On the novel function of the additive DBU. Catalytic stereoselective deprotonation by a mixed dimer of lithiated DBU and a chiral lithium amide †

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The additive DBU is used to increase the selectivity and reactivity of *e.g.* chiral lithium amides in both catalysed and non-catalysed asymmetric syntheses. This has been attributed to the coordinating ability of DBU favoring more reactive aggregates. However, we have found that LDA in THF deprotonates DBU to yield lithiated DBU (**1**) as shown by multinuclear NMR studies. Furthermore, compound **1** is found to form a mixed dimer (**5**) with *e.g.* the norephedrine-derived chiral lithium amide **2**. Results of an investigation of the stereoselectivity of this novel reagent in the epoxide deprotonation are also reported. Computational studies using PM3 and DFT show possible structures of **1** and **5** in line with the NMR results. In addition, the role of THF and DBU in the solvation of the aggregates has been investigated by computational modelling and favoured complexes in the equilibria between homo- and heterocomplexes are also reported.

Introduction

Chiral lithium amides are being developed and used for highly stereoselective deprotonations such as rearrangement of epoxides to yield enantiomers of allylic alcohols for use in synthesis of *e.g.* biologically active compounds.[1–9] There have been a number of attempts to run such stereoselective deprotonations under catalytic conditions.[10–12] The chiral lithium amide has been used in catalytic quantities and the less reactive lithium diisopropylamide (LDA) has commonly been used as a bulk base to regenerate the chiral lithium amide.[13–17] The enantioselectivity is usually lower under catalytic conditions than under non-catalytic conditions, presumably due to non-stereoselective deprotonation by LDA. However, addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the reaction mixture has in some cases been found to increase the stereoselectivity and influence the rate. It has generally been assumed that this is caused by specific solvation by DBU favoring more reactive aggregates.[16]

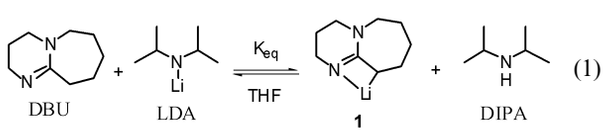
Results in this paper will demonstrate a new and more intricate role of the DBU. We report that DBU is lithiated by LDA or *n*-butyllithium (*n*-BuLi) under the conditions used in asymmetric deprotonations *e.g.* in THF-solutions. Lithiated DBU (**1**) is found to form a mixed dimer with a chiral lithium amide (Fig. 1). Results of an investigation of the stereoselectivity of this novel reagent in epoxide elimination are also reported. Computational studies show possible structures of the reagents and the role of THF and DBU in solvation of the reagent complex.

Results and discussion

Deprotonation of DBU

Addition of 1.0 equiv *n*-BuLi to a 0.3 M THF-d_8 solution of DBU held at 20 °C or −78 °C gave a yellow solution. ^{1}H and ^{13}C NMR spectra obtained at 20 °C and −80 °C showed that DBU had been deprotonated at C6 to afford **1** as the product.[18] ^{1}H,^{1}H-COSY and ^{1}H,^{13}C-HMQC experiments were performed on both DBU and **1** and assigned NMR chemical shifts are given in Table 1. ^{1}H,^{13}C- and ^{1}H,^{1}H-COSY and ^{1}H,^{13}C-HMQC spectra are to be found in the Supporting Information. †[19]

In another experiment, DBU was added to a 0.3 M solution of [^{6}Li]LDA in THF-d_8 and found to be deprotonated at the 6-position yielding [^{6}Li]**1**. In Fig. 2, the ^{6}Li NMR spectra obtained from titration of LDA by DBU at −75 °C are shown, clearly indicating the formation of [^{6}Li]**1** (δ 0.71–1.32) at the expense of LDA (δ 2.11). However, DBU was not completely deprotonated by LDA. An equilibrium between the reactants DBU/LDA and products **1**/diisopropylamine (DIPA) was obtained [eqn. (1)].



(1)

The singlet (δ 0.71–1.32) originating from **1** shifted downfield on addition of DBU, indicating that **1** is solvated by DBU.

Formation of heterodimers

Below results are reported that show that in mixtures of **1** and the chiral lithium amide **2** in THF, heterodimers are formed. The ^{6}Li spectra of a solution prepared from 0.025 mmol (*i.e.* 0.125 equiv/Li) of the ^{15}N labelled amine isotopologue **3b** of **2a** and 0.20 mmol [^{6}Li]LDA and 0.25 mmol DBU (Fig. 3a) show besides the singlets originating from the remaining [^{6}Li]LDA and [^{6}Li]**1**, respectively, two new doublets of equal intensity at δ 0.69 and δ 1.42 [J(^{6}Li,^{15}N] = 5.30 Hz and 4.19 Hz). The two doublets indicate the presence of a species with two non-equivalent lithiums and that each lithium is coupled to only one ^{15}N. ^{1}H and ^{13}C spectra show that **3b** had been deprotonated to provide **2b**. However, it was not the homodimer **4** of **2** that had formed, since the lithiums in **4** give rise to two triplets (see below).[20] Moreover, the two doublets cannot be due to a

† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C, and ^{1}H,^{1}H-COSY and ^{1}H,^{13}C-HMQC spectra. See http://www.rsc.org/suppdata/p2/b2/b205618f/

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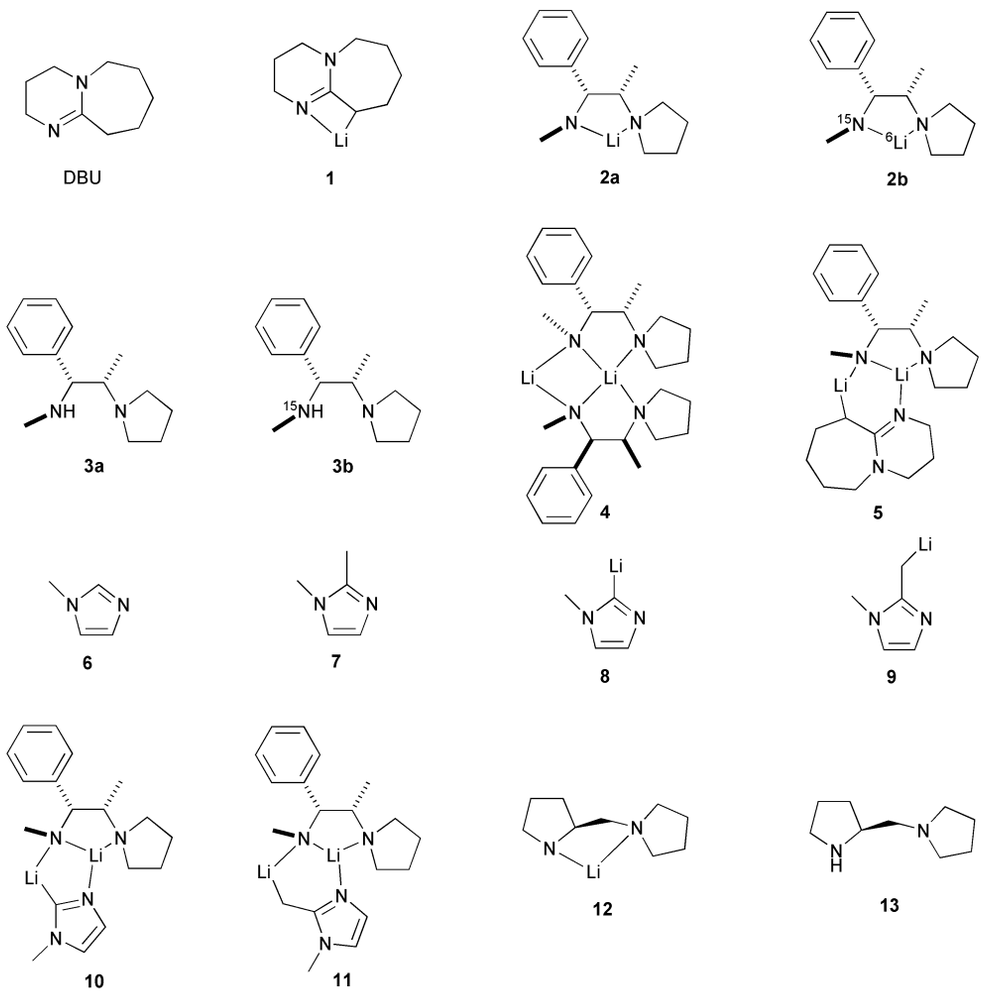


Fig. 1 Structures of labelled and non-labelled precursors and their lithiated counterparts and dimeric complexes.

mixed dimer of LDA and **2** since such a species is not formed in THF upon mixing LDA and **2**. Therefore, we propose that the two new doublets arise from the mixed heterodimer **5** formed from a monomer of **2** and a monomer of **1** (Fig. 1). In **5**, each ^{6}Li is bonded to a single ^{15}N, which is consistent with the results.

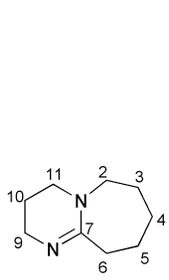
The ^{6}Li NMR spectrum, after addition of another 0.025 mmol **3b** (*i.e.* in total 0.25 equiv/Li) shows doublets with increased intensity (Fig. 3b). In Fig. 3c, the ^{6}Li spectrum obtained after addition of 0.075 mmol **3b** (0.375 equiv/Li) is shown. Obviously, the concentration of the heterodimer **5** has increased—mainly at the expense of **1** rather than LDA. The carbanionic compound **1** is a stronger base than LDA, which is also shown by the equilibrium spectra in Fig. 2. After addition of 0.1 mmol of the [^{15}N]-labelled diamine **3b** (*i.e.* in total 0.5 equiv/lithium), the singlets from [^{6}Li]LDA and [^{6}Li]**1** are essentially absent and now the heterodimer **5** is observed as the main lithiated species [J(^{6}Li,^{15}N) = 5.21 Hz and 4.19 Hz, respectively] (Fig. 3d). Thus, the carbanionic compound **1** is a strong enough base to deprotonate the diamine **3** to yield the novel heterodimer **5** built from a monomer of **2** and a monomer of **1**. The heterodimer **5** is also formed from amine **3** and lithiated DBU **1** generated from *n*-BuLi in absence of LDA.

The ^{6}Li NMR spectrum of 0.15 M solution of **2b** (Fig. 4a) prepared from equal amounts of [^{6}Li]*n*-BuLi and **3b** displays two triplets (δ 1.55 and δ 1.90) of equal intensity but with different splittings [J(^{6}Li,^{15}N) = 5.81 Hz and 3.75 Hz, respectively] originating from the homodimeric structure **4** of lithium amide **2**. Addition of DBU to this solution shifted only the two triplets to lower fields, presumably as a result of Li-solvation by DBU. After addition of 1.0 equiv DBU the triplet with the larger coupling constant [J(^{6}Li,^{15}N) = 5.81 Hz] had shifted to lower fields than the triplet with smaller coupling constant [J(^{6}Li,^{15}N) = 3.75 Hz]. Evidently, the homodimer **4** is not a strong enough base to deprotonate DBU. In addition, ^{1}H and ^{13}C NMR spectra clearly show that deprotonation of DBU does not occur under these conditions. (The ^{1}H spectra show 2 protons at δ 2.27, and the ^{13}C spectra show tertiary carbons at δ 164). Upon addition of 0.5 equiv [^{6}Li]*n*-BuLi two doublets of equal intensity appeared [δ 1.57, J(^{6}Li,^{15}N) = 4.19 Hz and δ 0.83, J(^{6}Li,^{15}N) = 5.22 Hz] (Fig. 4b). Furthermore, the ^{1}H and ^{13}C NMR spectra indicated that deprotonation of DBU had yielded the heterodimer **5**. Addition of another 0.5 equiv [^{6}Li]-*n*-BuLi resulted in the ^{6}Li spectra shown in Fig. 4c. Apparently, the heterodimer now is the dominating lithiated component in the solution. The high field doublet (δ 0.90) being broader than the other doublet (δ 1.60) indicates slow exchange involving solvating DBU. Upon addition of up to 0.5 equiv DBU to the above solution (Fig. 4d) the high field doublet became sharper probably due to faster ligand exchange at the high concentration of DBU. Further addition of 0.5 equiv DBU resulted in the ^{6}Li NMR spectrum shown in Fig. 4e consistent with the proposed solvent effect. The coupling constants [J(^{6}Li,^{15}N)] for the two doublets are 5.19 Hz and 4.19 Hz, respectively.

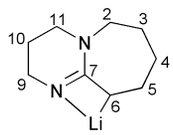
Thus these NMR findings show that DBU is deprotonated both by LDA and *n*-BuLi in THF solutions and that lithiated DBU (**1**) is involved in formation of a heterodimer together with a chiral lithium amide.

In a previous search for new useful bulk bases to be used in catalytic asymmetric deprotonations we have investigated 1-methylimidazole (**6**) and 1,2-dimethylimidazole (**7**) as bulk base precursors.[21,22] These compounds were like DBU found to be deprotonated by *n*-BuLi and yielded the carbenoid species

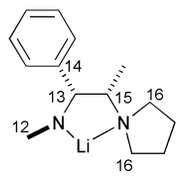
Table 1 Assigned ^{1}H and ^{13}C NMR chemical shifts at −75 °C in THF-d_8 for selected atoms in **2**, **3**, DBU, **1** and **5**



DBU



1



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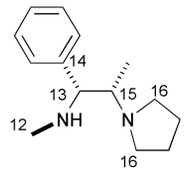

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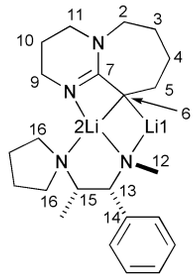
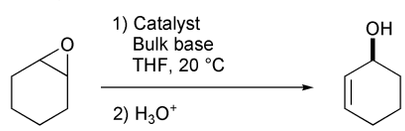


5

Atom	δ	δ	δ	δ	δ
H at C_2	3.15	3.14			
H at C_3	1.53	1.60			
H at C_4	1.60	1.45			
H at C_5	1.55	2.00			
H at C_6	2.27	2.68			
H at C_9	3.12	3.06			
H at C_{10}	1.70	1.68			
H at C_{11}	3.17	3.10			
C_2	53.36	54.76			
C_3	29.89	30.66			
C_4	31.00	30.19			
C_5	27.50	28.17			
C_6	38.15	59.89			60.72
C_7	160.1	164.9			165.4
C_9	49.45	45.33			
C_{10}	24.09	28.34–30.51			
C_{11}	49.19	50.97			
C_{12}			45.3	35.8	45.35
C_{13}			77.4	67.9	
C_{14}			149.0	143.3	149.8
C_{15}			72.6	67.1	
C_{16}			54.3–54.6	52.7–53.0	54.1–54.3

Table 2 Stoichiometric and catalytic deprotonation of cyclohexene oxide **14**



14 (*S*)-**15**

Entry	[**14**]/M	[DBU]/M	[DIPA]/M	[**6**]/M	[**7**]/M	[**3**]/M	[**13**]/M	[*n*-BuLi]/M	Reaction time/h	Yield (%)[a]	ee (%)[b]
1	0.1	0.5				0.02		0.22	56	93	69
2	0.1	0.5	0.2			0.02		0.22	69	82	16
3	0.1	0.5					0.02	0.22	7	89	79
4	0.1	0.2				0.1		0.3	240	57	89
5	0.1	0.5				0.1		0.3	60	88	94
6	0.1	0.5	0.2				0.02	0.22	7	81	74
7	0.1						0.1	0.1	8	78	80
8	0.1			0.2		0.02		0.22	198	96	93
9	0.1				0.2	0.02		0.22	13	96	93
10	0.1			0.2		0.1		0.3	25	96	96
11	0.1				0.2	0.1		0.3	25	96	96

[a] The yield of **15** was determined by using internal standard. [b] Determined by chiral GC.

2-lithio-1-methylimidazole (**8**) and the carbanionic species 2-(lithiomethyl)-1-methylimidazole (**9**), respectively (Fig. 1). The role of the bases **8** and **9** in the reactions was also found to be more intricate than just acting as bulk bases. Together with the chiral lithium amide catalyst they were found to form the heterodimers **10** and **11**, respectively.

Stereoselective deprotonation of cyclohexene oxide

The base lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidinide **12** derived from the amine **13** reported by Asami *et al.* has been used in several synthetic procedures to generate allylic alcohols in enantiomeric excess (Fig. 1).[13,23] It has been used in stoichiometric amounts to deprotonate cyclohexene oxide **14** to yield (*S*)-cyclohex-2-en-1-ol (*S*)-**15** in 80% ee (Table 2, entry 7). Running the reaction using **12** in catalytic amounts together with **1** as bulk base generated from DBU and *n*-BuLi, (*S*)-**15** is formed in 79% ee (entry 3). On the other hand, when lithium amide **12** is used in catalytic amounts in presence of excess LDA and DBU, the ee decreased to 74% ee (entry 6). The decrease in selectivity in the presence of LDA is probably due to the background reaction by LDA. These findings indicate that **1** is functioning as catalyst-regenerating base and participates in a catalytic cycle.

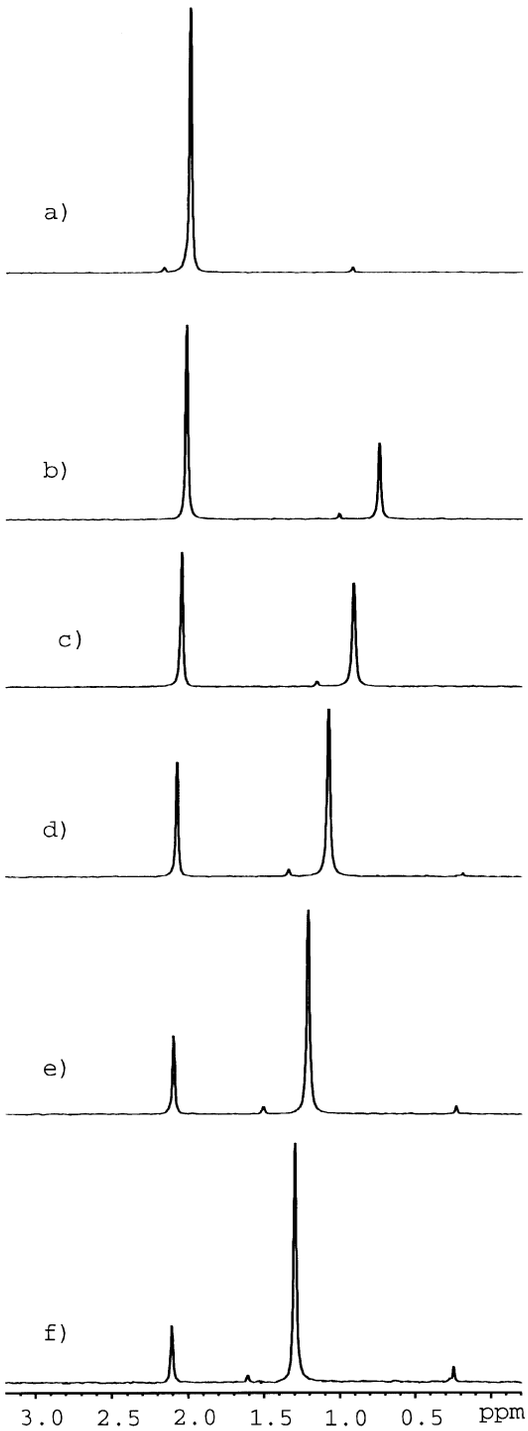


Fig. 2 ^{6}Li NMR spectra obtained at −75 °C of a THF-d_8 solution of 0.3 M [^{6}Li]LDA in the absence and presence of added DBU: a) 0.3 M [^{6}Li]LDA; b) 0.025 equiv DBU added; c) 0.5 equiv DBU added; d) 0.75 equiv DBU added; e) 1.0 equiv DBU added; and f) 1.25 equiv DBU added.

Employing the homodimer **4** as reagent in the deprotonation of **14** yields, as previously reported, (*S*)-**15** in 93% ee (entries 8–9).[20] Running the reaction using **2** in catalytic amounts together with **1** as bulk base generated from DBU and *n*-BuLi, (*S*)-**15** is formed in 69% ee (entry 1) due to change of reagent *i.e.* to the heterodimer **5**. If LDA is used as bulk base instead of **1**, in the reaction described above, the ee is drastically decreased to 16% (entry 2). When employing stoichiometric amounts of lithium amide **2** and bulk base **1** in THF the selectivity increases to 89% ee in the absence of excess DBU (entry 4) and to 94% ee in the presence of excess DBU (entry 5). Employing compounds **8** or **9**, higher enantiomeric excesses were obtained as previously reported (entries 10–11).[21,22] These results show that

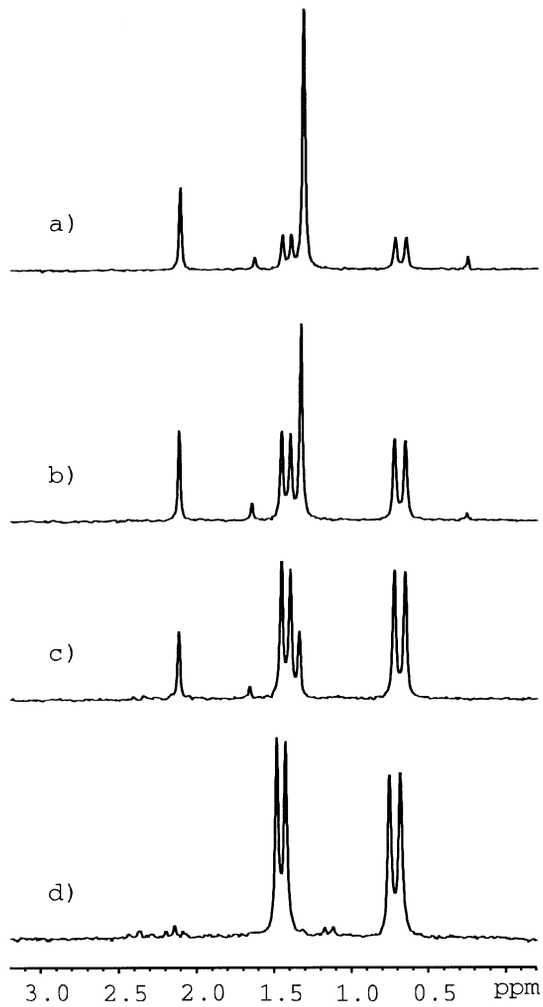


Fig. 3 ^{6}Li NMR spectra obtained at −75 °C of a THF-d_8 solution prepared from 0.20 mmol [^{6}Li]LDA and 0.25 mmol of DBU titrated with diamine **3b**: a) 0.025 mmol diamine **3b** added; b) 0.05 mmol diamine **3b** added; c) 0.075 mmol diamine **3b** added; and d) 0.1 mmol diamine **3b** added.

the choice of bulk base for a particular chiral ligand is significant. Amide **2** is most stereoselective in the presence of bulk base **9** and amide **12** is most stereoselective in the presence of bulk base **1**. Furthermore, the use of LDA is not required to obtain a catalytic cycle when employing **1**, **8** or **9**.

The generality of this behavior is currently being investigated.[24]

Computational investigations

Monomer and homodimer structures of lithiated DBU

The PM3 and DFT optimised structures of the monomer of C6-lithiated DBU **1** are given in Fig. 5. The structures of homodimer **16** of **1** are shown in Fig. 6 together with the THF- or DBU-solvated structures. The role of the solvent was examined by specific THF- and DBU-solvation. Conformational searches were performed to find the most stable conformation of the rings of DBU together with searches with respect to rotation around Li-solvent bonds. Atom numbering is given in Table 1.

Upon deprotonation–lithiation of DBU at C6, the monomer **1** is formed. DFT-optimisation (B3LYP/6–31+G(d)) of the structure results in lithium-coordination to N8 (1.9 Å), C6 (2.0 Å) and C7 (2.3 Å), thus tricoordination to the azaallylic system. Optimisation of **1** using PM3 results in weaker coordination by lithium to the azaallylic system than at DFT-level as seen from the longer bond distances. Deprotonation

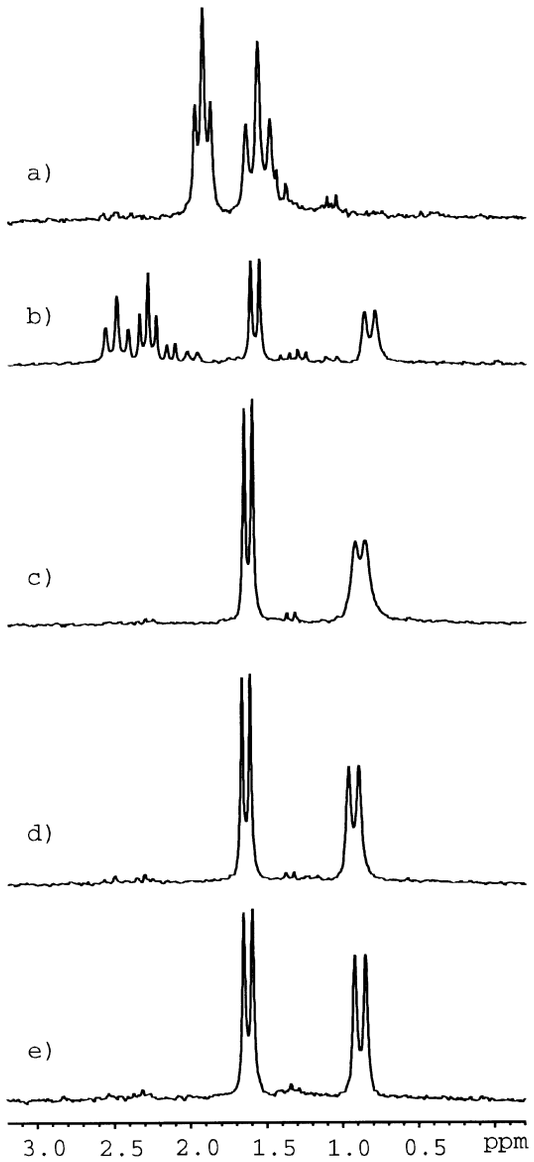


Fig. 4 ^{6}Li NMR spectra obtained at −75 °C of a THF-d_8 solution prepared from a solution of 0.15 M of **2b** and added DBU and [^{6}Li]*n*-BuLi: a) 0.15 M **2b**; b) 1.0 equiv DBU and 0.5 equiv [^{6}Li]*n*-BuLi added; c) 1.0 equiv DBU and 1.0 equiv [^{6}Li]*n*-BuLi added; d) 1.5 equiv DBU and 1.0 equiv [^{6}Li]*n*-BuLi added; e) 2.0 equiv DBU and 1 equiv [^{6}Li]*n*-BuLi added.

followed by lithiation at other positions than at C6 in DBU was also examined by PM3. All such isomers were found to have higher enthalpy than **1**, which is in agreement with the experimental findings.

Formation of the homodimer **16** from two monomers of **1** is strongly exothermic, −31.8 kcal mol^{-1} at pBP86/DN*//PM3-level and −26.7 kcal mol^{-1} at PM3//PM3-level. The most stable isomer at PM3//PM3-level is **16a**, while at pBP86/DN*//PM3-level isomer **16b** is calculated to be 8.1 kcal mol^{-1} more stable than **16a**. These two isomers differ in the conformations of the ring system of DBU. Optimisation of **16a** at B3LYP/6–31+G(d)-level results in shorter bonds between lithium and the azaallylic system than found at PM3-level. In the dimer each lithium is tricoordinated to the azaallylic system of one monomer and also coordinates the carbanionic carbon in the other monomer. Each lithium in the dimer coordinates to two carbanionic centers at 2.2–2.3 Å, to C7 at 2.4 Å and to an imine nitrogen at 1.9 Å at DFT-level. In the dimeric azaallylic moiety the Li–C7 bonds are 0.1 Å longer at DFT-level than in the monomer, while the Li–C6 bonds in the dimer are 0.3 Å longer than in the monomer using DFT.

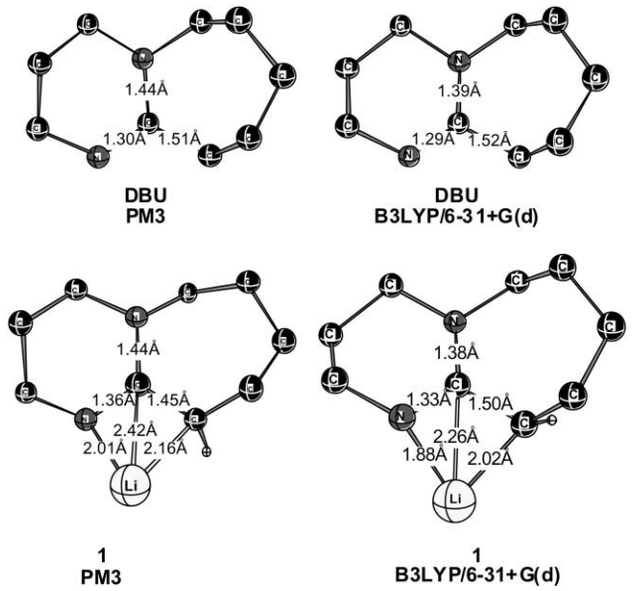


Fig. 5 PM3 and DFT (B3LYP/6–31+G(d)) optimised structures of DBU and lithiated DBU **1**.

Homodimer solvation

Specific solvation of the dimer **16** by one THF (**16·THF**) at PM3-level resulted in loss of the allylic carbon–lithium coordination in one of the monomeric units (Fig. 6). Li1 is solvated by THF (2.0 Å) and coordinates also to an imine nitrogen (2.1 Å) and a carbanionic carbon (2.3 Å). This makes the carbanionic carbon pentavalent. The other lithium (Li2) is tetracoordinated *via* the azaallylic moiety and the imine nitrogen (2.0 Å). In the azaallylic unit not having carbanion–lithium coordination, the bond distances are similar to those found in the monomer **1**. The solvation enthalpy is calculated to be −5.2 kcal mol^{-1}.

With monosolvation of **16** by DBU, the bond distances to lithium are all similar compared to the THF-solvated dimer. The distance between Li1 and the solvent is 2.1 Å, somewhat longer than for THF. The solvation enthalpy is found to be −14.7 kcal mol^{-1} at PM3//PM3-level.

In the THF-disolvated dimer **16·(THF)$_2$** the lithiums have only coordination to the nitrogens in the azaallylic moieties. Each lithium coordinates to two imine nitrogens at 2.1 Å, and a solvent molecule at 2.0 Å. In the azaallylic system the C6–C7 bonds are shortened by 0.14 Å to 1.36 Å upon loss of coordination to lithium and thus have more double bond character, while the C7–N8 bonds are elongated by 0.11 Å to 1.44 Å, *i.e.* have less double bond character.

Disolvation by DBU has a similar effect on the dimer as found for disolvation by THF: only lithium–nitrogen coordinations could be detected. The lithium–DBU distances are calculated to be 2.1 Å.

The solvation enthalpy from a second solvating THF is found to be −4.6 kcal mol^{-1} and the corresponding enthalpy for the second DBU is −13.2 kcal mol^{-1}. From results presented in a previous study we expect the solvation enthalpies for THF to be underestimated using PM3, while the solvation enthalpies for DBU are probably overestimated.[22]

Heterodimer structures

PM3- and DFT-optimised structures of the heterodimer **5** are given in Fig. 7. The structures represent the most stable isomers. Formation of heterodimer **5** from a monomer of lithium amide **2** and a monomer of lithiated DBU (**1**) is exothermic by −36.8 kcal mol^{-1} at PM3//PM3-level. In **5**, one lithium (Li1) is dicoordinated while the other (Li2) is tricoordinated. The N8–C7-bond is calculated to be 1.34 Å using DFT, similar to

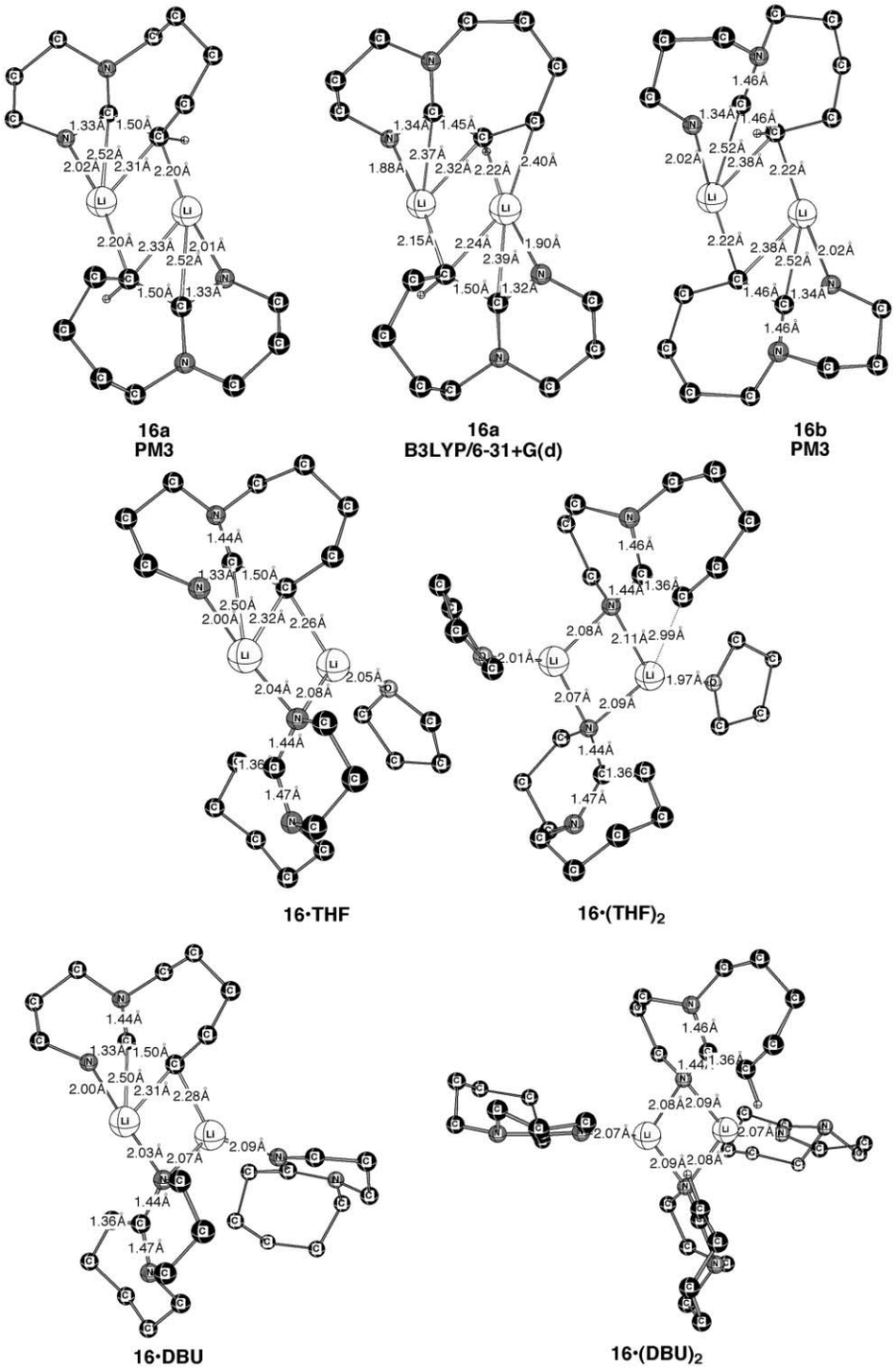


Fig. 6 PM3 and DFT (B3LYP/6–31+G(d)) optimised structures of homodimer **16** of lithiated DBU with and without solvation by THF and DBU.

the distance found in the homodimer **16**. The C6–C7-bond is slightly shorter in **5** than in the homodimer, 1.42 Å and 1.45 Å, respectively. The imine N8–Li2 bond is found to be 1.93 Å, while the carbanionic carbon coordinates to Li1 at a distance of 2.13 Å. No lithium coordination to C7 in the azaallylic system was found in the heterodimer **5**. The amide nitrogen originating from the monomer of **2** coordinates to both lithiums at 1.88 and 1.98 Å, respectively. Li2 has a third nitrogen coordination to the pyrrolidine nitrogen (2.1 Å).

Heterodimer solvation

Upon monosolvation of **5** by THF, Li1 rather than Li2 is solvated. The Li–O(THF) distance at PM3-level is calculated to be 2.0 Å and the solvation enthalpy at both PM3//PM3-level and pBP86/DN*//PM3-level is −6.8 kcal mol^{-1}. The bonds to the solvated lithium are somewhat elongated upon solvation.

Solvation of **5** by DBU results in a longer solvent–Li bond (2.1 Å) compared to solvation by THF (2.0 Å). Other bonds are almost unaffected by the solvent change. The solvation enthalpy is found to be −16.0 kcal mol^{-1} at PM3//PM3 level and −8.3 at pBP86/DN*//PM3-level.

Disolvation by THF results in a structure without pyrrolidine nitrogen–lithium coordination. The bond distance between Li2 and the second THF is 2.0 Å and the second solvation enthalpy is calculated to be only −1.7 kcal mol^{-1} at PM3 and −1.6 kcal mol^{-1} at pBP86/DN*//PM3-level.

Disolvation with DBU also results in a structure without pyrrolidine nitrogen–lithium coordination. The solvent–lithium bond distances are calculated to be 2.11–2.12 Å at PM3-

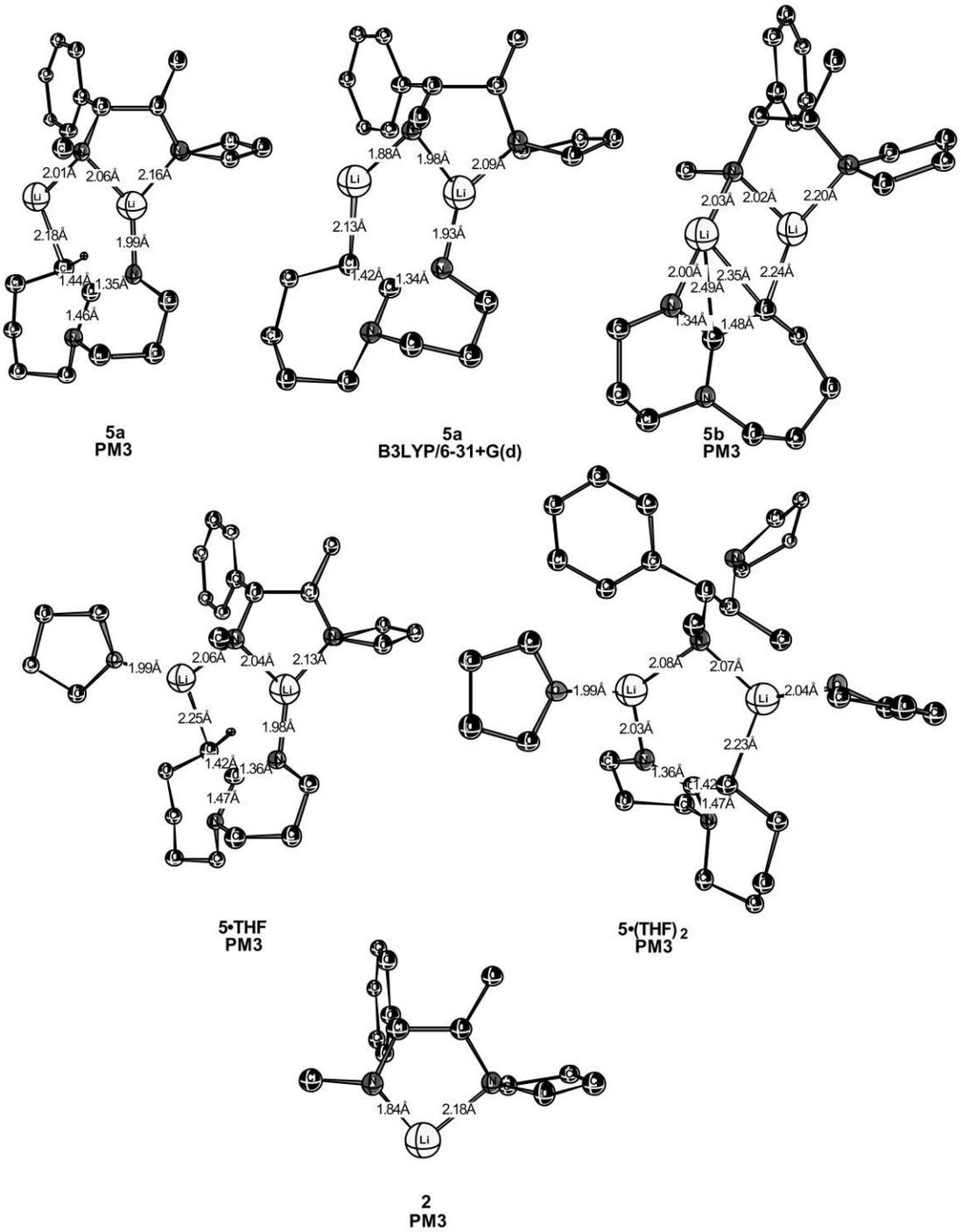


Fig. 7 PM3 and DFT (B3LYP/6–31+G(d)) optimised structures of the heterodimer **5** and monomer of **2** unsolvated and solvated by THF. Hydrogens are omitted for clarity.

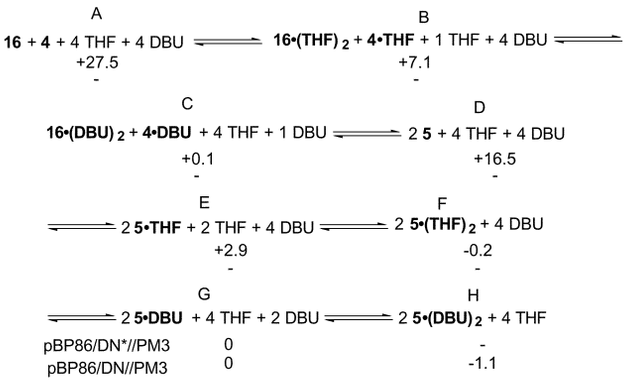
level and the calculated second solvation enthalpy for DBU is −8.0 kcal mol^{-1} using PM3//PM3 but only −0.6 kcal mol^{-1} at pBP86/DN//PM3-level.

In Scheme 1, studies of equilibria between homo- and heterodimers with and without solvation by THF or DBU are shown. Relative energies are calculated at pBP86/DN*//PM3 and pBP86/DN//PM3 levels of theory. State G, involving the DBU-monosolvated heterodimer **5·DBU** is used as the reference state. The DBU-disolvated heterodimer **5·(DBU)$_2$**, part of state H, is only 1.1 kcal mol^{-1} more stable than state G. This low solvation enthalpy indicates that the mono-solvated heterodimer is preferred. State E, involving the THF-monosolvated heterodimer, is found to be 2.9 kcal mol^{-1} less stable than the reference state. Thus, DBU solvates the heterodimer better than THF, in accordance with the observed solvent effect upon the NMR-spectra as described previously. Similar conclusions can be drawn for states B and C. The disolvated homodimers, part of state C, are only 0.1 kcal mol^{-1} less stable than state G.

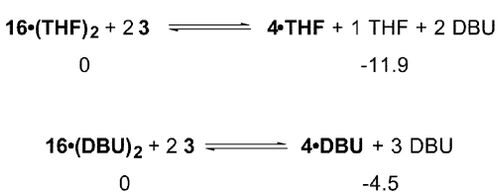
In Scheme 2, the basicity of the homodimer **16** of lithiated DBU **1** and homodimer **14** of lithium amide **2** is compared. It is found that thermodynamically it is favourable to deprotonate the diamine **3** with **16** rather than to deprotonate DBU with **4**. This correlates with the experimental observations.

Conclusion

DBU is deprotonated by LDA in THF and the product lithiated DBU (**1**) forms heterodimers with chiral lithium amides. Such heterodimers are the new reagents in the present stereoselective



Scheme 1 pBP86/DN*//PM3 and pBP86/DN//PM3 calculated relative enthalpies (kcal mol^{-1}) of states in equilibrium involving dimers with varying degree of solvation.



Scheme 2 pBP86/DN*//PM3 calculated relative enthalpies in kcal mol^{-1}.

deprotonations and presumably also in previous similar applications of DBU. The match between the bulk base and the chiral lithium amide determines the stereoselectivity. Compound **1** also functions as a bulk base in catalytic stereoselective deprotonations. The additive DBU is also functioning as a solvating ligand. Computational studies have given insights into structures of reagents and solvation.

Experimental

General

All syringes and glass vessels used were dried overnight in a vacuum oven (50 °C) before being transferred into a glove box (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 were carried out with gas-tight syringes. THF was distilled from sodium and benzophenone. The concentration of the commercially available *n*-BuLi (*ca.* 2.5 M in hexanes, Acros) was determined by titration.[20] THF-d_8 was distilled in a vacuum line and stored over molecular sieves (4 Å) in the glove box. Diisopropylamine, DBU, and cyclohexene oxide were purified by distillation from CaH_2 and were found to be >99.5% pure by NMR and GC. [^{6}Li]*n*-BuLi,[21] amine **3a**,[20] **3b**,[21] and **13**[23] were prepared as described. All GC 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 a carrier gas. t_R(**14**) = 3.25 min, t_R((*S*)-**15**) = 7.45 min, t_R((*R*)-**15**) = 7.90 min.

NMR spectroscopy

All NMR experiments were performed in Wilmad tubes (5 mm) fitted with a Wilmad/Omnifit Teflon valve assembly (OFV) and a Teflon/Silicon septum. 1D 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). ^{1}H,^{1}H-COSY and ^{1}H,^{13}C-HMQC NMR spectra were recorded with a Varian Unity 600 MHz. The ^{1}H and ^{13}C spectra were referenced to signals from residual protons at C2 (δ 1.73) and from C2 carbon (δ 25.57), respectively, in the solvent THF-d_8. Lithium resonances were referenced to external [^{6}Li] in a 0.3 M [^{6}Li]Cl in MeOH-d_4 (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 THF-d_8 (650 μl) in an NMR tube was added diisopropylamine (28 μl, 0.2 mmol). [^{6}Li]LDA was prepared by titration of diisopropylamine with [^{6}Li]*n*-BuLi (*ca.* 10 M, *ca.* 20 μl) by monitoring the disappearance of the signal from the methine protons in diisopropylamine at δ 2.85 and the appearance of the signal from methine protons in [^{6}Li]LDA at δ 3.05 at −75 °C. DBU (7.5 μl, 0.05 mmol, 0.25 equiv) was added and the solution was allowed to equilibrate for 45 minutes before spectra were recorded at −75 °C.

Typical deprotonation experiment of 14

Amine **3a** (4.4 μl, 0.02 mmol) and DBU (30 μl, 0.20 mmol) were added to THF (867 μl) in a reaction vessel in the glove box. After transfer of the vessel out of the glove box, *n*-BuLi (89 μl, 2.47 M in hexanes, 0.22 mmol) was added in a nitrogen atmosphere. The yellow solution was allowed to equilibrate at 20.00 ± 0.05 °C for 10 minutes prior to addition of cyclohexene oxide **14** (10 μl, 0.10 mmol). To follow the reaction, 50 μl samples were withdrawn from the reaction vessel at different intervals and diluted with diethyl ether (500 μl). The solutions were quenched in saturated NH_4Cl (250 μl) and washed with brine (250 μl). The reaction yield of **15** was determined by GC using a standard added after the quenching as previously described.[20]

Computational details

Geometries were optimised at PM3[25,26] and B3LYP/6–31+G(d) levels of theory.[27–31] In Spartan[32] the option HHON was used to correct for hydrogens in close contact.[33] All geometries were characterised as minima on the potential energy surface (PES) by the sign of the eigenvalues of the force constant matrix obtained from a frequency calculation. Reaction energies were calculated at pBP86/DN*//PM3,[32,34,35] pBP86/DN//PM3, and PM3//PM3-levels of theory.

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