A Novel Mixed Dimer of a Norephedrine-Derived Chiral Lithium Amide and 2-Lithium-1-methylimidazole, and Catalytic Enantioselective Deprotonation of Cyclohexene Oxide

Mohamed Amedjkouh, Daniel Pettersen, Sten O. Nilsson Lill, Öjvind Davidsson, and Per Ahlberg*[a]

Abstract: Improved stereoselectivity has been obtained by using 2-lithium-1-methylimidazole, **2**, as a replacement for lithium diisopropylamide (LDA) as a bulk base in catalytic deprotonations. The chiral lithium amide **6** of (1*R*,2*S*)-*N*-methyl-1-phenyl-2-pyrrolidinylpropanamine, **5**, has been found to deprotonate cyclohexene oxide **3** in the presence of compound **2** to yield (*S*)-cyclohex-2-en-1-ol, **4**, in 96% *ee*. Compound **2** is a carbenoid species conveniently generated from *n*BuLi and 1-methylimidazole, **1**. The base **2** has also been found to play a more intimate role in the deprotonation. Investigations by ^{1}H, ^{6}Li and ^{13}C NMR of the $^{6}Li/^{15}N$ isotopologue **8** of **6** have shown that **6** is homodimeric in THF and that, in the presence of **2**, it forms a novel heterodimer **10**. This heterodimer is found to be the dominant reagent in the initial state, rather than the homodimer of **6**. Computational investigations with PM3 and B3LYP/6–311+G(d,p) have shown possible structures of the heterodimers, as well as the role of THF and **1** in the solvation of the dimers. The results are in line with the NMR results. Favoured complexes in the equilibria between homo- and heterocomplexes are also reported.

Keywords: asymmetric catalysis · chiral lithium amide · heterodimer · multinuclear (^{1}H, ^{6}Li, ^{13}C) NMR · semiempirical calculations

Introduction

Homochiral lithium amides are being developed and used for highly stereoselective deprotonations of, for example, epoxides to yield enantiomers of allylic alcohols[1–3] for use in such syntheses as those of biologically active compounds.[4–9] Much remains to be known about the nature of these reagents in solution. Some have been shown to aggregate to homodimers and are thus the reagents in the deprotonations.[10–14] There have been a number of attempts to run stereoselective deprotonations under catalytic conditions.[15–17] The chiral lithium amide has been used in catalytic quantities and the less-reactive lithium diisopropyl amide (LDA) has been used as a bulk base by which the chiral lithium amide is regenerated from the chiral amine produced.[18–21] However, under these conditions the enantioselectivity obtained is usually lower than that obtained under noncatalytic conditions. The reason for this is presumably that the competitive, nonstereoselective deprotonation by LDA yields some racemic product.

To improve the degree of stereoselectivity in catalytic deprotonations, access to bulk bases that have lower kinetic basicity than LDA but comparable thermodynamic basicity is required. In our search for such bases, we made use of 1-methylimidazole, **1**, as a precursor. This compound undergoes carbon deprotonation at the C2 position with, for example, *n*BuLi to yield 2-lithium-1-methylimidazole, **2**, which is a carbenoid species (Scheme 1).[22, 23]

Since proton transfer to carbon is usually slower than to more electronegative atoms, such as nitrogen, compound **2** was expected to show lower kinetic basicity than a nitrogen base of similar thermodynamic basicity. In THF, we found by NMR that **2** has a basicity comparable to LDA. As expected, and in contrast to LDA, compound **2** did not measurably cause any deprotonation of cyclohexene oxide **3** to yield cyclohex-2-en-1-ol, **4**, even after very long reaction times. These properties indicated to us that **2** should be useful as a bulk base in catalytic asymmetric deprotonations.

In this paper, we also report on the advantage of compound **2** as a bulk base and on its more intimate role through the formation of a reagent heterodimer consisting of a monomer of **2** and a monomer of a homochiral lithium amide. The structure of the novel reagent has been elucidated from ^{1}H,

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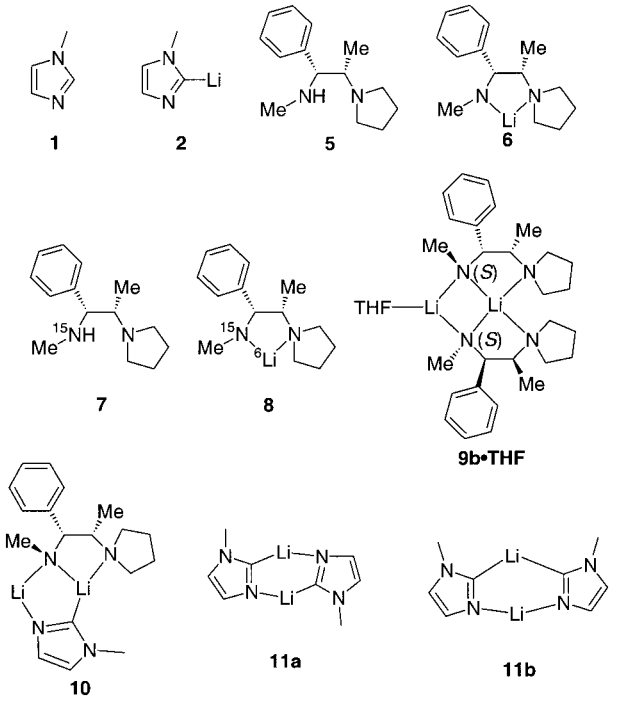
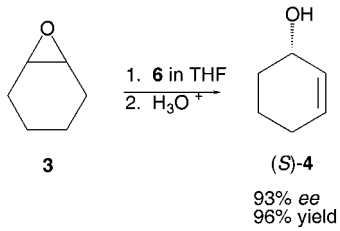


Scheme 1. Structures of labelled and nonlabelled precursors and their lithiated counterparts, shown together with homodimers **9** and **11** and the heterodimer **10**.

^{6}Li and ^{13}C NMR spectroscopy. Computational studies have shown possible structures of the heterodimers as well as the role of THF and **1** in the solvation of the dimers. Favoured complexes in the equilibria between homo- and heterocomplexes are also reported. Improved enantioselectivity, obtained with the new heterodimer **10**, is also reported.

Results and Discussion

Recently, the norephedrine-derived diamine **5** was synthesised, and the corresponding lithium amide **6** was found to deprotonate **3** in THF to yield (*S*)-**4** in 93% *ee* (Scheme 2).[24, 25]



Scheme 2. Enantiomerically specific deprotonation of **3**.

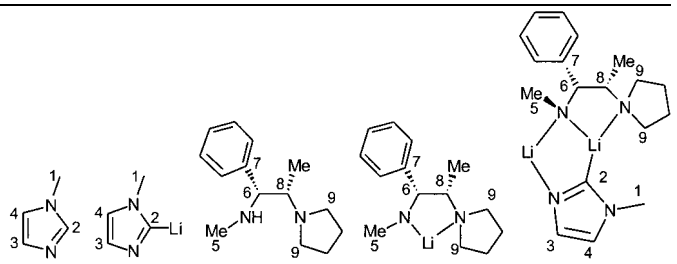
When this reaction was run under catalytic conditions with a reaction mixture composed of **6** (0.02 M), LDA (0.2 M) and **3** (0.1 M) in THF at 20 °C, the *ee* decreased to 22%. In contrast, the catalytic reaction mixture composed of **6** (0.2 M), **2** (0.2 M) and **3** (0.1 M) gave (*S*)-**4** in 93% *ee*, but the reaction was slower than the one with LDA. That the same *ee* was obtained as for the noncatalytic reaction of **6** with **3** suggests that **2** was operating as predicted. However, the use of the lithium carbenoid **2** in equimolar amounts to **6** in THF to deprotonate **3** resulted, to our surprise, in a deprotonation with increased enantioselectivity. Compound (*S*)-**4** was formed in 96% *ee*, and this enantiomeric excess remained constant during the whole reaction, as shown by chiral GC. This suggests that compound **2** is not functioning just as a bulk base, but is participating intimately in the deprotonation reaction.

These findings prompted us to investigate the nature of reagent **6** in the presence and absence of the lithium carbenoid **2**. For this purpose **7**, the ^{15}N isotopologue of **5**, and **8**, the ^{6}Li/^{15}N isotopologue of **6**, were prepared and studied in [D$_8$]THF by multinuclear NMR spectroscopy. ^{1}H, ^{6}Li and ^{13}C NMR spectra were obtained at different temperatures, and selected ^{1}H and ^{13}C NMR chemical shifts are shown in Table 1.

The ^{6}Li NMR spectrum of **8** at $-80\,^{\circ}$C mainly showed two triplets of equal intensity but with different splittings (Figure 1a). This shows that two different lithium atoms are present and that each of them is coupled, with the same coupling constant, to two labelled nitrogens (^{15}N). The coupling constants ($J(^{6}\mathrm{Li},^{15}\mathrm{N})$) for the two lithiums were found to be 5.8 Hz and 3.8 Hz. These results suggest that **6** is mainly present as homodimer **9** with nonequivalent lithium atoms in THF, and that one of the lithiums is tricoordinated while the other is tetracoordinated.[10] Possible structures of **9** that have different nitrogen configurations are shown in Scheme 3.

Computational studies by PM3 of comparable states of dimers with and without specific THF solvation show that the state containing **9b·THF** has the lowest enthalpy and, thus, may be the dimer isomer observed in solution.[24]

Table 1. Assigned ^{1}H and ^{13}C NMR chemical shifts at $-80\,^{\circ}$C in [D$_8$]THF for selected atoms in **1**, **2**, **7**, **8** and **10**.



	1 δ	**2** δ	**7** δ	**8** δ	**10** δ
H1 at C1	3.67	3.69			
H2 at C2	7.44	–			
H3 at C3	7.03	6.81			
H4 at C4	6.85	6.75			
C1	33.1	36.0			33.0
C2	139	204			201
C3	130	129			128
C4	121	117			116
C5			35.8	45.3	46.0
C6			67.9	77.4	77.9
C7			143	149	150
C8			67.1	72.6	71.7
C9			52.9	54.3	54.0

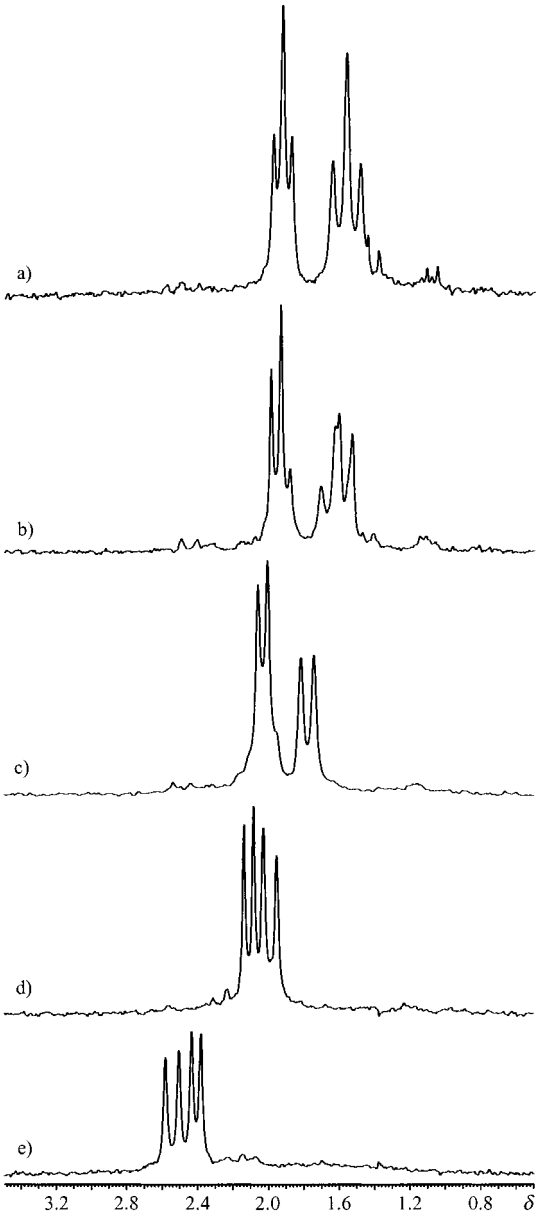
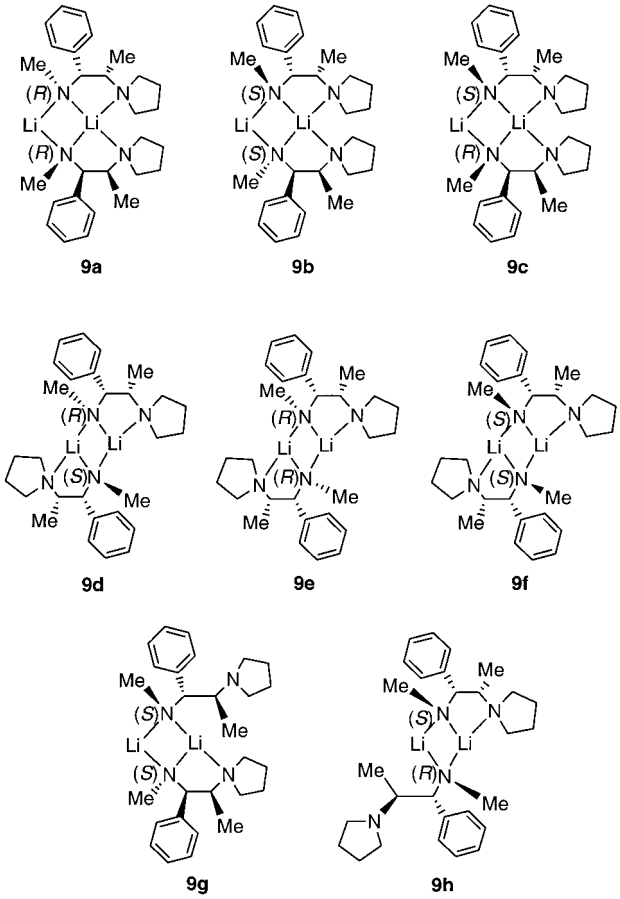


Figure 1. ^{6}Li NMR spectra obtained at $-80\,^{\circ}$C of solutions of **8** in [D$_8$]THF in the absence and presence of added **1**: a) 0.27 M **8**; b) 0.25 equiv of **1** added; c) 0.50 equiv of **1** added; d) 0.75 equiv of **1** added; e) 2.0 equiv of **1** added.



Scheme 3. Possible structures of homodimers of **6**.

Addition of 0.25 equivalents (equiv) of the imidazole **1** to a solution of **8** (0.27 M) in [D$_8$]THF resulted in dramatic changes in the ^{6}Li NMR spectrum. The intensity of the two triplets decreased and new signals, which overlapped the triplets, appeared (Figure 1b). Further addition of 0.25 equiv of **1** gave a spectrum that mainly consisted of two doublets of about equal intensity (Figure 1c). A separate experiment had shown that the ^{6}Li NMR spectrum of the ^{6}Li-lithiated **1**, that is the ^{6}Li isotopologue of **2**, only shows a singlet in [D$_8$]THF at $-80\,^{\circ}$C (cf. below). Thus, the two doublets formed upon addition of the 0.5 equiv of **1** together with ^{1}H and ^{13}C NMR spectra indicate that the lithium amide **8** had deprotonated the methylimidazole **1** at the 2 carbon to yield the diamine **7**, and that a new type of isotopically labelled dimer **10** had formed, which was composed of one monomer of **8** and one monomer of ^{6}Li-labelled **2**. In such a dimer, each ^{6}Li is coupled to only one ^{15}N. Selected ^{1}H and ^{13}C NMR chemical shifts of **10** are shown in Table 1. The two doublets shown in Figure 1c coalesce at $-55\,^{\circ}$C ($\Delta G^{\ddagger}_{218\,K} = 11.1 \pm 0.3$ kcal mol^{-1}). Computationally investigated structures of the heterodimer **10** are displayed in Scheme 4.

Evidently, the heterodimer **10** is more stable than both **11**, the homodimer of **2**, and **9**, the homodimer of **6**. Addition of a further 0.25 equiv of **1** only resulted in shifts of the doublets to lower field, since no **8** is available for deprotonation and heterodimer formation (Figure 1d). The shifts indicate that **1** is solvating the heterodimer. The addition of altogether two equivalents of **1** shifted the doublets further (Figure 1e); now the one with the larger coupling constant (J(^{6}Li,^{15}N) = 5.6 Hz) appeared at lower field than the one with the smaller coupling constant (J(^{6}Li,^{15}N) = 3.8 Hz).

This novel heterodimer was also prepared by starting with a solution of **1** (0.27 M) in [D$_8$]THF. When an equivalent amount of *n*Bu[^{6}Li] (about 10 M) was added, the ^{6}Li NMR mainly displayed a singlet (Figure 2a).

^{1}H and ^{13}C NMR spectra showed that this signal is due to the ^{6}Li-labelled lithium carbenoid **2**. After addition of 0.25 equiv of diamine **7**, the ^{6}Li NMR spectrum shown in Figure 2b was obtained; besides the singlet originating from ^{6}Li-labelled **2**, it shows the two doublets emanating from the labelled mixed dimer **10**. The measured coupling constants (J(^{6}Li,^{15}N)) are 5.5 Hz and 4.0 Hz. Evidently, the lithium

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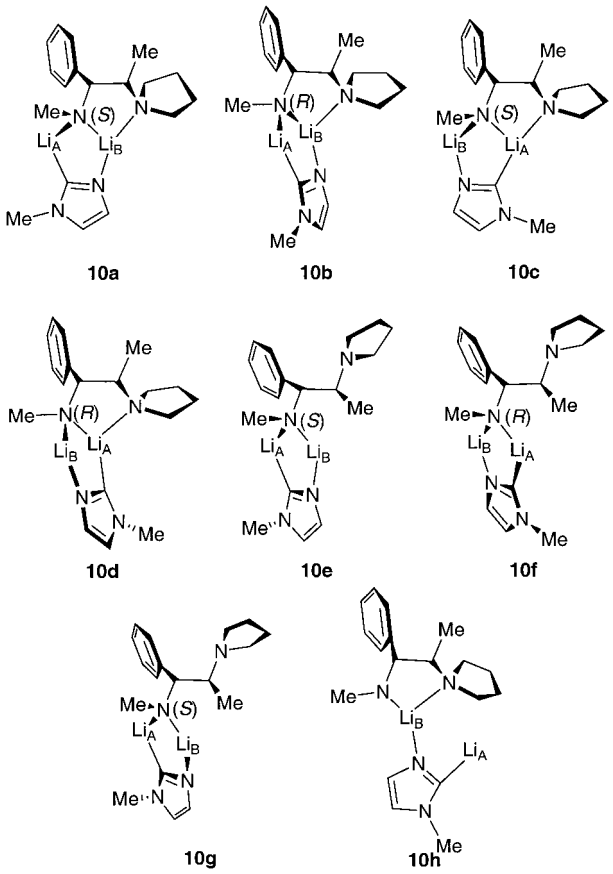

Scheme 4. Possible structures of heterodimers built from a monomer of **6** and a monomer of **2**.

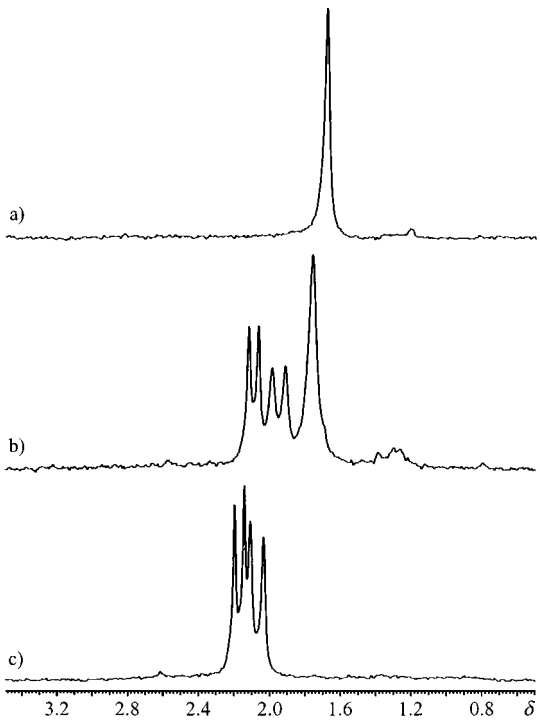

Figure 2. ^{6}Li NMR spectra obtained at $-80\,^{\circ}$C of solutions of ^{6}Li-labelled **2** in [D_8]THF in the absence and presence of added **7**: a) 0.27 M ^{6}Li-labelled **2**; b) 0.25 equiv of **7** added and c) 0.50 equiv of **7** added.

carbenoid **2** is a strong enough base to deprotonate the diamine **5** and yield a monomer of lithium amide **6** as part of a mixed dimer, together with a monomer of **2**. The deprotonation of **5** by **2** produces the 1-methylimidazole, **1**. The ^{6}Li NMR chemical shifts indicate that both the heterodimer **10** and the remaining **2** are solvated by **1**. The spectrum after addition of 0.5 equiv of **7** in total displayed essentially only two doublets (shifted); this showed that only the heterodimer **10** was present (Figure 2c).

The reactivity of **10** is similar to that of **6**. Recently, it has been shown that the rate-limiting transition state in the deprotonation of **3** by **6** in THF is composed of a dimer of **6** and one molecule of **3**.[24] Possibly, the **10**-promoted elimination of **3** is making use of a rate-limiting transition state built from the heterodimer **10** and one molecule of **3**. The scope and limitations of the above findings in asymmetric deprotonations are currently being explored. Below, results of PM3 and DFT (B3LYP/6–311+G(d,p)) investigations of possible solvated and nonsolvated hetero- and homodimeric structures together with equilibrium enthalpies are discussed.

Computational investigations: Some of the PM3- and DFT-calculated structures are shown in Figures 3–6, below. Others are found in the Supporting Information.

Of the unsolvated heterodimers (Scheme 4), **10a** and **10c** were found to have the lowest, and almost identical, enthalpy. These two isomers differ in the orientation of the imidazoloid ring. In each isomer, the two lithium atoms are part, together with the carbenoid carbon, the imine nitrogen of the imidazoloid and the amide nitrogen, of a five-membered ring in an envelope conformation. Li_A bonds to both the amide nitrogen and the carbenoid carbon, while Li_B is bonded both to the amide and imine nitrogens. Li_B also has a long bond (ca. 2.6 Å) to the carbenoid carbon (Figure 3). In **10a**, Li_B is also internally coordinated to the pyrrolidine nitrogen, while in **10c** Li_A is coordinated to the pyrrolidine nitrogen. Thus in **10a**, one lithium is dicoordinated and the other tetracoordinated, while in **10c** both lithiums are tricoordinated. On optimising **10a** with DFT, the Li_B–carbenoid-carbon bond is elongated from 2.6 Å to 2.7 Å. In contrast, the other bonds to Li are shortened, for example the Li_A–amide-nitrogen bond is shortened by 0.1 Å.

Upon specific monosolvation by THF at the PM3 level, the solvent coordinates preferably to the lithium that is not internally coordinated to the pyrrolidine nitrogen. In **10c·THF**, the long lithium–carbenoid-carbon bond is elongated (ca. 2.8 Å), while in **10a·THF** the corresponding C–Li bond is almost unchanged (ca. 2.6 Å). Compounds **10a·THF** and **10c·THF** are of similar energy. Specific monosolvation by 1-methylimidazole, **1**, has a similar effect on the structure as found for THF, although the solvation enthalpy is much larger for **1** (-21 kcal mol^{-1}) than for THF (-7 kcal mol^{-1}). The solvation enthalpies calculated by using B3LYP/6–311+G(d,p)//PM3 are -14 and -10 kcal mol^{-1}, respectively. Disolvation by THF yields only an additional solvation enthalpy of about -2 kcal mol^{-1} by using PM3 compared with -6 kcal mol^{-1} by DFT. PM3 is known[26–28] to underestimate solvation enthalpies of ethereal solvents by 3–4 kcal mol^{-1}, so taking the entropy of solvation[27, 28] (ca. 5 kcal mol^{-1}) into

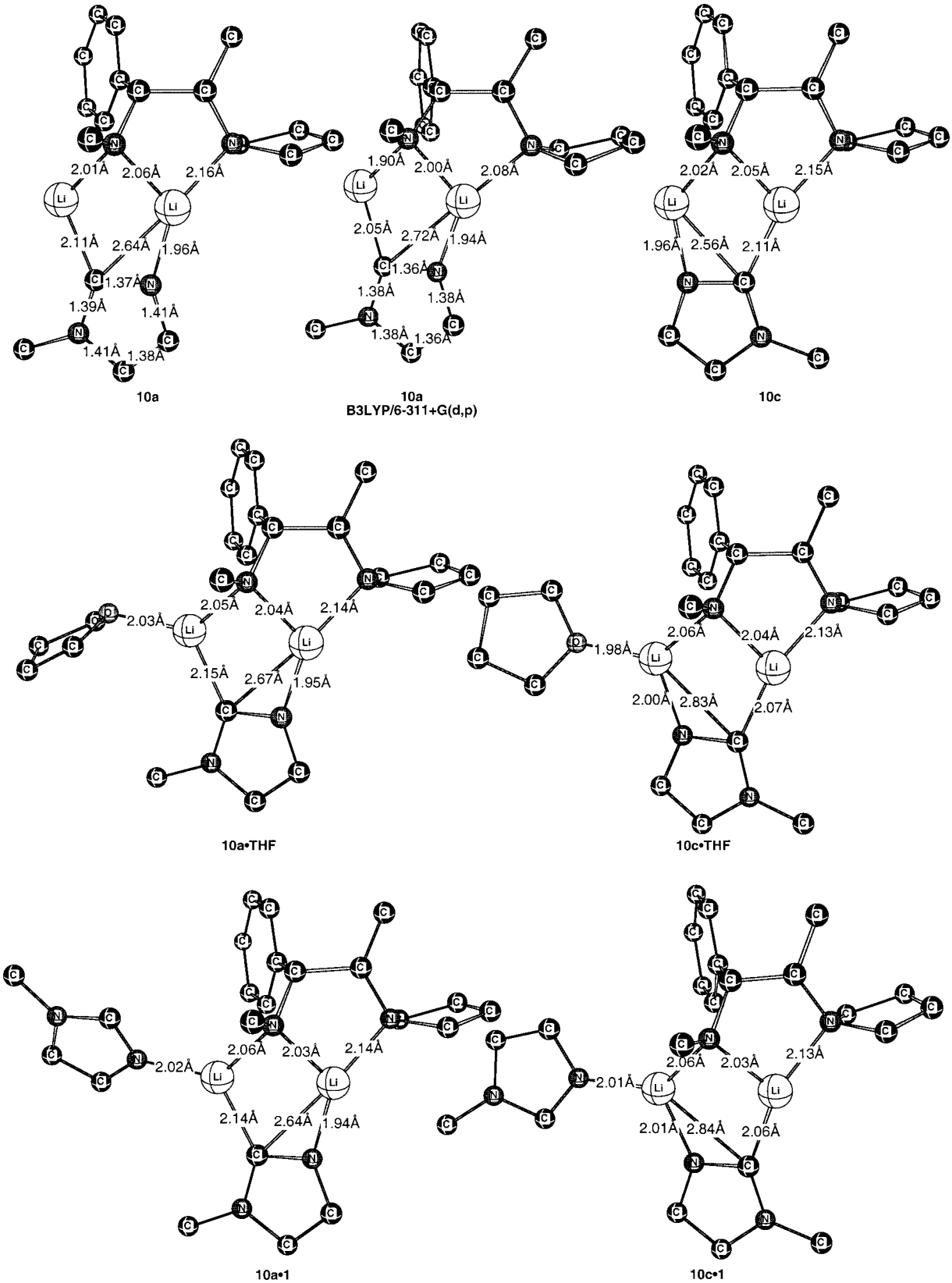

Figure 3. PM3- and DFT-calculated non- and monosolvated heterodimer structures. Hydrogens are omitted for clarity.

account as well predicts that the heterodimers are most likely a mixture of both mono- and disolvated species in THF. Upon disolvation, it is energetically favourable to break the coordination to the pyrrolidine nitrogen (Figure 4). For example, **10e**–**10g** were found to have more negative solvation enthalpies than structures that had pyrrolidine coordination. Several structures were found to be of almost equal enthalpy (cf. Figure 4 and Supporting Information). The

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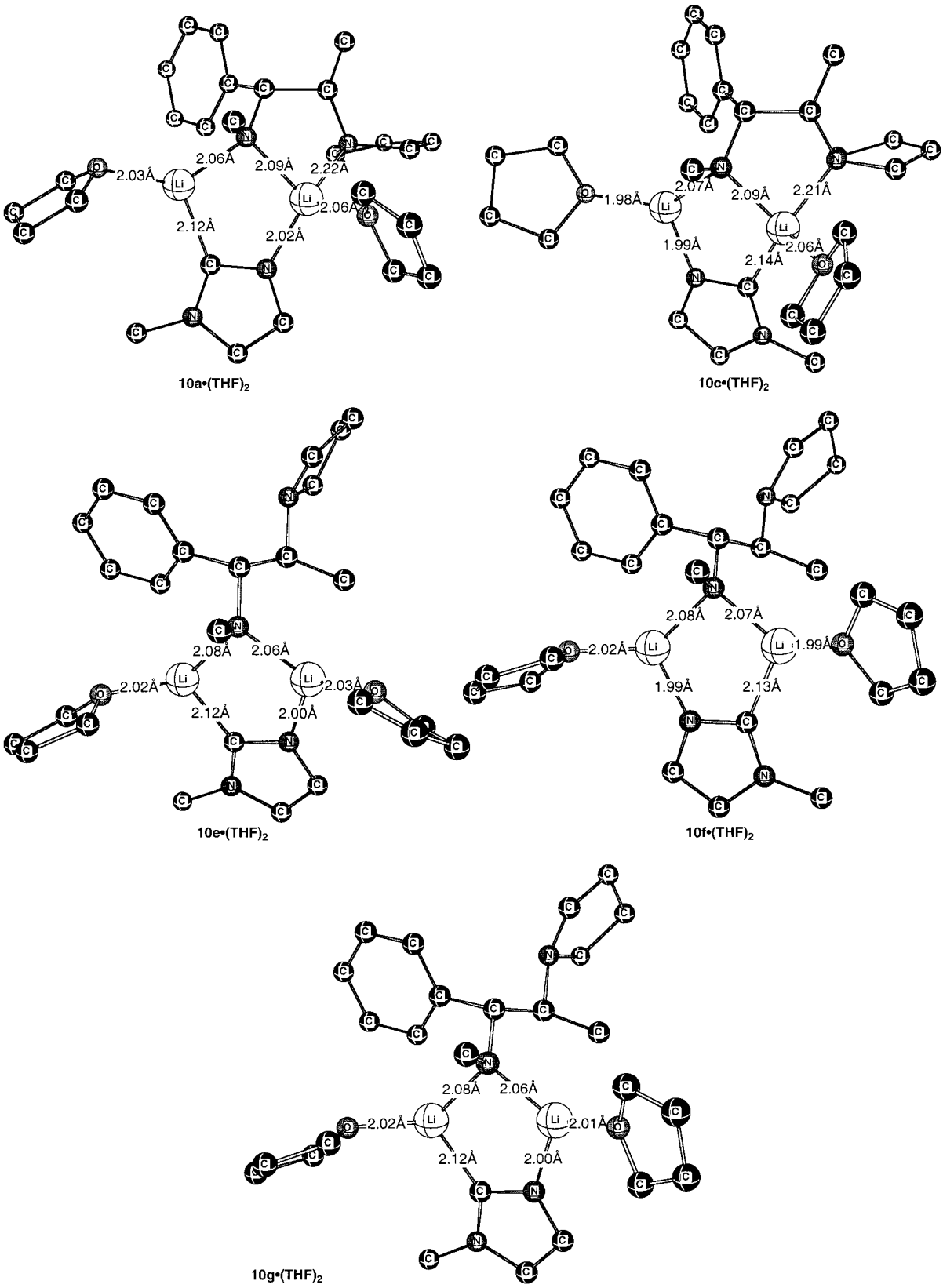

Figure 4. PM3-calculated THF-disolvated heterodimer structures. Hydrogens are omitted for clarity.

solvation enthalpy from a second molecule of **1** was calculated to be -15 kcal mol^{-1}. To evaluate the PM3-calculated solvation enthalpies for **1**, PM3 enthalpies were compared with single-point energies calculated by using B3LYP/6$-$311$+$G(d,p)//PM3 on the **1**-mono- and -disolvated monomers of CH_3Li and NH_2Li. It was found that PM3 overestimates the solvation enthalpy of **1** by 2$-$8 kcal mol^{-1}. If an entropy of solvation of about 5 kcal mol^{-1} is assumed, the heterodimers

10 are expected to be essentially completely disolvated by **1** as long as >2 equiv of **1** are present (Figure 5). DFT, on the other hand, gives only a second solvation enthalpy of -3 kcal mol^{-1} for **10e**·**1**$_2$. In the PM3-calculated disolvated structures, the carbenoid carbon is coordinated to only one lithium. Also, with two solvating molecules of **1**, it was found that breaking the pyrrolidine nitrogen coordination was energetically favourable. DFT calculations on **10a**·**1**$_2$ and **10e**·**1**$_2$ showed that the isomer without pyrrolidine-nitrogen coordination was 0.3 kcal mol^{-1} more stable. **10e**·**1**$_2$ was

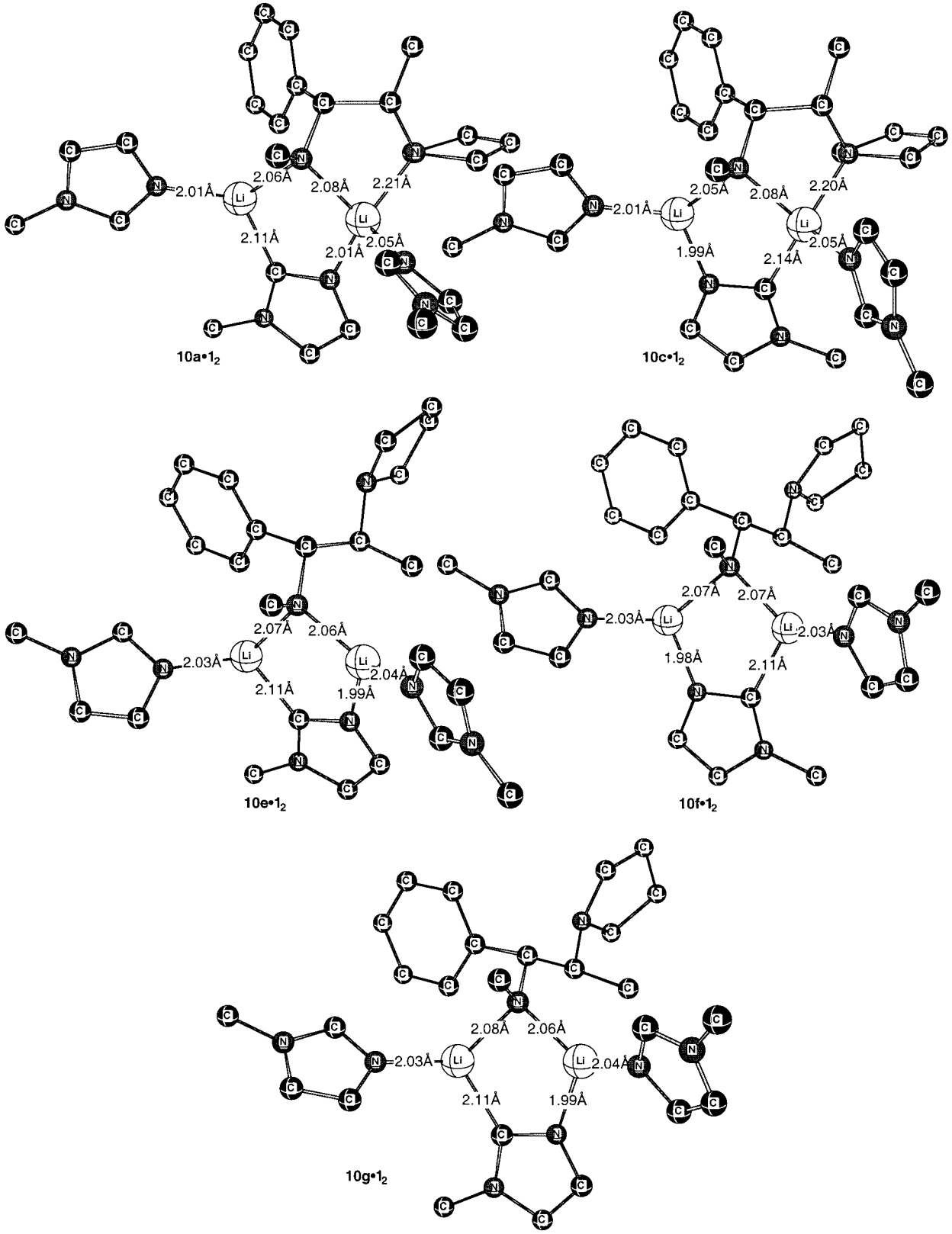

Figure 5. PM3-calculated heterodimer structures disolvated by **1**. Hydrogens are omitted for clarity.

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calculated to have the lowest enthalpy also at PM3 level. The distance from the amine nitrogen to the nearest lithium in **10e·1**$_2$ was calculated to be 4.7 Å.

PM3 and B3LYP/6–311+G(d,p) optimised structures of **11** are shown in Figure 6. At PM3 level, **11** involves bonding of Li to both C and N within each monomer. At DFT level, the Li–carbenoid-carbon bond is elongated from 2.4 Å (at PM3 level) to about 2.7 Å. Other bonds to lithium are shorter at DFT than at PM3 level. The calculated structure is similar to the crystal structure of the homodimer (3-lithium-4-*tert*-butyl-thiazol-2-ylidene-glycoldimethyl ether)$_2$.[22] The calculated energy difference between the isomers **11a** and **11b** is almost equal at both DFT and PM3 levels (0.24 and 0.42 kcal mol^{-1}, respectively).

In Scheme 5, some results of the studies of equilibria between homodimers **9** and **11** and heterodimers **10** with or without solvation by THF or 1-methylimidazole **1** are shown. Relative energies have been calculated both at the PM3//PM3 and at the B3LYP/6–311+G(d,p)//PM3 level of theory.

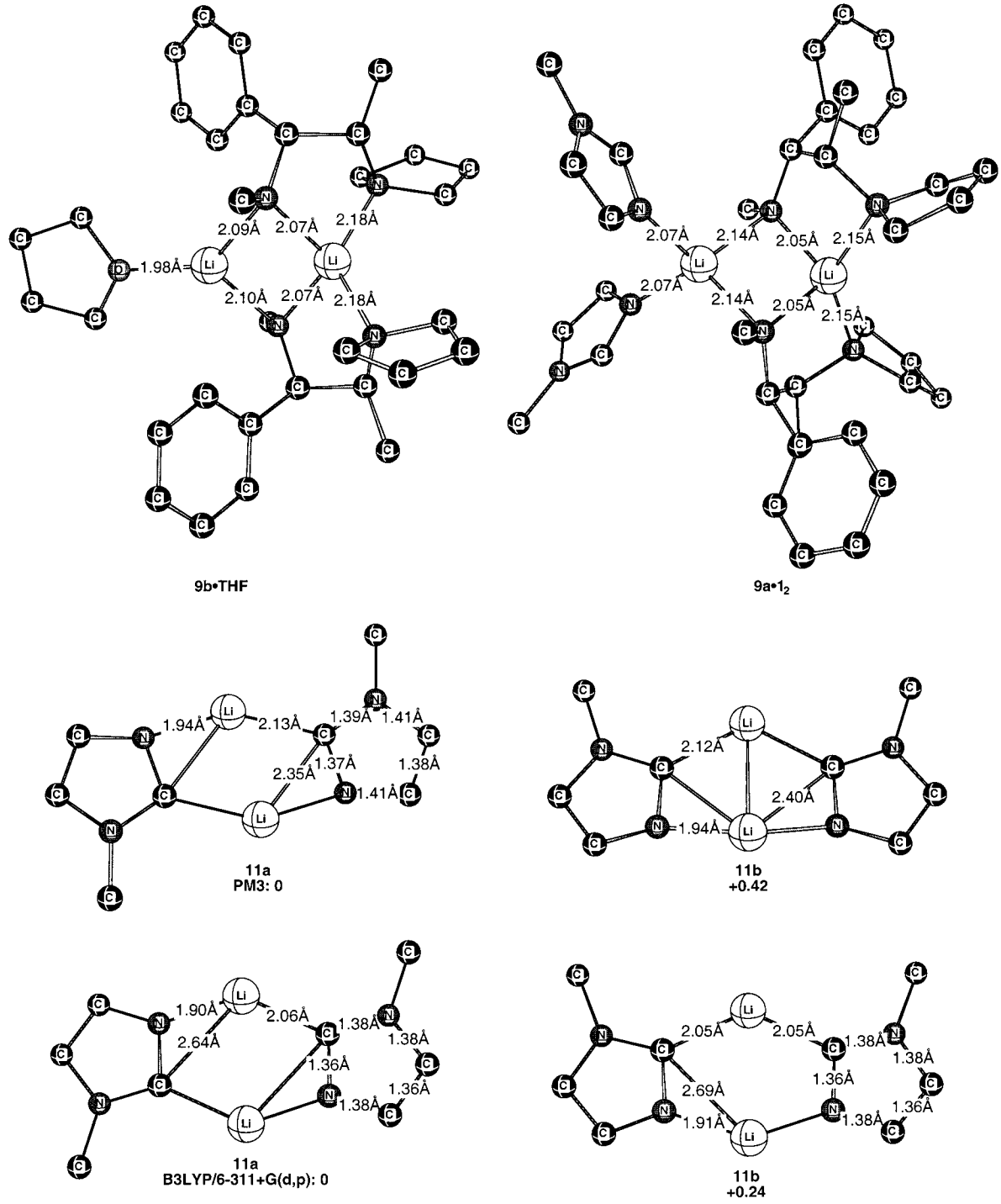
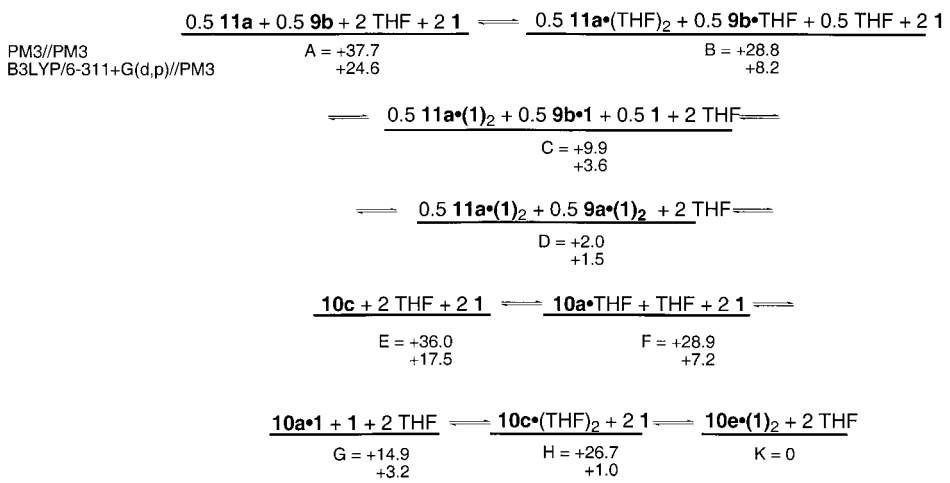


Figure 6. PM3- and DFT-calculated structures of homodimers of **6** and **2**. The homodimer **9** is monosolvated by THF and disolvated by **1**. Hydrogens are omitted for clarity. **11a** and **11b** are isomers, and their relative energies are given in kcal mol^{-1}.



Scheme 5. PM3- and DFT-calculated enthalpies in kcal mol^{-1} of states in equilibrium involving dimers with varying degrees of solvation. State K is used as a reference state.

Of all states in Scheme 5, state K, which involves solvation of each Li in **10e** by one molecule of **1**, is the most stable one and is used as a reference state. In the equilibrium between the nonsolvated dimers, state E is favoured over A by 1.7 kcal mol^{-1} with PM3 and by 7.1 kcal mol^{-1} with DFT. THF solvation of **11a** and **9b** makes state B 8.9/16.4 kcal mol^{-1} more stable than state A (Figure 6). The solvation energies obtained by solvation by imidazole **1** are larger than for solvation by THF. Thus, state C is 18.9/4.6 kcal mol^{-1} more stable than B. The most stable state involving the **1**-disolvated homodimers **11a** and **9a** is 2.0/1.5 kcal mol^{-1} less stable than state K. State K is 14.9/3.2 kcal mol^{-1} more stable than G with **10a** monosolvated by **1**. With the assumption that PM3 overestimates **1** solvation and an estimated solvation entropy of about 5 kcal mol^{-1}, **10** is indicated to be preferably disolvated by **1**. State H with the THF-disolvated heterodimer **10c·(THF)$_2$** is 26.7/1.0 kcal mol^{-1} higher in enthalpy than K. This enthalpy difference indicates that **1** will replace THF in the solvation of the dimers. This prediction agrees with the NMR observations, in which the lithium signals are shifted upon addition of **1** to a THF solution of the heterodimer **10**.

Conclusion

In summary, we found that the imidazoloid **2** is a strong enough base to deprotonate the diamine **5** to yield **6**, which forms the mixed dimer **10** with the remaining **2**. On the other hand, interestingly, **6** is found to be able to deprotonate **1** to yield **2** which forms the heterodimer **10** with the remaining **6**. Evidently, the thermodynamically most stable complex in solution is the heterodimer **10**, and this complex is thus the new reagent in the enantioselective deprotonation of the *meso*-epoxide **3** yielding an enhanced stereoselectivity (96% *ee*).

Computational investigations by PM3 and B3LYP/6–311+G(d,p) have shown possible structures for the hetero- and homodimers, and the role of THF and **1** in the solvation of the dimers, in line with the NMR results. Favoured complexes in the equilibria between homo- and heterocomplexes have also been calculated.

Experimental Section

General: All syringes and glass vessels used were dried overnight in a vacuum oven (50 °C) before being transferred into a glovebox (Mecaplex GB 80 equipped with a gas-purification system that removes oxygen and moisture) under a nitrogen atmosphere. The typical moisture content was less than 0.5 ppm. All handling of the lithium compounds was carried out in the glovebox with gas-tight syringes. The solvent used, THF, was distilled from sodium and benzophenone. The rearrangements of **3** were performed in a nitrogen atmosphere. The concentration of the commercially available *n*BuLi (ca. 2.5 M in hexanes, Acros) was determined by titration.[24] [D$_8$]THF was stored over molecular sieves (4 Å) in the glovebox. Compound **1** (Sigma–Aldrich) was distilled over CaH_2. *n*Bu[^{6}Li] was prepared as previously described.[29] Methyl[^{15}N]amine hydrochloride (98% + isotopic and chemical purity) was purchased from Cambridge Isotope Laboratories. All GC analyses were run on a chiral stationary-phase column (CP-Chirasil-DEX CB, 25 m, 0.32 μm) from Chrompack. The column was held at 95 °C (injector 225 °C, detector 250 °C) with helium (2 mL min^{-1}) as a carrier gas. t_R(**3**) = 3.25 min, t_R((*S*)-**4**) = 7.45 min, t_R((*R*)-**4**) = 7.90 min.

Synthesis of (1*R*,2*S*)-*N*-methyl-1-phenyl-2-pyrrolidinylpropan[^{15}N]amine 7: A modification of a procedure described earlier for the synthesis of **5** was used for the synthesis of **7**.[24, 30] After purification by short-path distillation, the precursor amino alcohol (2.05 g, 10 mmol) was dissolved in THF under a nitrogen atmosphere in a flask equipped with septa and cooled to 0 °C in an ice bath. Triethylamine (4.25 mL, 30 mmol) was added to the stirred solution, and methanesulfonyl chloride (1.48 mL, 20 mmol) was added dropwise with a syringe over 20 min while a yellow precipitate formed. The ice bath was removed and the mixture was stirred for another 1.5 h at RT. Triethylamine (7.1 mL, 50 mmol) and methyl[^{15}N]amine hydrochloride (1 g, 15 mmol) were added sequentially to the reaction mixture. Upon addition of water (3 mL), the remaining precipitate dissolved; this resulted in a clear solution, which was stirred at RT for another 48 h. The aqueous phase was extracted with diethyl ether (3 × 40 mL), and the collected organic layers were washed with $NaHCO_3$ (10%, 2 × 40 mL) and brine (40 mL). The organic phase was dried over Na_2SO_4, and evaporation in vacuum gave a brownish oil as residue. Distillation at reduced pressure through a Vigreux column and chromatography (silica gel) starting with dichloromethane (100%), then with a gradient up to dichloromethane/methanol (95:5) yielded the amine **7** as an colourless oil. Yield: 1.43 g, 66% (>99% NMR, >99.2% *ee* of (1*R*, 2*S*)-**7**, chiral GC); b.p. 65–67 °C / 3 × 10^{-2} mbar; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.15–7.30 (m, 5H; Ph), 3.85 (d, J = 3.2 Hz, 1H; PhCHN), 2.54–2.57 (m, 4H; NCH_2), 2.34 (s, 3H; NMe), 2.26–2.28 (m, J = 3.2 Hz, 1H; CHN), 1.90 (br s, 1H; NH), 1.75–1.83 (m, 4H; CH_2), 0.80 (d, J = 6.4 Hz, 3H; Me); ^{13}C NMR (125 MHz, [D$_8$]THF, 25 °C): δ = 143.3, 128.8, 128.7, 127.2 (Ph), 67.9 (CHN), 67.8 (CHN), 53.0 (NCH_2), 35.8 (NHMe), 25.3 (CH_2), 13.4 (Me).

NMR, general: All NMR experiments were performed in Wilmad tubes (5 mm) fitted with a Wilmad/Omnifit Teflon valve assembly (OFV) and a Teflon/Silicon septum. NMR spectra were recorded on a Varian Unity 500 spectrometer equipped with a 5 mm ^{1}H, ^{6}Li, ^{13}C triple-resonance probe head, custom built by Nalorac. Measuring frequencies were 499.9 MHz (^{1}H), 125.7 MHz (^{13}C) and 73.57 MHz (^{6}Li). The ^{1}H and ^{13}C spectra were referenced to signals from residual protons at C2, and the C2 carbon in the solvent [D$_8$]THF: δ = 1.73 and δ = 25.57, respectively. Lithium resonances were referenced to external ^{6}Li in [^{6}Li]Cl (0.3 M) in [D$_4$]MeOH (δ = 0.0) in a separate NMR tube. The typical 90° ^{6}Li pulse was 20 ms. The probe temperature was calibrated by using a methanol thermometer.

Typical NMR experiment: Amine **7** (44 μL, 0.2 mmol) was added to [D$_8$]THF (700 μL) in an NMR tube. The lithium amide **8** was generated by

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titration of **7** with *n*Bu[^{6}Li] (ca. 10 M, 20 μL) while monitoring the disappearance of the benzylic proton of **7** at $\delta = 3.8$ and the appearance of the benzylic proton of **8** at $\delta = 4.0$ at $-80\,^\circ$C. The 1-methylimidazole, **1**, (4 μL, 0.05 mmol, 0.25 equiv) was added, and the solution was allowed to equilibrate for 15 minutes before spectra were recorded. ^{6}Li spectra were recorded with at = 2 s, d1 = 18 s and nt = 32.

Typical rearrangement of 3: Amine **5** (4.4 μL, 0.02 mmol) and 1-methylimidazole **1** (16 μL, 0.20 mmol) were dissolved in THF (880 μL) in a reaction vessel in the glovebox. After the vessel was transferred from the glovebox, *n*BuLi (89 μL, 2.47 M in hexanes, 0.22 mmol) was added under nitrogen. The yellow reaction solution was allowed to equilibrate at $20.00 \pm 0.05\,^\circ$C for 10 minutes in a thermostat (Heto Birkerød). The reaction was started by adding cyclohexene oxide **3** (10 μL, 0.10 mmol) to the reaction mixture. In order to follow the reaction, samples (50 μL) were withdrawn from the reaction vessel at different intervals, and diethyl ether (0.5 mL) was added. The solutions were quenched in saturated NH_4Cl (0.25 mL) and washed with brine (0.25 mL). The samples were analysed by chiral gas chromatography. The reaction yield of **4** was determined by using an internal standard relative to **4** at the end of the reaction as previously described.[24]

Computational details: Geometries were optimised at the PM3 level of theory.[31–33] In Spartan, the option HHON[34] was used to correct for hydrogens in close contact.[35, 36] All geometries were characterised as minima on the potential energy surface by use of the sign of the eigenvalues of the force-constant matrix obtained from a frequency calculation. Selected structures were optimised by using B3LYP/6–311 + G(d,p)[37–40] as implemented in Gaussian 98.[41] Reaction energies were calculated at PM3//PM3, B3LYP/6–311 + G(d,p)//PM3, or B3LYP/6–311 + G(d,p)// B3LYP/6–311 + G(d,p) levels of theory.

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