lithium amide (*S*)-^{6}Li-^{15}N-**8** was prepared in situ, upon treatment of a solution of (*S*)-^{15}N-**7** in THF-d_8 in an NMR tube[25] with Bu^{6}Li, under an argon atmosphere using standard vacuum line techniques (Scheme 2). A similar procedure applied to (*RS*)-^{15}N-**7** gave a solution of racemic lithium amide (*RS*)-^{6}Li-^{15}N-**8** in THF-d_8.

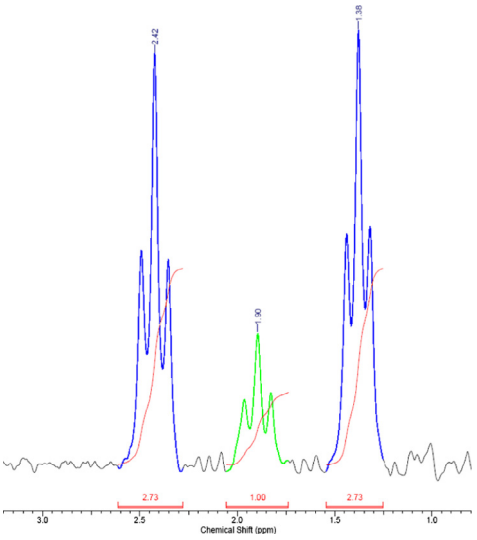
The analysis of (*S*)-^{6}Li-^{15}N-**8** by ^{6}Li NMR spectroscopy[17] at 173 K (−100 °C), showed the presence of three triplet peaks centred on δ_{Li} 1.38, 1.90 and 2.42 ppm (with associated coupling constants of 5.0, 5.0 and 4.4 Hz) in a respective 2.7:1.0:2.7 ratio, indicating the presence of three distinct environments for ^{6}Li nuclei. The triplet splitting pattern is consistent with each ^{6}Li nucleus directly coupling to two equivalent ^{15}N nuclei (for which $I = ½$), which suggests the presence of lithium amide dimers; no evidence for the existence of any other species was apparent. For enantiopure (*S*)-**8**, there exist two possible C_2-symmetric dimers, *trans*-(*S*,*S*)-**9** and *cis*-(*S*,*S*)-**10**. The former, *trans*-(*S*,*S*)-**9**, has the two Li nuclei in chemically and magnetically inequivalent environments, whilst the latter, *cis*-(*S*,*S*)-**10**, has both Li nuclei in chemically and magnetically equivalent environments. These data therefore suggest that the major species present in solution is dimer *trans*-(*S*,*S*)-**9**, and that the ratio of *trans*-(*S*,*S*)-**9** to *cis*-(*S*,*S*)-**10** is ~5.5:1. Both of the N nuclei in **9** and both of the N nuclei in **10** are in equivalent environments and thus, as expected, the ^{15}N NMR spectrum[17] of



Scheme 2. Reagents and conditions: (i) ^{6}Li chunks, hexane, rt, •))), 16 h, then rt, 2 days; (ii) (*S*)-^{15}N-**7**, THF-d_8, 0 °C then −78 °C.



(**A**) ^{6}Li NMR spectrum of (*S*)-^{6}Li-^{15}N-**8**.



(**B**) ^{15}N NMR spectrum of (*S*)-^{6}Li-^{15}N-**8**.

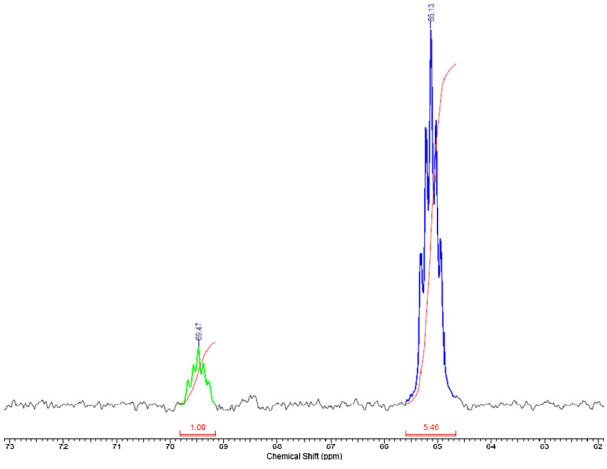


Figure 1. ^{6}Li and ^{15}N NMR spectra of (*S*)-^{6}Li-^{15}N-**8** at 173 K.

(*S*)-^{6}Li-^{15}N-**8** at 173 K comprised only two peaks of approximate quintet splitting ($4.4 < J_{NLi} < 5.0$ Hz), centred on δ_N 65.1 and 69.5 ppm, in a 5.5:1.0 ratio respectively. The relative intensities within the approximate quintets of 1:2:3:2:1 are consistent with each ^{15}N nucleus coupling to two ^{6}Li nuclei (for which $I = 1$), providing further support for the presence of dimers **9** and **10** (Fig. 1).

A ^{6}Li–^{6}Li EXSY indicated exchange between the 'inner' triplet (centred on δ_{Li} 1.90 ppm, corresponding to **10**) and both of the 'outer' triplets (centred on δ_{Li} 1.38 and 2.42 ppm, corresponding to **9**), although no exchange between the two triplet peaks associated with **9** was observed. This is indicative of equilibration of **9** and **10** occurring via a non-dissociative mechanism (i.e., ring-opening via a Li–N bond breaking process followed by rotation and ring-closure).[26] Direct exchange between the two triplet peaks associated with **9** would be observed if it were to fully dissociate and then reform, suggesting that this process is slow relative to the NMR timescale. Addition of 0.5 equiv of *tert*-butyl cinnamate

(in 0.1 equiv portions) to the solution of (*S*)-^{6}Li-^{15}N-**8**[27] produced no significant difference in the 5.5:1.0 ratio of **9** to **10**, again consistent with this being the equilibrium ratio but hence precluding any potential insight into the relative consumption of **9** versus **10** during the course of the conjugate addition reaction. Interestingly, however, two new doublet signals appeared in the ^{6}Li NMR spectrum (at δ_{Li} 0.35 and 1.36 ppm) as *tert*-butyl cinnamate was added; in the presence of 0.5 equiv of *tert*-butyl cinnamate these were the only detectable signals, suggesting that a 1:1 lithium β-amino (*Z*)-enolate/lithium amide complex (in which each ^{6}Li nucleus is connected to only one ^{15}N nucleus) had formed in preference to either of dimers **9** or **10** (Fig. 2).

Variable temperature ^{6}Li and ^{15}N NMR spectra (recorded between 173 K and 273 K, in 10 K intervals) revealed similar behaviour: peak broadening was initially noted, with eventual coalescence at approximately 223 K, consistent with much more rapid exchange at higher temperatures. A single peak was observed at 273 K and is attributed to the time averaged populations of ^{6}Li and ^{15}N nuclei in various oligomers at this temperature. It is noteworthy that the 5.5:1.0 ratio of **9** to **10** decreased before coalescence, indicating an increase in the population of **10** at higher temperatures: for example, at 193 K the ratio of **9** to **10** was 3.6:1.0. From these VT ^{6}Li NMR spectra it is possible to evaluate the approximate value of the free energy for the process that effects the coalescence of the two triplet peaks attributed to dimer **9**.[28] The Eyring equation may be written as:

$$\Delta G^{\ddagger} = \mathrm{RT}[ln(k_B T/k_c h)],$$

where T is the temperature of coalescence (in K), k_c is the rate of coalescence (in Hz), and the other symbols have their usual meanings.[29] An approximate value of k_c may be determined directly from the NMR spectrum as:

$$k_c = \Delta\delta_v(\pi/\sqrt{2}),$$

where $\Delta\delta_v$ is the difference in the chemical shifts of the two peaks in question (in Hz).[30] Taking the coalescence temperature as 223 K and the difference in the chemical shifts of the two triplet signals associated with **9** as 76.5 Hz, then $\Delta G^{\ddagger} \approx +45$ kJ mol^{-1}.[31]

Analysis of (*RS*)-^{6}Li-^{15}N-**8** by ^{6}Li NMR spectroscopy[17] at 173 K gave a more complex spectrum compared to that obtained from enantiopure (*S*)-^{6}Li-^{15}N-**8**. Not unexpectedly, signals associated with dimers *trans*-(*RS*,*RS*)-**9** and *cis*-(*RS*,*RS*)-**10**, comprising two lithium amide monomers with the same configuration, were present. However, for (*RS*)-^{6}Li-^{15}N-**8** there also exists the possibility of formation of dimers *cis*-(*RS*,*SR*)-**11** and *trans*-(*RS*,*SR*)-**12**, comprising two lithium amide monomers with opposite configurations. Subtraction of the ^{6}Li NMR spectrum of (*S*)-^{6}Li-^{15}N-**8** from that of (*RS*)-^{6}Li-^{15}N-**8** gave a spectrum containing three triplet peaks centred on δ_{Li} 1.37, 1.97 and 2.62 ppm in a respective 1:1:1 ratio; it was postulated that these signals arose due to the presence of dimers **11** and **12** (in a 2:1 ratio, respectively). A ^{6}Li–^{6}Li EXSY experiment indicated exchange between both of the 'outer' triplets and the 'inner' triplet, supporting the presence of **11** (with the Li nuclei in non-equivalent environments) which undergoes exchange via a non-dissociative mechanism with **12** (with the Li nuclei in equivalent environments). Direct exchange between the two triplet peaks associated with **11** was not observed and neither was there any evidence for exchange of **9** or **10** with **11** or **12**, again consistent with full dissociation and reformation of the various dimers being slow relative to the NMR timescale. The ^{15}N NMR spectrum[17] of (*RS*)-^{6}Li-^{15}N-**8** at 173 K revealed the presence of four, 1:2:3:2:1-quintet signals in the ratios 6.3:5.2:2.6:1.0. As before, two of these signals correspond to dimers *trans*-(*RS*,*RS*)-**9** and *cis*-(*RS*,*RS*)-**10**, in the ratio 6.3:1.0, whilst the 2:1 ratio of the other two signals compares favourably with the ratio of *cis*-(*RS*,*SR*)-**11** to *trans*-(*RS*,*SR*)-**12** obtained from the ^{6}Li NMR spectrum. From these data, it can be concluded that (*RS*)-^{6}Li-^{15}N-**8** exists as a mixture of all possible diastereoisomeric dimers **9**, **10**, **11** and **12** in the ratio 6.3:1.0:5.2:2.6, respectively. The ratio of **9** to **10** is 6.3:1.0 [in contrast to 5.5:1.0 observed for (*S*)-^{6}Li-^{15}N-**8**] and the ratio of **11** to **12** is 2.0:1.0, whilst the ratio of (**9** + **10**) to (**11** + **12**) is 1.0:1.1[32] (Fig. 3).

Variable temperature ^{6}Li and ^{15}N NMR spectroscopic analysis of (*RS*)-^{6}Li-^{15}N-**8** showed similar behaviour to that observed for (*S*)-^{6}Li-^{15}N-**8**, with initial line broadening and eventual coalescence being observed as the temperature of the sample was increased, consistent with an increased rate of exchange between dimers **9**–**12**. Empirical analysis also indicated a change in the dimer ratio at higher temperatures, consistent with a shift in the position of equilibrium. The simultaneous increase in the rate of exchange and shift in the position of equilibrium precluded calculation of the rates of exchange (and hence free energy of activation) from line-broadening analysis in this case.

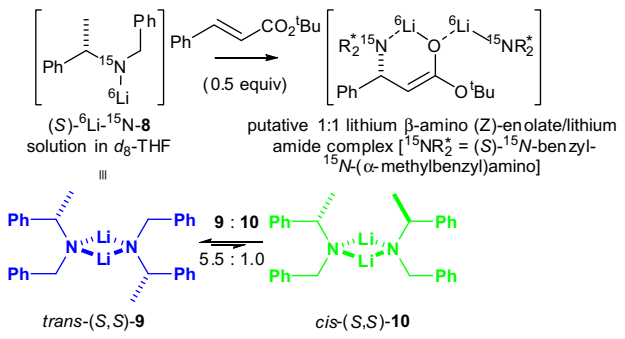


Figure 2. Addition of *tert*-butyl cinnamate to a solution of (*S*)-^{6}Li-^{15}N-**8**.

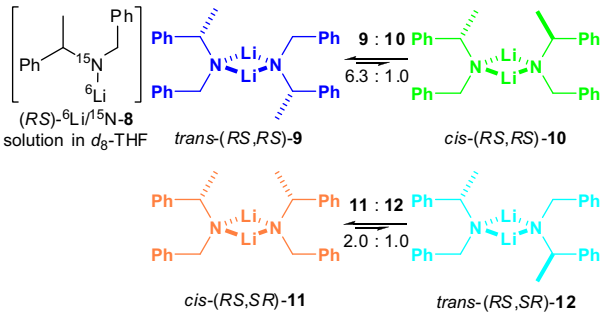
3. Conclusion

In conclusion, an efficient procedure for the synthesis of (*S*)-^{15}*N*-benzyl-^{15}*N*-(α-methylbenzyl)amine has been devised, starting from (*S*)-2-phenylpropanoic acid and using a Hoffman-type rearrangement as the key step. Deprotonation of a solution of this amine in THF-d_8 with Bu^{6}Li at low temperature gave a solution of the corresponding doubly labelled ^{6}Li/^{15}N lithium amide, which is known to be a versatile enantiopure ammonia equivalent in conjugate addition reactions to a range of α,β-unsaturated esters. Analysis of this species by ^{6}Li and ^{15}N NMR spectroscopy reveals the presence of lithium amide dimers as the only observable species. Although a lithium amide dimer may not necessarily represent the reactive species for conjugate addition reaction, either a monomeric or dimeric reactive species is accommodated by our transition state mnemonic for this class of reaction. As rapid lithium exchange within the dimers (via a ring-opening and ring-closing process) was observed, this suggests that the active species for conjugate addition is most likely either a ring-open or ring-closed dimeric lithium amide. The ready distinction of the various dimers of this lithium amide, as compared to achiral (e.g., lithium dibenzylamide) and C_2-symmetric (e.g., lithium bis-*N*,*N*-α-methylbenzylamide) counterparts, presents unique opportunities for further mechanistic study.

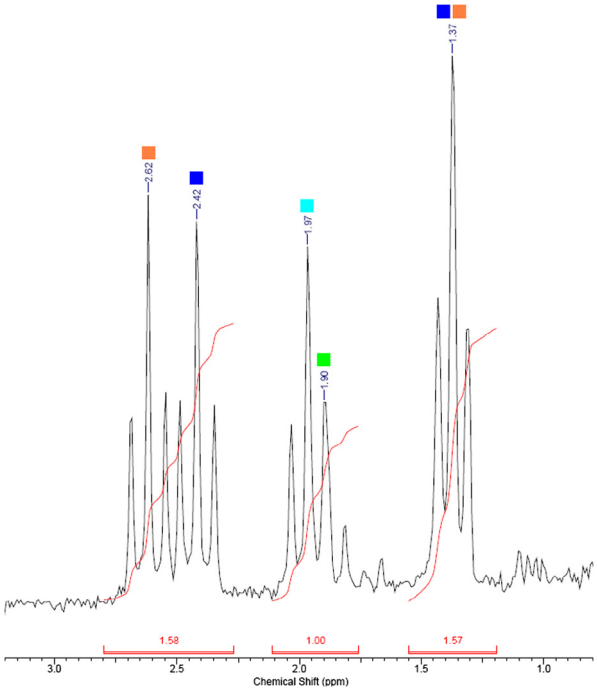
4. Experimental section

4.1. General experimental details

Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under



(**A**) ^{6}Li NMR spectrum of (*RS*)-^{6}Li-^{15}N-**8**.



(**B**) ^{15}N NMR spectrum of (*RS*)-^{6}Li-^{15}N-**8**.

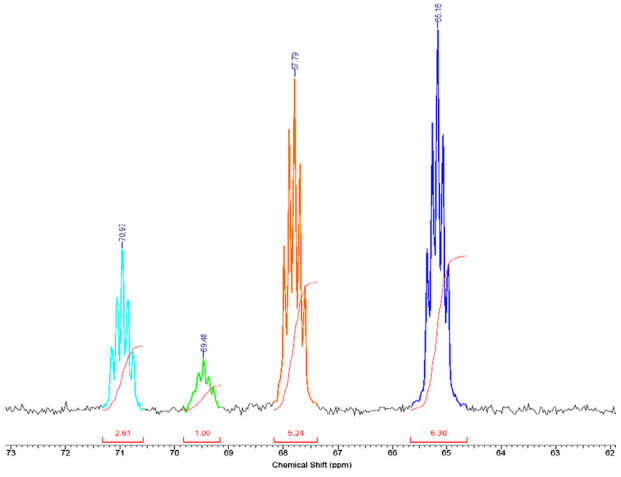


Figure 3. ^{6}Li and ^{15}N NMR spectra of (*RS*)-^{6}Li-^{15}N-**8** at 173 K.

nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[33] Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. ^{1}H NMR spectra were recorded at ambient temperature in $CDCl_3$. ^{6}Li and ^{15}N NMR spectra were recorded on a Bruker AV2500 instrument equipped with a BBO probe, at 173 K in THF-d_8. ^{6}Li spectra were referenced to 1.0 M aq LiCl and ^{15}N spectra were referenced to liquid NH_3 at 298 K. ^{6}Li–^{6}Li EXSY spectra were recorded using the standard phase sensitive NOESY pulse sequence, 64 scans, with D1 = 0.5 s and D8 = 400 ms.

4.2. (*S*)-*N*(3)-Phenylacetyl-4-isopropyl-5,5-dimethyloxazolidin-2-one 2

BuLi (2.5 M in hexanes, 0.84 mL, 2.10 mmol) was added dropwise to a stirred solution of **1**[19] (300 mg, 1.91 mmol) in THF (20 mL) at −78 °C. After 30 min, phenylacetyl chloride (383 mg, 2.48 mmol) was added and stirring was continued for a further 30 min at −78 °C. The reaction mixture was then allowed to warm to rt over 30 min before being quenched with satd aq NH_4Cl (5 mL). The resultant mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/EtOAc, 15:1) gave **2** as a colourless oil (512 mg, 97%);[18] $[\alpha]_D^{25}$ + 52.2 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.9, *Me*CHMe), 0.96 (3H, d, *J* 6.9, *Me*CHMe), 1.32 (3H, s, C(5)*Me*$_A$), 1.50 (3H, s, C(5)*Me*$_B$), 2.11 (1H, septet d, *J* 6.9, 3.2, *C*HMe$_2$), 4.14 (1H, d, *J* 3.2, C(4)*H*), 4.26 (1H, d, *J* 15.0, *C*H_AH$_B$Ph), 4.38 (1H, d, *J* 15.0, CH$_A$*H*$_B$Ph), 7.25–7.36 (5H, m, *Ph*).

4.3. (*S,S*)-*N*(3)-2′-Phenylpropanoyl-4-isopropyl-5,5-dimethyloxazolidin-2-one 3

LiHMDS (1.0 M in hexanes, 0.87 mL, 0.87 mmol) was added dropwise to a stirred solution of **2** (200 mg, 0.73 mmol) in THF (10 mL) at −78 °C. After 30 min, MeI (114 mg, 0.80 mmol) was added and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was then quenched with satd aq NH_4Cl (5 mL) and the organic layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo to give **3** in 97:3 dr. Purification via flash column chromatography (eluent pentane/EtOAc, 15:1) and recrystallisation (EtOAc/pentane) gave **3** as a white crystalline solid (176 mg, 84%, >99:1 dr);[18] mp 107–108 °C; $[\alpha]_D^{23}$ + 103 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, *Me*CHMe), 0.99 (3H, s, C(5)*Me*$_A$), 1.08 (3H, d, *J* 6.8, *Me*CHMe), 1.44 (3H, s, C(5)*Me*$_B$), 1.53 (3H, d, *J* 7.0, C(3′)H_3), 2.15 (1H, septet d, *J* 6.8, 3.3, *C*HMe$_2$), 4.02 (1H, d, *J* 3.3, C(4)*H*), 5.15 (1H, q, *J* 7.0, C(2′)*H*), 7.21–7.35 (5H, m, *Ph*).

4.4. (*S*)-2-Phenylpropanoic acid 4

2.0 M aq LiOH (10 mL) was added to a stirred solution of **3** (4.20 g, 14.5 mmol) in THF (10 mL) at rt. After 12 h the reaction mixture was acidified to pH 1 using 2.0 M aq HCl. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were concentrated in vacuo to give **4** as a colourless oil (2.13 g, 98%); $[\alpha]_D^{23}$ + 72.4 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.51 (3H, d, *J* 5.4, C(3)H_3), 3.72 (1H, q, *J* 5.4, C(2)*H*), 7.23–7.37 (5H, m, *Ph*).

4.5. (*S*)-^{15}*N*-2-Phenylpropanamide 5

(*S*)-**4** (2.63 mL, 17.5 mmol) was added to a solution of $SOCl_2$ (1.46 mL, 20.0 mmol) and benzotriazole (2.38 g, 20.0 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After 20 min the turbid solution was filtered through a pad of $MgSO_4$ and concentrated in vacuo. The residue

was dissolved in Et_2O (10 mL) the resultant solution was cooled to 0 °C and ice-cold 10 M aq NaOH (10 mL) was added, followed by $^{15}NH_4Cl$ (1.0 g, 18.4 mmol). After 30 min the aqueous layer was extracted with Et_2O (10 mL). The combined organic extracts were dried and concentrated in vacuo to give (*S*)-^{15}N-**5** as a white crystalline solid (2.64 g, 98%); mp 85–87 °C; $[\alpha]_D^{23} + 62.1$ (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, d, *J* 7.2, C(3)H_3), 3.60 (1H, q, *J* 7.2, C(2)*H*), 5.30–5.52 (2H, br s, NH_2); 7.28–7.42 (5H, m, *Ph*).

An analogous procedure starting from (*RS*)-**4** (2.63 mL, 17.5 mmol) gave (*RS*)-^{15}N-**5** as a white crystalline solid (2.71 g, 99%).

4.6. (*S*)-^{15}*N*-α-Methylbenzylamine 6

I,*I*-Bis(trifluoroacetoxy)iodobenzene (5.20 g, 12.8 mmol) and H_2O (15 mL) were added sequentially to a stirred solution of (*S*)-^{15}*N*-**5** (1.8 g, 12.8 mmol) in MeCN (15 mL) at rt. After 8 h the reaction mixture was acidified with 10 M aq HCl (3 mL) and washed with Et_2O (2 × 5 mL).[34] The resultant aqueous solution was then neutralised (to pH 7–8) using 1.0 M aq NaOH and washed with Et_2O (5 × 10 mL).[35] The resultant aqueous solution was then basified (to pH 14) using 2.0 M aq NaOH and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give (*S*)-^{15}N-**6** as a colourless oil (1.50 g, 96%); $[\alpha]_D^{24} - 28.4$ (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, dd, *J* 6.6, 3.1, C(α)*Me*), 1.39 (2H, s, NH_2), 4.12 (1H, q, *J* 6.6, C(α)*H*), 7.18–7.46 (5H, m, *Ph*).

An analogous procedure starting from (*RS*)-^{15}N-**5** (1.8 g, 12.8 mmol) gave (*RS*)-^{15}N-**6** as a colourless oil (1.50 g, 96%).

4.7. (*S*)-^{15}*N*-Benzyl-^{15}*N*-(α-methylbenzyl)amine 7

Benzaldehyde (0.42 mL, 4.2 mmol) was added to a stirred solution of (*S*)-**5** (500 mg, 4.2 mmol) in EtOH (5 mL) and the resultant solution was heated at reflux for 4 h. The reaction mixture was then allowed to cool to rt, and then cooled further to 0 °C. $NaBH_4$ (82 mg, 4.2 mmol) was added portionwise. The resultant white suspension was allowed to warm to rt and stirred for 3 days. The mixture was then concentrated in vacuo, the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. The residue was dissolved in Et_2O (2 mL) and the resultant solution was added dropwise to saturated ethereal HCl (50 mL). The resultant white suspension was then filtered and the solid was washed with Et_2O (2 × 5 mL). The resultant white solid was recrystallised (CH_2Cl_2/30–40 °C petrol, 1:1), then added portionwise to a stirred solution of 2.0 M aq NaOH (20 mL) at 0 °C. After 5 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give (*RS*)-^{15}N-**7** as a colourless oil (870 mg, 98%, >98% ee);[23] $[\alpha]_D^{24} - 53.2$ (*c* 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45–1.51 (3H, app br s, C(α)*Me*), 3.59 (1H, d, *J* 13.2, NCH_AH_BPh), 3.72 (1H, d, *J* 13.2, NCH_AH_BPh), 3.80 (1H, q, *J* 6.5, C(α)*H*), 4.71 (2H, s, NH_2), 7.18–7.46 (10H, m, *Ph*).

An analogous procedure starting from (*RS*)-^{15}N-**6** (0.5 g, 4.2 mmol) gave (*RS*)-^{15}N-**7** as a colourless oil (870 mg, 98%).

4.8. Butyl^{6}lithium

Finely cut ^{6}Li chunks (1.05 g, 150 mmol) were added to a solution of BuCl (7.85 mL, 75 mmol) in hexane (60 mL) under Ar at rt. The solution was placed in a sonicator for 16 h (until large metal pieces were consumed). The resultant purple solution was then allowed to stand for 2 days at rt.

Meanwhile, a large 5 cm diameter Schlenk-type flask (quickfit adaptors at both ends with Youngs tap separating the bottom adaptor section and a key operated tubing adapter near the top quickfit neck) containing a Whatman No. 1 sinter was half-filled with flame dried Celite and sealed via the top quickfit adaptor with a suba-seal. The flask was placed under positive pressure of Ar via the key operated tubing adaptor. A 100 mL, two-necked round-bottomed flask was attached to the Schlenk flask via the lower quickfit adaptor, and small bore cannula was connected between the second neck of the flask and a 250 mL, two-necked round bottomed flask, which was placed under vacuum.

The purple Bu^{6}Li solution was transferred via wide bore cannula onto the bed of flame-dried Celite and filtered under suction into the first round bottomed flask, then transferred into the second round bottomed flask (placed in a dry ice-bath at −78 °C) via cannula to give a pale yellow solution of Bu^{6}Li (0.6 M, 53 mL, 54%); δ_{Li} (73.6 MHz, THF-d_8, 173 K) 1.57, −1.09, −0.37, 0.03, 0.36.

4.9. ^{6}Lithium (*S*)-^{15}*N*-benzyl-^{15}*N*-(α-methylbenzyl)amide 8

Bu^{6}Li (0.6 M in hexane, 0.45 mL, 0.27 mmoL) was added to a flame dried NMR tube,[25] sealed in a Schlenck tube under Ar, and carefully placed under vacuum (to avoid bumping). After a period of 30 min, a solution of (*S*)-^{15}N-**7** (58 mg, 0.27 mmol) in THF-d_8 (0.5 mL) was added, and the NMR tube was sealed with a cap and Nescofilm, and placed in a dry-ice bath at −78 °C. The resultant pink, 0.54 M solution of (*S*)-^{6}Li-^{15}N-**8** was analysed by NMR spectroscopy;[25] δ_{Li} (73.6 MHz, THF-d_8, 173 K) 1.38 (t, *J* 4.4), 1.90 (t, *J* 5.0), 2.42 (t, *J* 5.0); δ_N (50.7 MHz, THF-d_8, 173 K) 65.1 (app qunitet), 69.5 (app quintet).

An analogous procedure starting from (*RS*)-^{15}N-**7** (58 mg, 0.27 mmol) gave a 0.54 M solution of (*RS*)-^{6}Li-^{15}N-**8**;[25] δ_{Li} (73.6 MHz, THF-d_8, 173 K) 1.37 (app t), 1.90 (t, *J* 5.0), 1.97 (t, *J* 4.9), 2.42 (t, *J* 5.0), 2.62 (t, *J* 5.1); δ_N (50.7 MHz, THF-d_8, 173 K) 65.2 (app qunitet), 67.8 (app qunitet), 69.5 (app quintet), 71.0 (app quintet).

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