2-(Lithiomethyl)-1-methylimidazole as a non-reactive bulk base and its novel mixed dimer with a chiral lithium amide in catalytic stereoselective deprotonation †

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The search for non-reactive bulk bases in replacement of lithium diisopropylamide (LDA) for improved enantioselectivity of chiral lithium amide-catalysed deprotonations led to the use of 1,2-dimethylimidazole **9** as a precursor. Deprotonation of **9** with *n*-BuLi in THF results in the compound 2-(lithiomethyl)-1-methylimidazole **8** as shown by NMR. This carbanionic compound is found to be less reactive than LDA in deprotonation of cyclohexene oxide **10**, but having comparable basicity to that of LDA. Catalytic amounts of the chiral lithium amide **4** of (1*R*,2*S*)-*N*-methyl-1-phenyl-2-pyrrolidinopropanamine **5** deprotonates cyclohexene oxide **10** in the presence of compound **8** and yields (*S*)-cyclohex-2-enol (*S*)-**11** in 93% ee. On the other hand, using LDA as a bulk base gives an ee of only 22%. Interestingly, stoichiometric deprotonation by **4** in the presence of **8** in THF results in (*S*)-**11** in 96% ee. Thus, the results indicate that compound **8** is playing a more intimate role in the deprotonation than just acting as a bulk base. Therefore, the reagents involved in the reactions have been investigated by ^{1}H, ^{6}Li and ^{13}C NMR using isotopically labelled compounds. The results show that lithium amide **4**, which is homodimeric in THF, in the presence of **8** forms heterodimer **12** composed of one monomer of carbanionic **8** and one monomer of **4**. This novel heterodimer is found to be the deprotonating reagent causing the increased enantioselectivity. It is concluded that lithium amide **4** is not basic enough to deprotonate **9**, but that **8** is a strong enough base to deprotonate diamine **5**. This contrasts with the behaviour of 1-methylimidazole **1** which was found to be deprotonated by **4** to yield the mixed dimer **3**. Computational investigations using PM3 and B3LYP/6-31+G(d) show possible structures of the heterodimer **12** and homodimer **14** of **8**, and the role of THF and **9** in the solvation of the dimers. Favoured complexes in the equilibria between homo- and heterocomplexes are reported. It is concluded that **9** will completely replace THF in the solvation of the dimers even at low concentrations of **9**.

Introduction

Chiral lithium amides are being developed and used for highly stereoselective deprotonations of, *e.g.*, epoxides to yield enantiomers of allylic alcohols[1–3] for use in synthesis of biologically active compounds.[4–10] Much remains to be discovered about the nature of these reagents in solution. Some have been shown to aggregate to homodimers, which are thus the reagents in the deprotonations.[11–14] There have been a number of attempts to run the stereoselective deprotonations under catalytic conditions.[15–17] The chiral lithium amides have been used in catalytic quantities and the less reactive lithium diisopropylamide (LDA) has commonly been used as a bulk base, *i.e.* as a catalyst-regenerating 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 non-catalytic conditions. The reason for this is presumably that non-stereoselective deprotonation by LDA yields racemic product.

To improve the degree of stereoselectivity of catalytic deprotonations, access to bases that have lower kinetic basicity than LDA, but comparable thermodynamic basicity, are required. In our search for such bases we have recently investigated 1-methylimidazole **1** as a precursor.[22] This compound undergoes carbon deprotonation at the C2-position by, *e.g.*, *n*-butyllithium (*n*-BuLi) to yield the carbenoid species 2-lithio-1-methylimidazole **2** (Fig. 1).

Since proton transfers to carbon are usually slower than to more electronegative atoms like 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 comparable basicity to LDA. As predicted, and in contrast to LDA, compound **2** did not measurably yield any deprotonation of cyclohexene oxide **10** to yield cyclohex-2-enol **11** even after very long reaction times, and thus compound **2** could be used as a bulk base (Table 1, entry 2). It was also found to have a more intimate role through the formation of the reagent heterodimer **3** consisting of a monomer of **2** and a monomer of the homochiral lithium amide **4** generated from the diamine **5**. The heterodimer **3** gave increased enantioselectivity upon deprotonation of epoxide **10** compared with the homodimer of **4**. The structure of this novel heterodimer reagent was in part elucidated using ^{1}H, ^{6}Li and ^{13}C NMR and isotopically labelled compounds. Computational studies have shown possible structures for the heterodimer **3** and the role of THF and **1** in the solvation of the dimers. These results inspired us to explore the potential of heterodimers in catalytic, as well as non-catalytic, deprotonations.

In this paper, we report, as a useful non-reactive bulk base, the carbanionic compound **8** prepared from 1,2-dimethylimidazole **9** (Fig. 1) and *n*-BuLi in THF. Compound **8** did not measurably yield any deprotonation of **10** even after very long reaction times (Table 1, entry 3). Catalytic amounts of **4** in the presence of **8** were found to give a much faster deprotonation of

† Electronic supplementary information (ESI) available: ^{13}C NMR spectra and PM3 enthalpies. See http://www.rsc.org/suppdata/p1/b1/b104336f/

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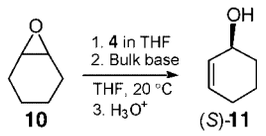
Table 1 Deprotonation of cyclohexene oxide **10**



Entry	[**10**][a]/M	[**4**][a]/M	[**2**][a]/M	[**8**][a]/M	[LDA][a]/M	ee[b] (%)	Yield[c] (%)	Time[d] (*t*/h)
1	0.1	0.2				93	96	25
2	0.1		0.2				0	252
3	0.1			0.2			0	149
4	0.1	0.02			0.2	22	82	32
5	0.1	0.02		0.2		93	96	13
6	0.1	0.1		0.1		96	96	23
7	0.1	0.02	0.2			93	96	198
8	0.1	0.1	0.1			96	96	28

[a] Total concentration. [b] Determined by chiral GLC, see Experimental section. [c] Standard was used, see Experimental section. [d] The reaction was stopped at the time stated.

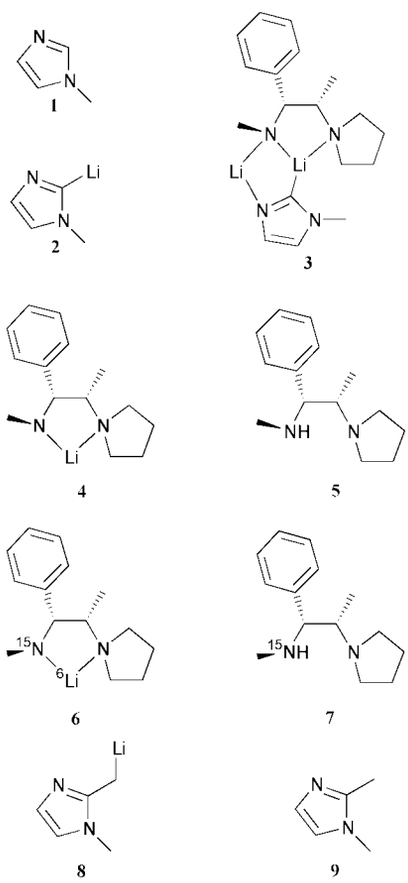


Fig. 1 Structures of labelled and non-labelled precursors and their lithiated counterparts.

10, than that by **4** in the presence of **2** but the increase of stereoselectivity compared with LDA was similar.

The reagent structures have been investigated by multinuclear NMR using isotopically labelled compounds and compound **8** was found to form the novel heterodimer **12** with the lithium amide **4**. This heterodimer is the new reagent in the deprotonation of epoxide **10**. Heterodimers like **3** and **12** may also have great potential as chiral reagents in stereoselective addition to carbonyl and imine functions, *etc.*

Results and discussion

The norephedrine-derived diamine **5** was recently developed to serve as a precursor for the enantioselective lithium amide ligand **4** which deprotonates **10** in THF to yield (*S*)-**11** in 93% ee (Table 1, entry 1).[23,24] When this reaction was run under catalytic conditions using a reaction mixture initially composed of 0.02 M **4**, 0.2 M LDA and 0.1 M **10** in THF at 20 °C the ee decreased to 22% (entry 4). In contrast, using **8** as a bulk base in the catalytic reaction mixture composed of 0.02 M **4**, 0.2 M **8** and 0.1 M **10** gave (*S*)-**11** in 93% ee (entry 5) and the reaction was faster than that with LDA or **2** as bulk base. That the same ee was obtained using **8** as a base in the catalytic reaction as for the non-catalytic reaction of **4** suggests that **8** has been operating as predicted. However, using the carbanionic **8** in equimolar amounts to the lithium amide **4** in THF to deprotonate **10** resulted, to our surprise, in increased enantioselectivity. Allylic alcohol (*S*)-**11** was formed in 96% ee (entry 6), and this enantiomeric excess remained constant during the whole reaction as shown by chiral GLC. This suggests that compound **8** is not functioning only as a bulk base but is also participating intimately in the deprotonation reaction.

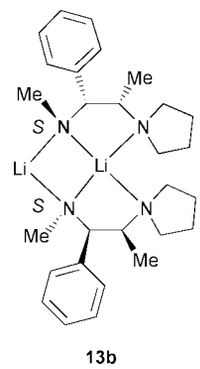


Fig. 2 Possible structure of homodimer **13**.

These findings initiated an investigation of the nature of the reagent **4** in both the presence and the absence of **8**. Previous investigations of the ^{6}Li and ^{15}N isotopologue **6** (Fig. 1) of **4** in THF using ^{1}H, ^{6}Li and ^{13}C NMR spectroscopy at −80 °C have shown that **4** is present mainly as a homodimer **13** (*cf.* below) with non-equivalent lithiums in THF and that one of the lithiums is tetracoordinated and the other tricoordinated. Possible structures of such aggregates with different nitrogen configurations have previously been reported.[23]

Computational studies by PM3 of the states of dimers with and without specific THF solvation predict that the state **13b**·THF has the lowest enthalpy and thus may be the dimer isomer observed in solution (Fig. 2).[23]

Mixed dimer of 4 and 8

Deprotonation (by, *e.g.*, *n*-BuLi) of 1,2-dimethylimidazole **9** has been suggested to take place at either a ring carbon or at the

Table 2 Assigned ^{1}H and ^{13}C NMR chemical shifts at −80 °C in [D_8]THF for selected atoms in **4**, **5**, **8**, **9**, and **12**[b]

Atom	**4** δ	**5** δ	**8** δ	**9** δ	**12** δ
H at C^1			2.95 (3H)	3.54 (3H)	
H at C^3			1.6–1.2 (2H, br)[a]	2.25 (3H)	
H at C^4			5.99 (1H)	6.64 (1H)	
H at C^5			6.06 (1H)	6.88 (1H)	
C^1			32.42	32.62	32.30
C^2			166.7	145.1	164.1
C^3			22.16 (br)[a]	13.10	12.93
C^4			110.8	121.0	112.7
C^5			123.7	127.4	122.9
C^6	45.3	35.8			45.50
C^7	77.4	67.9			76.83
C^8	149.0	143.3			148.9
C^9	72.6	67.1			71.16
C^{10}	54.3–54.6	52.7–53.0			54.1–54.3

[a] At higher temperatures, *e.g.* rt, the signal is sharp. Upon lowering of the temperature the signal becomes broader. [b] The relative orientation of the imidazoloid part has not been determined. Only one of the two possible orientations is shown.

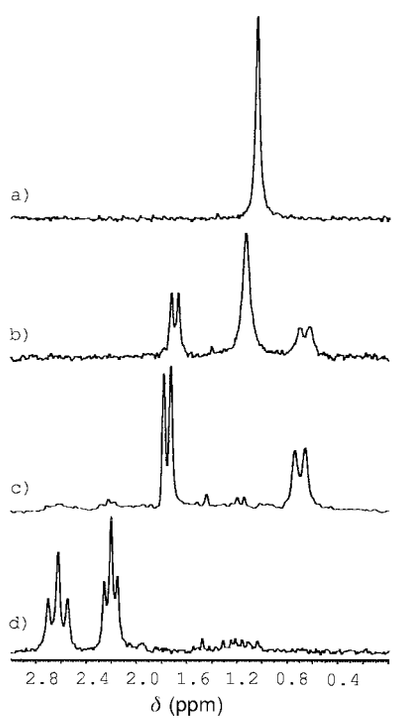


Fig. 3 ^{6}Li NMR spectra, obtained at −80 °C, of [D_8]THF solutions of ^{6}Li-labelled **8** in the absence and the presence of added amine **7**: a) 0.14 M ^{6}Li-labelled **8**; b) 0.25 eq. of **7** added; c) 0.50 eq. of **7** added and d) 1 eq. of **7** added.

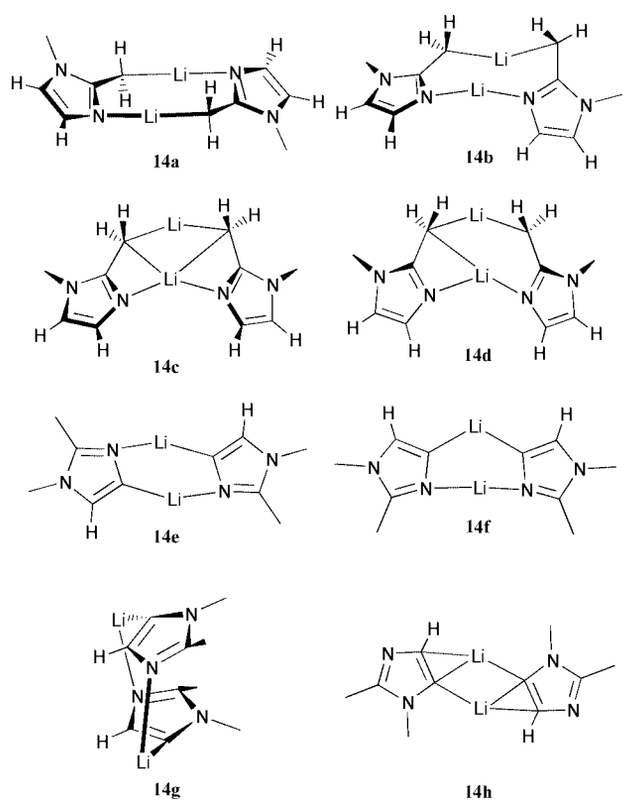


Fig. 4 Possible structures of homodimer **14**.

C2-methyl depending on conditions.[25–27] However, no NMR evidence for the lithiated species has previously been reported. Addition of 1 eq. of *n*-BuLi to 0.14 M THF solutions of **9** held at 20 °C or −78 °C gave yellow solutions. ^{1}H and ^{13}C NMR spectra obtained in the range 20 °C to −100 °C clearly showed a species deprotonated at the C2-methyl group rather than at any of the ring carbons, *i.e.* compound **8** was the exclusive product. NMR chemical shifts are given in Table 2 and ^{1}H and ^{13}C NMR spectra are found in the supplementary information.

Furthermore, a 0.14 M THF solution of **9** was titrated with *n*-Bu[^{6}Li] and the solutions were studied by ^{6}Li NMR (Fig. 3).

A broad singlet was observed at −80 °C after addition of 0.25 eq. *n*-Bu[^{6}Li], which sharpened upon further additions. The ^{6}Li spectrum obtained after addition of 1 eq. of *n*-Bu[^{6}Li] is shown in Fig. 3a. The singlet shows that all lithiums are equivalent. ^{1}H and ^{13}C NMR shows that compound **8** was the product, *i.e.* that the deprotonation had taken place at the C2-methyl. Possibly, **8** is present as homodimers in THF, and in Fig. 4 such structures are displayed.

The PM3 and B3LYP/6-31+G(d) optimised structures of homodimers **14** of lithiated **9** having lowest enthalpies are shown in Fig. 5.

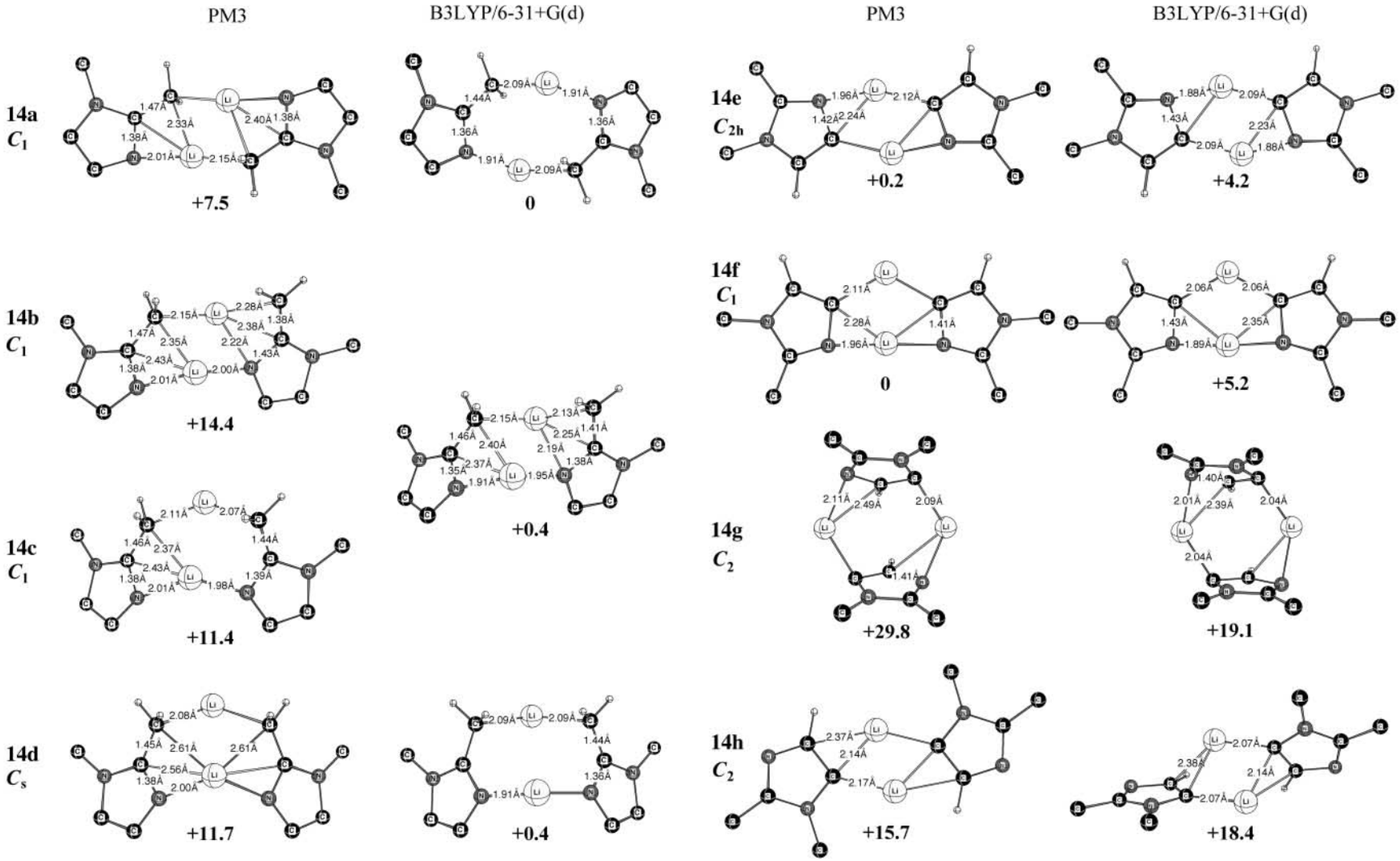


Fig. 5 PM3 and DFT [B3LYP/6-31+G(d)]-optimised structures of homodimers **14a**–**14h**. Some hydrogens are omitted for clarity. Relative energies in kcal mol^{-1} (1 cal = 4.184 J) are given together with symmetry constraints used in optimisations. **14b** and **14c** converged into the same minimum at DFT-level.

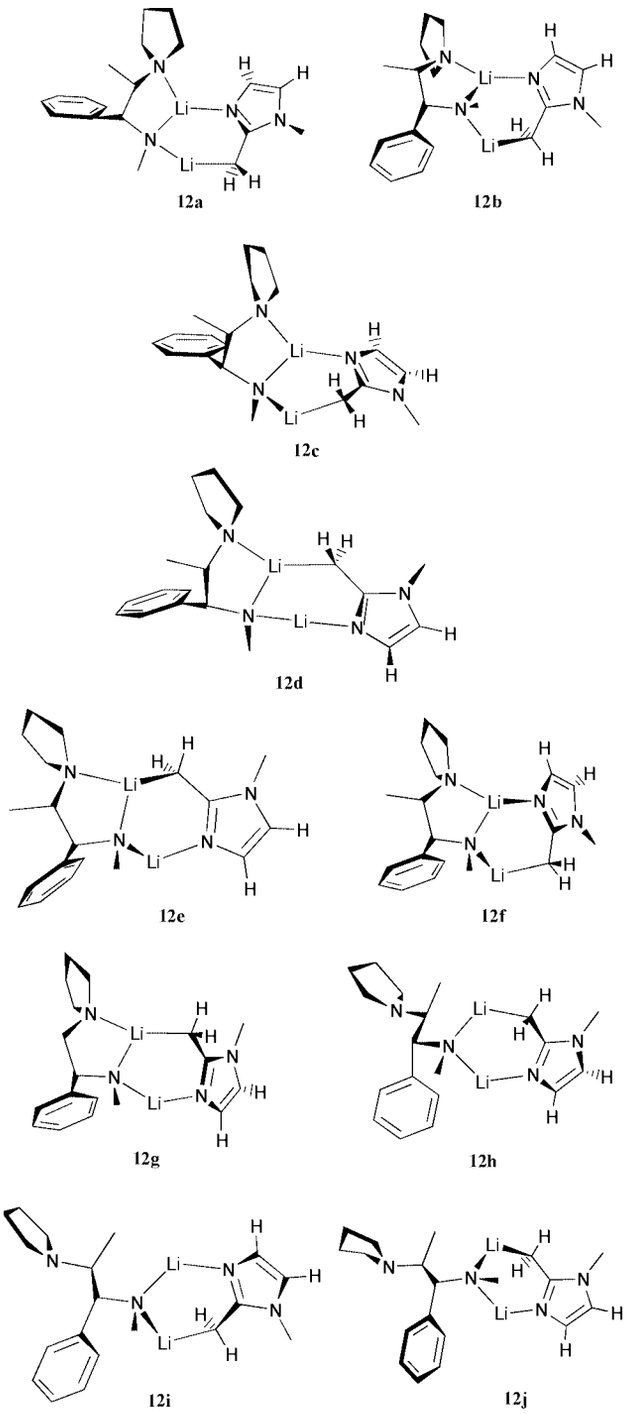


Fig. 6 Possible structures of heterodimer **12**.

Addition of 0.25 eq. of ^{15}N-labelled diamine **7** to this 0.14 M THF solution of ^{6}Li-labelled **8** resulted in the ^{6}Li NMR spectrum shown in Fig. 3b. It shows, besides the broad singlet originating from the ^{6}Li isotopologue of **8**, two doublets – one on each side of the singlet. The measured coupling constants $J(^{6}\text{Li},^{15}\text{N})$ are 4.07 Hz and 5.86 Hz, respectively. The highfield doublet is broader than the lowfield one, and this may be due to slower exchange involving solvation. The two doublets indicate the presence of two non-equivalent lithiums and that each lithium is coupled to only one ^{15}N. ^{1}H and ^{13}C NMR showed that **9** also appeared as a product together with the lithium amide **4**. Thus, the results suggest that a new species had been formed which is not the homodimer **13** since it has previously been shown that the lithiums in **13** give rise to two triplets (*cf.* below).[22] However, consistent with the observations is that the mixed dimer **12**, built from a monomer of **4** and a monomer of **8**, has been formed (Fig. 6).

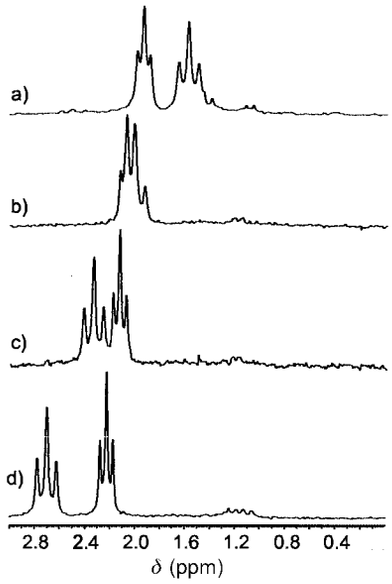


Fig. 7 ^{6}Li NMR spectra, obtained at −80 °C, of [D_8]THF solutions of **6** in the absence and the presence of added **9**: a) 0.14 M **6**; b) 0.25 eq. of **9** added; c) 0.50 eq. of **9** added and d) 1.0 eq. of **9** added.

Thus, the carbanionic compound **8** appears to be a strong enough base to deprotonate the diamine **5** to yield a mixed dimer **12** of a monomer of **4** and a monomer of **8**. The ^{6}Li NMR chemical shift of the signal from remaining ^{6}Li-labelled **8** indicates that **8** is solvated by **9**. This interpretation is also consistent with the ^{1}H and ^{13}C NMR spectra.

The spectrum after addition of altogether about 0.50 eq. of **7** showed that the singlet from ^{6}Li labelled **8** had essentially disappeared (Fig. 3c) and that the heterodimer **12** was the major lithiated species present. However, two minor bands had appeared at lower field (δ 2.20 and 2.65, respectively) emanating from the homodimer **13** of **4** as confirmed by ^{13}C NMR. The doublets and the signals from **4** appear at lower fields, indicating that the heterodimer **12**, as well as the homodimer **13**, are solvated by **9**. In Fig. 3*d* the spectrum obtained after addition of *ca.* 1 eq. of **7** is shown. The two triplets show that the homodimer **13** now is the major component of the mixture and thus its concentration had increased at the expense of the heterodimer **12**.

In another experiment, a 0.14 M THF solution of the homodimer of **6** was prepared from **7** and *n*-Bu[^{6}Li] as previously found.[22] The ^{6}Li NMR spectrum at −80 °C showed mainly two triplets of equal intensity but with different splittings (Fig. 7a). Thus, two different lithiums are present and each of these is coupled with equal coupling constants to two labelled nitrogens (^{15}N), respectively. The coupling constants $J(^{6}\text{Li},^{15}\text{N})$ for the two lithiums were found to be 5.81 Hz and 3.75 Hz, respectively.

Addition of 0.25 eq. of 1,2-dimethylimidazole **9** to a 0.14 M solution of **6** in THF gave a ^{6}Li NMR spectrum displaying two overlapping triplets (Fig. 7b). The triplets from the homodimer of **6**, *i.e.* ^{6}Li-labelled **13** had shifted to lower fields as a result of solvation by **9** when added. Addition of another 0.25 eq. of **9** gave further shifts to lower fields and the now separated triplets were observed (Fig. 7c). The triplet with the larger coupling constant [$J(^{6}\text{Li},^{15}\text{N})$ = 5.81 Hz] had shifted to lower fields than the one with the smaller coupling constant [$J(^{6}\text{Li},^{15}\text{N})$ = 3.75 Hz]. Further addition of **9** resulted only in further shifts of the triplets. Even after the addition of 1 eq. of **9**, no singlet indicating the presence of **8** could be detected (Fig. 7d). Consistent results were also obtained by ^{1}H and ^{13}C NMR. Thus, it is concluded that the lithium amide **4** is not basic enough to deprotonate 1,2-dimethylimidazole **9**, but the carbanionic **8** is obviously a strong enough base to deprotonate diamine **5**. This

contrasts the behaviour of 1-methylimidazole **1** which was found to be deprotonated by **4** to yield the mixed dimer **3**. These findings show that heterodimer **12** is the new reagent in the deprotonation of **10**. This reagent is also regenerated by the bulk base **8**.

LDA also deprotonates DBU yielding lithiated DBU, which like **8** forms chiral heterodimers with **4**. Such heterodimers are reagents in reactions where DBU is used as an additive.

Recently it has been shown that the rate-limiting transition state for the deprotonation of **10** by **4** in THF is composed of a dimer of **4** and one molecule of **10**.[23] Possibly the **12**-promoted elimination of **10** is making use of a rate-limiting transition state built from the heterodimer **12** and one molecule of **10**.

Below, results of PM3 and B3LYP investigations of possible solvated and non-solvated structures of dimers **12** and **14** together with equilibrium enthalpies are discussed.

Computational investigations

The PM3 and B3LYP/6-31+G(d)-optimised structures of compound **14** are shown in Fig. 5 and include dimers of monomers lithiated at 2-methyl, C4, and C5 ring positions. Tables of calculated enthalpies, energies, and Cartesian coordinates are found as supplementary information.

Optimisations using PM3 indicate that the most stable species are **14e** and **14f**, which are lithiated at the C4-ring position. Lithiation at the C2-methyl position results in isomers **14a**–**14d** where isomer **14a** is the most stable of these with 7.5 kcal mol^{-1} higher enthalpy than **14f**. Each of the lithiums in **14a** coordinates to the two carbanionic carbons (2.15 and 2.33 Å, respectively). The core of the structure is a planar, four-membered-ring C–Li–C–Li unit, with each Li internally coordinated to an imine nitrogen (2.01 Å) and an imidine carbon (2.40 Å). Dimer **14h**, the most stable isomer formed from lithiation at the C5 ring position, was found to have 15.7 kcal mol^{-1} higher enthalpy than **14f**. Specific monosolvation by THF of isomers **14a**–**14f** was performed, resulting in the isomer **14f**·THF having the lowest enthalpy. Its solvation enthalpy was calculated to be −6.2 kcal mol^{-1}. The isomer **14a**·THF was about 12 kcal mol^{-1} less stable. Solvation of **14f** by a second THF resulted only in destabilisation. Thus, the results from the PM3 calculations are not consistent with the NMR experiments that show that lithiation takes place exclusively at the C2-methyl position of **9** in THF.

Optimisations using B3LYP/6-31+G(d) on unsolvated PM3-optimised structures showed that isomers lithiated at the C2-methyl and not at a ring carbon were the most stable isomers, in contrast to PM3 results. Now, the dimer **14a** was found to have the lowest energy, and **14e** was calculated to have *ca.* 4 kcal mol^{-1} higher energy. C5-lithiated dimers were found to have *ca.* 20 kcal mol^{-1} higher energy than **14a**.

Optimisation of **14a** resulted in shorter imine nitrogen–Li bonds (1.91 Å, Fig. 5) than at PM3-level (2.01 Å). The C–Li–C–Li four-membered ring is opened and each Li coordinates only to one carbanionic carbon, at a distance of 2.09 Å. Also, the lithium coordination to the imidine carbon is lost at the DFT level, thus making the lithium dicoordinated, and being part of an eight-membered ring. Isomers **14b** and **14c** converged to the same minimum at DFT level, only 0.4 kcal mol^{-1} higher in energy than **14a**. In **14b** each lithium is four-coordinated, with coordination to an imidine carbon, an imine nitrogen, and a carbanionic carbon. In addition to this, one lithium is coordinated to a second imine nitrogen, while the other lithium is coordinated to a second carbanionic carbon, thus making the lithiums non-equivalent. The coordination of lithium resembles that in allyllithiums. In isomer **14d**, which is only 0.4 kcal mol^{-1} higher in energy than **14a**, the coordination between lithium and imidine carbon is lost and hence the isomer forms an eight-membered ring. Also in **14d** the two lithiums are non-equivalent. Thus, the DFT results show that isomer **14a**, with equivalent lithiums, is favoured in agreement with the obtained NMR results.

Interestingly, in some isomers of homodimers **14**, tetracoordinated carbons, with four bonds in a nearly planar arrangement, are found. At PM3-level the sum of bond angles around the imidine carbon is found to be near 362° in compounds lithiated at the C2-methyl (**14a**–**d**), and 360° in isomers **14e**, **14f**, and **14h**, lithiated at C4 and C5, respectively. Each isomeric structure was found to have no imaginary frequencies, *i.e.* they are true minima. At DFT-level the isomers **14a** and **14d** are no longer tetracoordinated, while in both **14b** and **14c** the sum of bond angles is found to be 364°. In **14e** and **14f** the sum of bond angles is calculated to be 360 and 365°, respectively. Recently, a study of potentially observable lithium compounds with planar tetracoordinated carbons including dilithiated imidazoles was published.[28] The authors concluded that solvation would not perturb the planarity.

The most stable PM3-optimised structures of compound **12** are shown in Figs. 8–10. Tables of calculated enthalpies and Cartesian coordinates are found as supplementary information.

Of the unsolvated heterodimers lithiated at the C2-methyl, **12b**, **12e** and **12g** were found to have the lowest, and almost identical enthalpy, at PM3-level of calculations. Isomers **12b** and **12e** differ in orientation of the dimethylimidazoloid part. The two lithium atoms form, together with the imidine carbon, the imine nitrogen, and the carbanion carbon of the dimethylimidazoloid, and the amide nitrogen of **4**, a non-planar 6-membered ring. The two isomers **12e** and **12g** differ in the conformation of this 6-membered ring. Breaking of the internal pyrrolidine nitrogen coordination results in structures **12h**–**j** (Fig. 6) found to be *ca.* 1.5 kcal mol^{-1} higher in enthalpy than **12e**. Only in isomer **12d** could a coordination of the carbanionic carbon to two lithiums be detected (C–Li distances are 2.2 and 2.4 Å, respectively). In other isomers only one lithium is coordinated to the carbanionic carbon, while the distance to the other lithium is increased (C–Li distances are 2.1 and >3.1 Å, respectively).

Specific monosolvation of heterodimers by THF resulted in **12b**·THF (Fig. 8) being lowest in enthalpy with a solvation enthalpy of −7.6 kcal mol^{-1}. The solvent coordinates in most isomers of **12** preferably to the lithium not internally coordinated to the pyrrolidine nitrogen. Disolvation by THF, on the other hand, resulted in **12e**·$(THF)_2$ having lowest enthalpy with a total solvation enthalpy of −9.5 kcal mol^{-1}. Thus, the second THF only gave further stabilisation by 1.9 kcal mol^{-1}. Using **9** as ligand, we found that **12b**·**9** is the favoured isomer with a solvation enthalpy of 19.9 kcal mol^{-1}. Disolvated **12h**·$(9)_2$ is calculated to have a total solvation enthalpy of −32.9 kcal mol^{-1}, thus the second molecule of **9** contributes by a further 14.7 kcal mol^{-1}. In this isomer the lithium–pyrrolidine nitrogen coordination is absent. Thus, **9** binds the heterodimer much more strongly than does THF.

In Scheme 1 some results of the studies of equilibria between homodimers **14** and **13**, and heterodimers **12** with and without specific solvation by THF or 1,2-dimethylimidazole **9** are shown. The most stable state, and used as a reference, is state K in which each Li in **12h** is solvated by 1 molecule of 1,2-dimethylimidazole **9**. In the equilibrium between the unsolvated dimers the state E, with heterodimer **12e**, is favoured over state A, containing homodimers **13b** and **14a**, by 1.3 kcal mol^{-1}. THF solvation of **13b** and **14** results in state B being 7.4 kcal mol^{-1} more stable than state A. The solvation energies obtained by solvation by 1,2-dimethylimidazole **9** were found to be much larger than for solvation by THF. Thus, state C is 18.2 kcal mol^{-1} more stable than B. The state involving the **9**-disolvated homodimers **14a** and **13a** (state D) is 5.7 kcal mol^{-1} less stable than the heterodimeric reference state K. State K is 13.0 kcal mol^{-1} more stable than state G which contains **12b** monosolvated by **9**. State H, containing the THF-disolvated

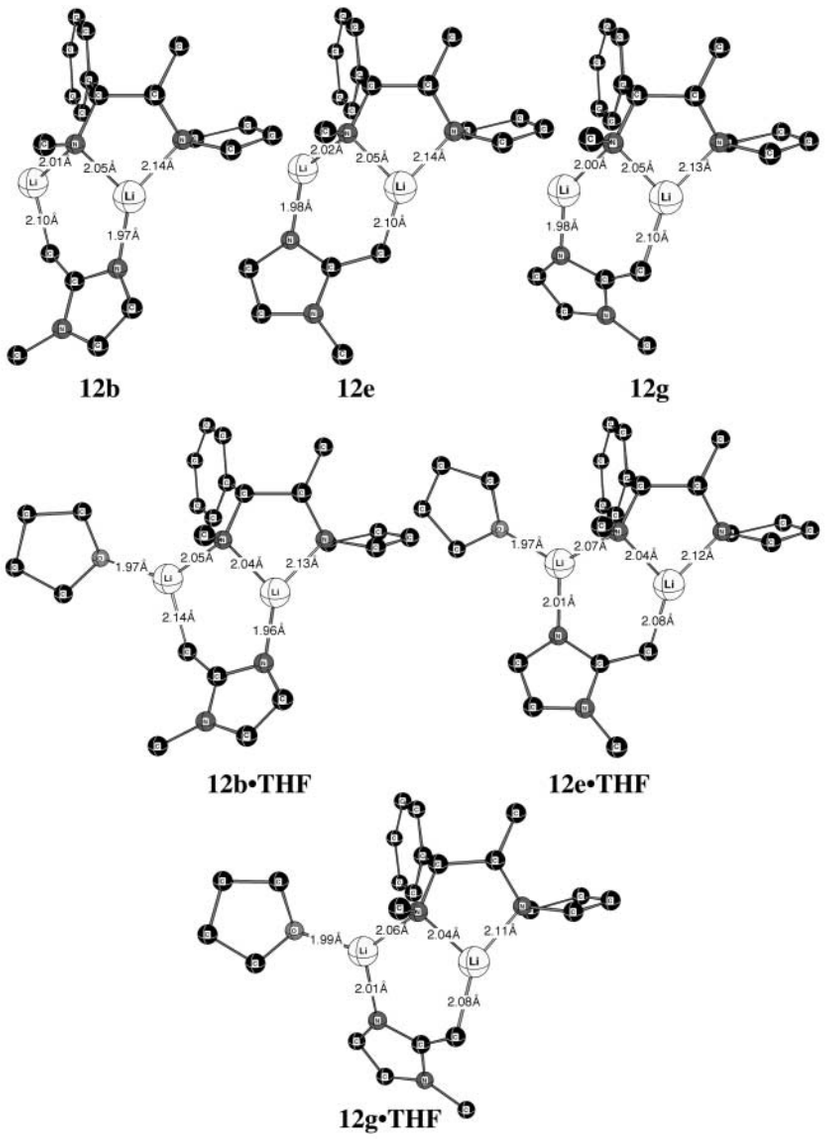
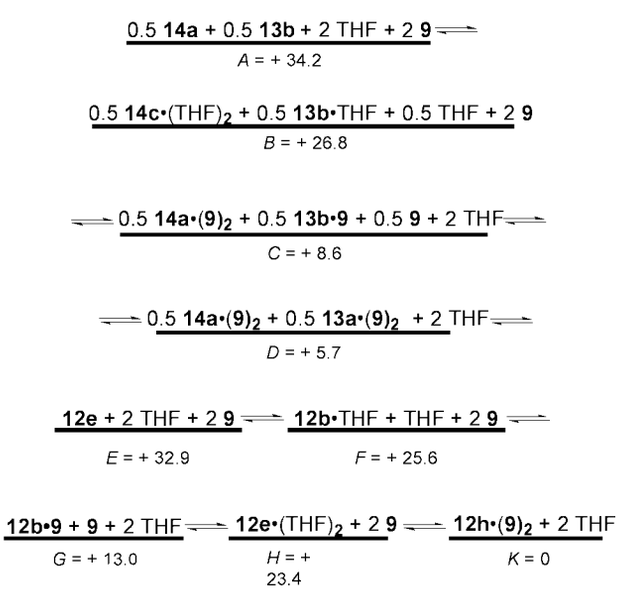


Fig. 8 PM3-calculated unsolvated and THF-solvated structures of heterodimer **12**. Hydrogens are omitted for clarity.



Scheme 1 PM3-calculated enthalpies (kcal mol^{-1}) of states in equilibrium involving dimers with varying degrees of solvation.

heterodimer **12e**•$(THF)_2$ has 23.4 kcal mol^{-1} higher enthalpy than state K. Based on this large enthalpy difference it is concluded that **9** will completely replace THF in the solvation of the dimers even at low concentrations of **9**. This prediction agrees with the NMR observations in which the lithium signals are shifted upon addition of **9** to a THF solution of the heterodimer **12**. A similar effect was observed both by NMR and by calculations in the study of solvation of heterodimer **3** by 1-methylimidazole **1**. Calculated solvation energy of heterodimer **3** with **1** was somewhat higher than solvation energy for heterodimers **12** with **9** (−36.0 kcal mol^{-1} and −32.9 kcal mol^{-1}, respectively).

The scope and limitations of the above findings in asymmetric deprotonations are currently under investigation.

Conclusions

The carbanionic compound 2-(lithiomethyl)-1-methylimidazole **8** is reported as an efficient, non-reactive, bulk base for use in catalytic deprotonations. Compound **8** is shown by multinuclear NMR to form a heterodimer **12** together with a monomer of lithium amide **4**. Complex **12** is the new reactive species in the deprotonation of **10** and is regenerated by the bulk base **8**. Catalytic amounts of **4** in the presence of **8** are found to give fast deprotonation of **10** with increased enantioselectivity. PM3 and B3LYP/6-31+G(d) calculations have shown possible structures for dimers **12** and **14**. For structure **14**, only DFT results are consistent with preferred C2-methyl lithiation as shown by NMR. Favoured states in the equilibria between homo- and heterocomplexes are reported. It is concluded that the dimers

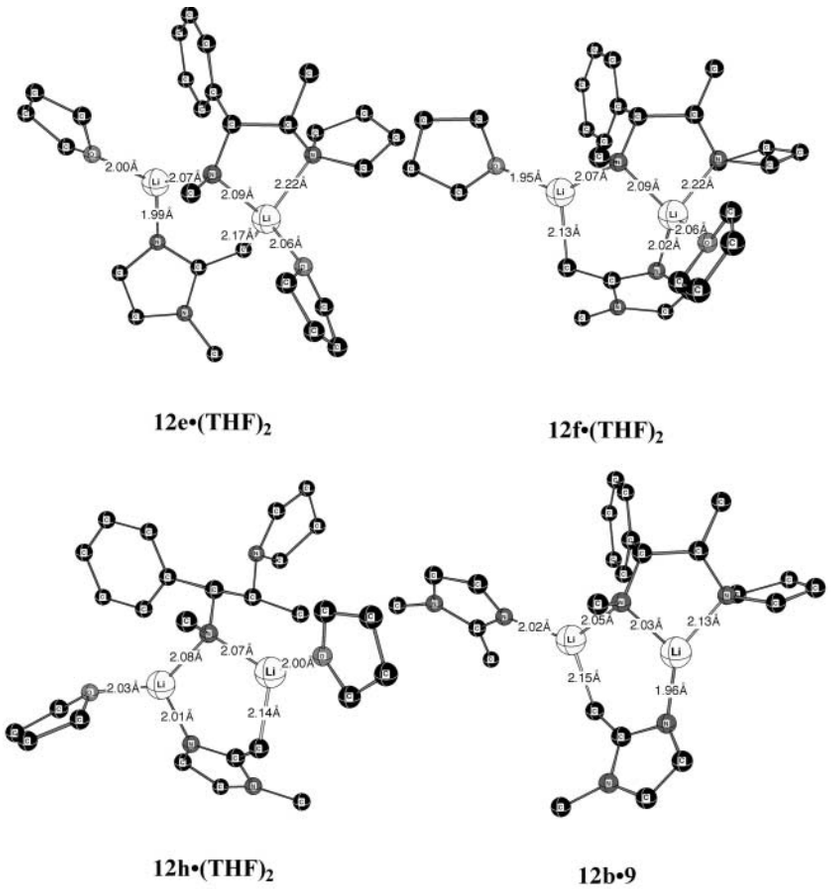


Fig. 9 PM3-calculated THF- and **9**-solvated structures of heterodimer **12**. Hydrogens are omitted for clarity.

12 and **14** are preferably solvated by 1,2-dimethylimidazole **9** rather than by THF.

Experimental

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) containing a nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. All handling of the compounds was carried out with gas-tight syringes. Solvent THF used was distilled from sodium and benzophenone. The concentration of the commercially available *n*-BuLi (≈ 2.5 M in hexanes, Acros) was determined by titration.[23] [D_8]THF was distilled in a vacuum line and stored over molecular sieves (4 Å) in the glovebox. Cyclohexene oxide **10** was distilled from CaH_2. Compound **9** (Aldrich, 98%, mp 35–37 °C) was purified by distillation prior to use and was by NMR and GLC found to be not less than 99.5% pure. *n*-Bu[^{6}Li],[29] Amine **5** and amine **7**[22] were prepared as previously described. All GLC analysis was run on a chiral stationary phase column (CP-Chirasil-DEX CB; 25 m; 0.32 μm) from Chrompack. The column was held at 90 °C (injector 225 °C, detector 250 °C) using helium (2 ml min^{-1}) as carrier gas; t_R(**10**) 3.25 min, t_R[(*S*)-**11**] = 7.45 min, t_R[(*R*)-**11**] = 7.90 min.

NMR, general

All NMR experiments were performed in Wilmad tubes (5 mm) fitted with a Wilmad/Omnifit Teflon valve assembly (OFV) with a Teflon/Silicon septum. NMR spectra were recorded with a Varian Unity 500 spectrometer equipped with a 5-mm 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 (δ 1.73) and from C2 carbon (δ_C 25.57), respectively, in the solvent [D_8]THF. Lithium resonances were referenced to external [^{6}Li] in 0.3 M [^{6}Li]Cl in [D_4]MeOH (δ 0.0) in a separate NMR tube. The probe temperature was measured using a calibrated methanol thermometer from Varian Inc.

Typical NMR experiment

To [D_8]THF (650 μl) in an NMR tube was added **9** (50 μl, 0.1 mmol; 2.0 M stock solution in [D_8]THF). ^{6}Li-labelled compound **8** was prepared by titration of **9** with *n*-Bu[^{6}Li] (*ca.* 10 M; *ca.* 10 μl) by monitoring the disappearance of the signal from the C2-methyl protons in **9** at δ 2.25 and the appearance of the signal from methylene protons in **8** at δ 1.48 at −50 °C. Amine **7** (11 μl, 0.05 mmol, 0.25 eq.) was added and the solution was allowed to equilibrate for 45 minutes before spectra were recorded at −80 °C. ^{6}Li spectra were recorded with: *at* = 2 s, *d*1 = 18 s and *nt* = 32.

Typical rearrangement experiment of 10

Amine **5** (4.4 μl, 0.02 mmol) and **9** (100 μl, 0.20 mmol; 2.0 M stock solution in THF) were added to THF (797 μl) in a reaction vessel in the glovebox. After transfer out of the glovebox, *n*-BuLi (2.47 M in hexanes; 89 μl 0.22 mmol) was added under nitrogen. The yellow reaction solution was allowed to equilibrate at 20.00 ± 0.05 °C for 10 minutes in a thermostat (Heto Birkerød). The reaction was started by addition of cyclohexene oxide **10** (10 μl, 0.10 mmol) to the reaction mixture. To follow the reaction, samples (50 μl) were withdrawn from the reaction vessel at different intervals and diethyl ether (500 μl) was added. The solutions were quenched in saturated aq. NH_4Cl (250 μl) and washed with brine (250 μl). The samples were analysed by chiral GLC. The reaction yield of alcohol **11** was determined using a standard added after the quenching, as previously described.[23]

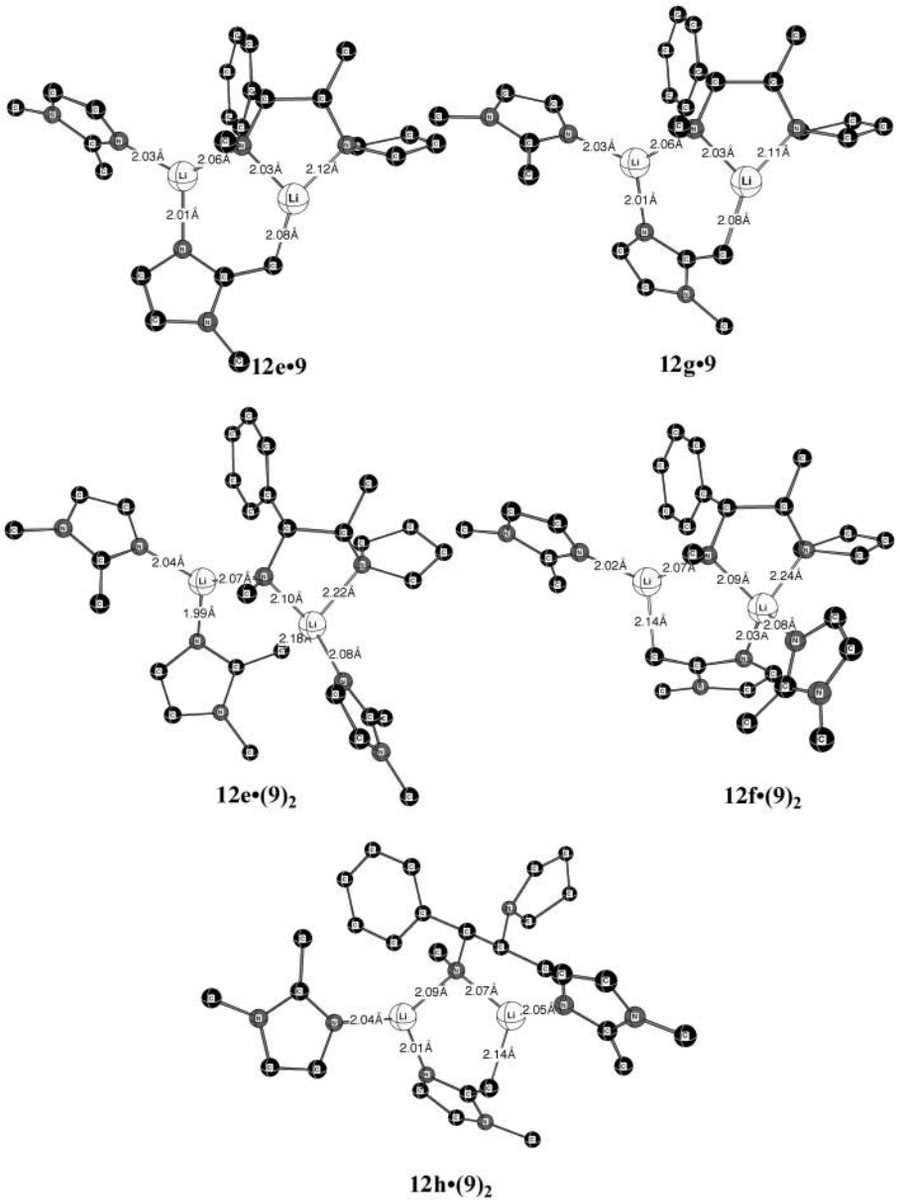


Fig. 10 PM3 calculated **9**-solvated structures of heterodimer **12**. Hydrogens are omitted for clarity.

Computational details

Geometries were optimised at the PM3-level of theory.[30,31] In Spartan[32] the option HHON[33] was used to correct for hydrogens in close contact.[34,35] All geometries were characterised as minima on the potential-energy surface (PES) by use of the sign of the eigenvalues of the force constant matrix obtained from a frequency calculation. Reaction energies were calculated at PM3-level of theory. Single-point calculations using B3LYP/6-31+G(d)[36–40] were performed on selected geometries using Gaussian 98.[41] Optimisations at B3LYP/6-31+G(d) level was performed using the GDIIS algorithm.[42,43]

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