Kinetic and NMR Spectroscopic Studies of Chiral Mixed Sodium/Lithium Amides Used for the Deprotonation of Cyclohexene Oxide

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Abstract: The mixed-metal complex formed from *n*-butylsodium, *n*-butyllithium, and a chiral amino ether has been studied by NMR spectroscopy. Three different mixed-metal amides were used as chiral bases for the deprotonation of cyclohexene oxide. The selectivity and initial rate of reaction were compared for sodium–amido ethers, lithium–amido ethers, and mixtures of sodium and lithiumamido ethers in diethyl ether and tetrahydrofuran, respectively. The mixed sodium/lithium amides are more reactive than the single sodium and lithium amides, whereas the stereoselectivities are higher when lithium amides are used. The alkali-metal/γ-amido ethers exhibit both higher initial reaction rates and stereoselectivities than their β-amido ether analogues. NMR spectroscopic studies of mixtures of *n*-butylsodium (*n*BuNa), *n*-butyllithium (*n*BuLi), and the γ-amino ethers in diethyl ether show the exclusive formation of dimeric mixed-metal amides. In diethyl ether, the lithium atom of the mixed-metal amide is internally coordinated and the sodium atom is exposed to solvent; however, in tetrahydrofuran, both metals are internally coordinated.

Keywords: amides · asymmetric synthesis · lithium · mixed-metal complexes · NMR spectroscopy

Introduction

The asymmetric deprotonation of prochiral ketones and epoxides by chiral lithium amides derived from 1,2-diamines has received much attention.[1,2] There has also been a steady growth of structural and mechanistic knowledge of these systems gained by X-ray diffraction analysis, NMR spectroscopy, kinetic studies, and computational methods.[3] These reactions are useful in organic synthesis even though they often require stoichiometric amounts of the chiral lithium amide. Recently, the use of less reactive achiral "bulk" bases has resulted in catalytic deprotonations with high stereoselectivities, although the observed selectivity often drops when less than 10% of the chiral base is used.[1,4] The reaction rates for the enantioselective deprotonation reactions by chiral lithium amides are generally low and the reaction may require more than 24 h for completion.[5] However, the use of the heavier alkali metals sodium or potassium, instead of lithium, results in a more powerful base from which the rate of deprotonation should be considerably higher than that of the corresponding lithium amide.[6] Andrews and co-workers have reported that the use of sodium diisopropylamide (NDA) for the deprotonation of ketones gives a higher selectivity for the kinetically favored enolate than lithium diisopropylamide (LDA).[7] Despite the fact that sodium and potassium amides are common reagents in organic synthesis, the use of heavy alkali metal amides in asymmetric synthesis has not been explored. To the best of our knowledge, the study by Johansson and Davidsson has generated the only report in which mixed sodium/lithium amides derived from chiral 1,2-diamines have been used in stereoselective deprotonation of cyclohexene oxide (Scheme 1).[8]

The study showed that the mixed-metal amide gives a significantly lower selectivity in the reaction (10% enatiomeric excess (*ee*) compared to 70% *ee* when the lithium amide is used). Based on various NMR observations, it was suggested that a lithium chelate is formed and that sodium is exposed to the diethyl ether (Et_2O) solvent. The selectivity with such a complex is expected to be lower in the epoxide-opening reaction, since the epoxide coordinates to the larger sodium cation. The lithium–oxygen and lithium–nitrogen bond lengths in crystal structures are approximately 2.0 Å, while

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Supporting Information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. The ^{1}H and ^{13}C NMR shifts for the lithium–amide complex Li-**1** and the $^{6}Li,^{1}H$-HOESY spectra for the lithium–amide complexes in Et_2O and THF are presented in the Supporting Information.

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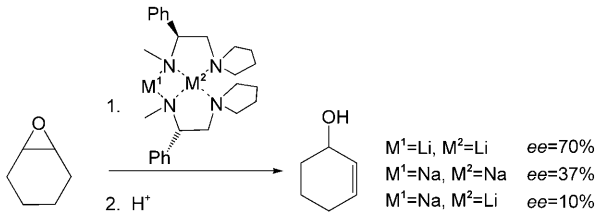


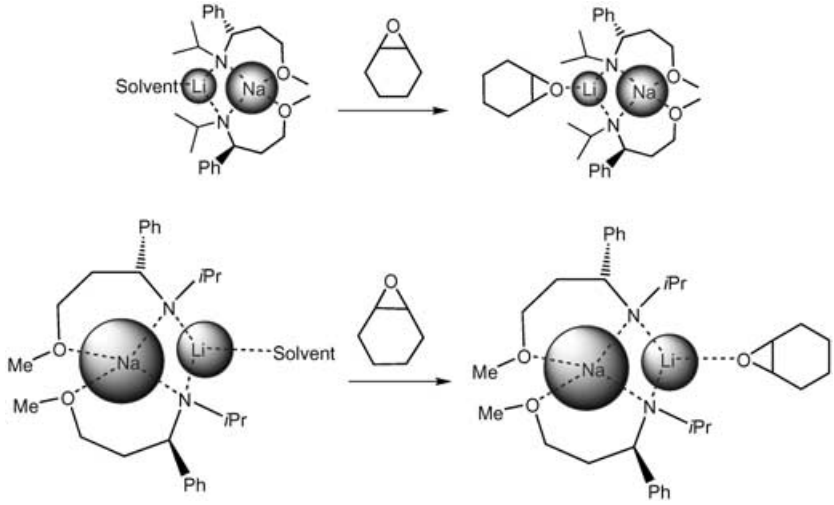
Scheme 1. The stereoselective deprotonation of cyclohexene oxide mediated by chiral lithium, sodium, and sodium/lithium amide complexes in Et_2O.

These results suggest that it should be possible to design amide dimers with sodium internally chelated and lithium exposed to the solvent and, therefore, also the incoming epoxide (Scheme 3). The larger sodium cation and the six-membered chelate would then push the chiral centers closer to the lithium cation and ultimately form a compound that combines the stereoselectivity of the lithium amide and the reactivity of the sodium amide.

Here, we report on the NMR studies of lithium and mixed sodium/lithium amides formed from the chiral γ-amino ether **1** in both Et_2O and tetrahydrofuran (THF). The mixed-metal amide is capable of forming six-membered chelates. Along with the NMR studies, we also report the initial rate and enantioselectivity of the deprotonations of cyclohexene oxide by using the lithium, sodium, and mixed-metal amides of the chiral γ-amino ethers **1** and **2**, and the chiral β-amino ether **3** in Et_2O and THF.

the sodium–oxygen and sodium–nitrogen bond lengths are approximately 2.5 Å,[7,9,10] that is, the considerably longer sodium–oxygen bond length should force the stereogenic center of the amide away from the approaching epoxide.

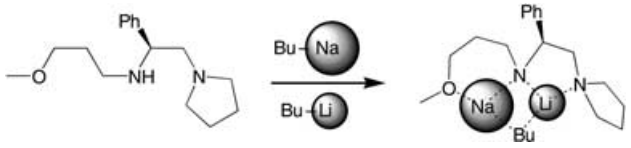
Mixed complexes of organolithium and organosodium compounds have been found in the solid state. Mulvey and co-workers have reported on the crystal structure of a mixed lithium/sodium–benzyl compound and a mixed tetrameric ladder structure, with a central ring containing lithium and the outer ring containing sodium.[11] Furthermore, Williard and Nichols have characterized mixed lithium/sodium, lithium/potassium and sodium/potassium amides of hexamethyldisilazane in the solid state and in solution by NMR spectroscopy.[10,12]



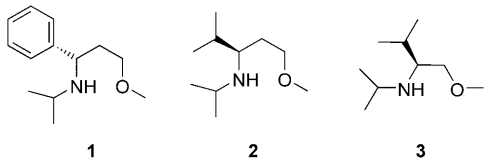
Scheme 3. The desired chiral mixed-metal lithium/sodium amide with coordination of the cyclohexene oxide to the lithium metal.

More recently we reported that the chelate ring size controls the positioning of *n*BuNa in chiral mixed-metal amides.[13] Tridentate amines with the ability to form five- or six-membered chelates were treated with a mixture of *n*BuNa and *n*BuLi. This led to the exclusive formation of complexes with lithium in the five-membered chelate and sodium in the six-membered chelate (Scheme 2).

This indicates that the larger sodium cation prefers to occupy the six-membered chelate, while the smaller lithium prefers the five-membered chelate. The six-membered chelate is also more flexible than the corresponding five-membered chelate as the "bite-angles" are allowed to adjust to sodium.



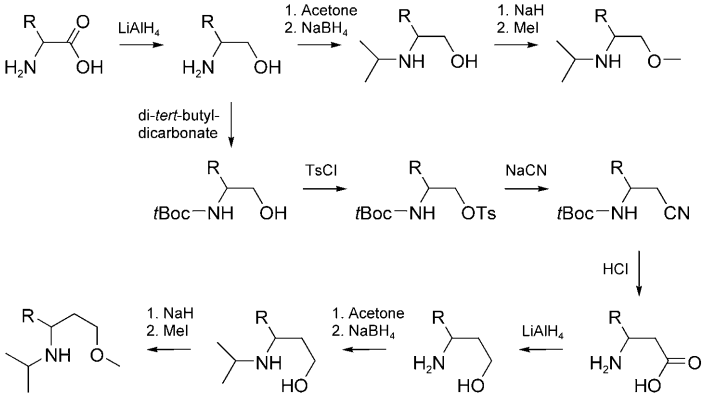
Scheme 2. Observed metal arrangement in the mixed complex formed by *n*BuNa, *n*BuNa, and a chiral tridentate amine.



Results and Discussion

Synthesis of the chiral amino ethers: The synthesis of the chiral γ-amino ethers **1** and **2** was achieved through the reduction of common chiral α-amino acids that subsequently had the amine functionality protected by a *tert*-butoxycarbonyl (*t*BOC) group and the alcohol converted into a *p*-tosyl leaving group. The homologation was carried out by using sodium cyanide with subsequent acid hydrolysis to convert the resulting nitriles into carboxylic acids and to

remove the *t*BOC group.[14] After reduction to the corresponding primary γ-amino alcohols, alkylation of both the amine and alcohol functionalities yielded the desired secondary γ-amino ethers (Scheme 4). The synthesis of the β-amino ether **3** has previously been published.[15]



Scheme 4. Synthesis of the β- and γ-amino ethers.

Deprotonation of cyclohexene oxide by mixed sodium/lithium–amide complexes: The asymmetric deprotonation reactions were performed by adding *n*BuLi and/or *n*BuNa to a solution of the chiral amino ether in Et_2O or THF at −78 °C. After a few minutes at −78 °C, the solution was equilibrated at 20 °C and the cyclohexene oxide was added. Aliquots of the reaction mixture were quenched and the reaction monitored by the appearance of the enantiomers of the 2-cyclohexene-1-ol, by means of chiral gas chromatography. The initial rates of the reactions in Et_2O and THF are given in Table 1.

The sodium amides were significantly more reactive than the corresponding lithium amides as expected; however, the mixed-metal complexes were even more reactive in both THF and Et_2O. It should be noted that the high initial rates of the mixed-metal amides tended to decrease after a few percent conversion when the reaction was carried out in Et_2O. This was not the case in THF, as the enantioselectivity was lower using the mixed-metal amides and the sodium amides, as deduced from experiments conducted with the corresponding lithium amides. However, employing the sodium amides as opposed to the more reactive mixed-metal complexes had no detrimental effect on the enantioselectivity. When Et_2O was used as solvent, the stereoselectivities were generally significantly lower for the lithium amides than for the corresponding sodium amides; however, amine **1** was an exception.

The comparison of the reactivity and selectivity of the metal amides of the chiral γ-amino ether **2** and the chiral β-amino ether **3**, both derived from valine, gave an idea of what effects the homologation of the amino ether had on the reaction. The initial rates were significantly higher by using the lithium, sodium, and the mixed-metal complexes of **2** than those of **3** in THF. In Et_2O the initial rates were of the same magnitude for the metal amides of both amines. The same trend held for the enantioselectivity, which in THF was higher when the chiral γ-amino ether **2** was used. In Et_2O the observed difference in enantioselectivity when **2** and **3** were employed was very small.

NMR studies of mixtures of *n*BuLi and compound 1: To study of the mixed-metal amide formed by the chiral γ-amino ether **1**, *n*BuNa, and *n*BuLi by NMR spectroscopy, it is necessary to first characterize the lithium amide. The sections below describe the NMR spectroscopic study of the complexes formed by **1** and *n*BuLi in Et_2O and THF, followed by characterization of the mixed-metal complex.

Characterization of lithium amides in Et_2O: Addition of [^{6}Li]*n*BuLi (0.1 mmol) to **1** (0.07 mmol) in [D_{10}]Et_2O (0.6 mL) at −78 °C resulted in a mixture of the dimeric C_2-symmetric lithium amide (Li-**1**)$_2$, characterized by two ^{6}Li NMR signals at $\delta = 1.5$ and 2.0 ppm, and the mixed complex *n*BuLi/Li-**1**, characterized by two ^{6}Li NMR signals at $\delta = 2.3$ and 2.7 ppm (see Figure 1). In the ^{13}C NMR spectra the α-carbon signal at $\delta = 12.3$ ppm from the mixed complex was a quintet with $^1J(^{13}C,^6Li) = 8.9$ Hz. The signals from the mixed complex and free *n*BuLi increased, while those of the (Li-**1**)$_2$ complex decreased upon further addition of *n*BuLi (0.03 mmol). The equilibrium constant (K) was estimated to be 0.02 M from the signal intensities in the ^{6}Li NMR spectrum at −77 °C.

The two-dimensional (2D) ^{6}Li,^{1}H HOESY experiment has previously been utilized in several detailed structural investigations of organolithium compounds and was used to measure heteronuclear Overhauser effects between lithium and protons at short distances.[16] The ^{6}Li,^{1}H HOESY of the mixture of (Li-**1**)$_2$, *n*BuLi/Li-**1**, and free *n*BuLi in Et_2O at −77 °C revealed NOEs between the

Table 1. Initial rates and enantioselectivities obtained from the deprotonation of cyclohexene oxide (0.10 mmol) after 10 min of reaction (less than 15% conversion) using different lithium, sodium, and mixed-metal complexes (0.20 mmol) in THF and Et_2O (1.0 mL) at 20.0 °C.

		THF		Et_2O	
Amine	Alkali metal reagent	Initial rate [M s^{-1}]	*ee* [%]	Initial rate [M s^{-1}]	*ee* [%]
(*S*)-**1**	*n*BuLi	2.1×10^{-6}	46(*R*)	2.5×10^{-6}	27(*R*)
(*S*)-**1**	*n*BuNa	10.6×10^{-6}	24(*R*)	6.6×10^{-6}	17(*R*)
(*S*)-**1**	*n*BuLi/*n*BuNa	14.1×10^{-6}	25(*R*)	13.7×10^{-6} [a]	9(*R*)
(*R*)-**2**	*n*BuLi	5.2×10^{-6}	48(*S*)	3.3×10^{-6}	3(*S*)
(*R*)-**2**	*n*BuNa	21.6×10^{-6}	30(*S*)	13.9×10^{-6}	19(*S*)
(*R*)-**2**	*n*BuLi/*n*BuNa	28.2×10^{-6}	27(*S*)	21.5×10^{-6} [a]	19(*S*)
(*S*)-**3**	*n*BuLi	1.6×10^{-6}	33(*S*)	3.8×10^{-6}	4(*S*)
(*S*)-**3**	*n*BuNa	6.5×10^{-6}	25(*S*)	12.5×10^{-6}	22(*S*)
(*S*)-**3**	*n*BuLi/*n*BuNa	9.0×10^{-6}	23(*S*)	13.6×10^{-6} [a]	8(*S*)

[a] Average initial rates after 5 minutes of reaction (less than 5% conversion).

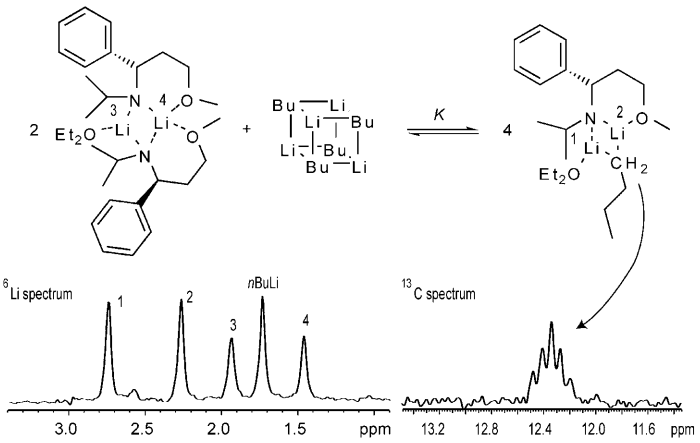


Figure 1. The ^{6}Li NMR spectrum of the (Li-**1**)$_2$ complex (0.03 M) in equilibrium with the mixed complex *n*BuLi/Li-**1** (0.02 M) in 0.6 mL [D$_{10}$]Et$_2$O at −77 °C (left), and the region of the ^{13}C NMR spectrum showing the α-carbon of the *n*BuLi/Li-**1** complex (right).

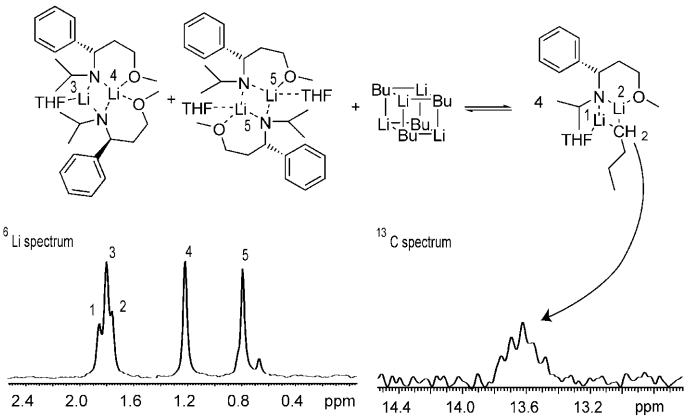


Figure 2. The ^{6}Li NMR spectrum of the (Li-**1**)$_2$ complex (0.12 M) in equilibrium with the mixed complex *n*BuLi/Li-**1** (0.04 M) in 0.6 mL [D$_8$]THF at −87 °C (left), and the poorly resolved α-carbon signal of the *n*BuLi/Li-**1** complex in the ^{13}C NMR spectrum (right).

lithium atoms and the protons of **1** in addition to NOEs between the lithium atoms and the butyl α-protons of *n*BuLi/Li-**1**. Both the lithium amide and the mixed complex showed NOEs between the upfield lithium and the methoxy protons.

Characterization of lithium amides in THF: There were three signals, at $\delta = 0.8$, 1.2, and 1.8 ppm in the ^{6}Li NMR spectrum from a mixture of [^{6}Li]*n*BuLi (0.1 mmol) and complex **1** (0.1 mmol) in [D$_8$]THF (0.6 mL) at −87 °C (see Figure 2). These signals were assigned to two different structures of the dimeric lithium amide, either with the methoxy coordination to only one of the lithium atoms (yielding two ^{6}Li signals) or with a symmetric coordination to both lithium atoms (one ^{6}Li signal). THF coordinates lithium more strongly than Et$_2$O, and therefore THF promotes symmetrically coordinated amides in which both lithium atoms are coordinated by solvent. The intensity ratio between the three ^{6}Li signals, two from the asymmetric complex and one from the symmetric complex, was approximately 1:1:1. The two ^{6}Li NMR signals from the mixed complex Li-**1**/*n*BuLi at $\delta = 1.9$ and 1.8 ppm appeared in the ^{6}Li spectrum upon further addition of *n*BuLi (0.1 mmol). In the ^{13}C NMR spectrum the α-carbon at $\delta = 13.6$ ppm from complexed *n*BuLi appeared as a poorly resolved quintet ($^{1}J(^{13}\mathrm{C},^{6}\mathrm{Li}) = 8.7$ Hz).

The ^{6}Li,^{1}H HOESY of the mixture of the two dimeric complexes of Li-**1** in THF at −87 °C showed NOEs between the lithium atoms and the protons of **1** for both complexes. The symmetrically coordinated Li-**1** showed an NOE cross-peak between the lithium atom and the methoxy protons, while the asymmetric Li-**1** showed an NOE between the upfield lithium atom and the methoxy protons. The chelated lithium signal appeared more upfield than that of the solvent-coordinated lithium atom in both Et$_2$O and THF. Consequently, the upfield lithium signal of the THF-solvated Li-**1**/*n*BuLi was assigned to the methoxy chelate.

NMR studies of the mixed sodium/lithium amide (Li-1/Na-1): The sodium amides formed by *n*BuNa and compound **1** in Et$_2$O and THF were studied by NMR spectroscopy. In THF, two sets of signals appeared in the ^{13}C and ^{1}H spectra from what seems to be the Na-**1** complex and the mixed *n*BuNa/Na-**1** complex with the *n*BuNa proton signals at $\delta = -1.0$ ppm. In Et$_2$O, only the Na-**1** complex was observed, in addition to the homo aggregate of *n*BuNa, which appeared at $\delta = -1.1$ ppm in the ^{1}H spectrum. Unfortunately, these sodium amide complexes could not be fully characterized.

The ^{6}Li NMR spectrum of a solution of a mixture of **1** (0.18 mmol), *n*BuNa (0.09 mmol), and *n*BuLi (0.09 mmol) in [D$_{10}$]Et$_2$O (0.6 mL) has only one ^{6}Li NMR signal $\delta = 1.3$ ppm at −88 °C. Both the ^{13}C and ^{1}H spectra showed the presence of only one set of signals (Table 2), different from those of the corresponding lithium amides. This indicated that all of the amine must be complexed within one mixed-metal complex (Li-**1**/Na-**1**), since there is only one half equivalent of lithium and sodium cations per amine. There was only one set of NMR signals at all temperatures (−60 to −100 °C), suggesting that there was only one major dimeric complex. The single set of ^{13}C NMR resonances from the Li-**1**/Na-**1** complex indicated that it had C_2 symmetry.

Heteronuclear ^{6}Li,^{1}H NOEs were employed to determine the position of the lithium cation in the mixed complex. The ^{6}Li,^{1}H HOESY spectra of the mixed-metal complex Li-**1**/Na-**1** in [D$_{10}$]Et$_2$O were recorded at −88 °C with mixing

Table 2. Chemical shifts for the mixed-metal complex (Li-**1**/Na-**1**) formed by **1** (0.18 mmol), *n*BuNa (0.09 mmol), *n*BuLi (0.09 mmol), and THF (0.11 mmol) in Et$_2$O (0.6 mL) at −88 °C.

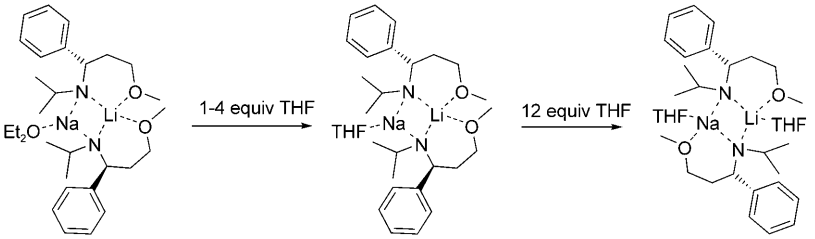
	O*CH*$_3$	O*CH*$_2$	CH*CH*$_2$	Ph*CH*	N*CH*	CH*CH*$_3$	CH*CH*$_3$	THF
δ ^{1}H [ppm]:	3.36	3.5, 3.8	2.26	3.64	2.60	1.05	1.11	3.43, 1.7
δ^{13}C [ppm]:	60.0	76.2	39.4	70.0	50.4	23.1	28.6	68.1, 26.2

times of 0.7 and 1.0 s. Surprisingly, NOEs were observed between the lithium signal and the proton signals of the methoxy group at $\delta = 3.40$ ppm. We also observed several ^{6}Li,^{1}H NOE cross-peaks between the methoxy, CH_2, CH_3, and PhCH protons of **1** and lithium, supporting the formation of a mixed-alkali complex. This indicated that lithium was internally coordinated, contrary to what was expected. However, this does not exclude the possibility that these NOEs appear as a result of a rapid exchange of sodium with lithium. This was further examined by the addition of one equivalent of protonated THF (0.11 mmol) per lithium atom to a solution of **1** (0.18 mmol), *n*BuNa (0.07 mmol), and *n*BuLi (0.11 mmol) in [D_{10}]Et_2O (0.65 mL) followed by ^{6}Li,^{1}H HOESY experiments. The THF ligand has a greater affinity for alkali metals and is expected to replace Et_2O. This difference in coordination has been observed by significant changes in ^{6}Li chemical shifts of various chiral lithium amides.[17] The presence of only a few equivalents of THF had no significant effect on the ^{6}Li spectrum, indicating that it does not disrupt the C_2-symmetric structure.

With one equivalent of THF per lithium added, the ^{6}Li,^{1}H-HOESY spectrum revealed no cross-peaks between the THF protons and the lithium atom of the mixed-metal complex (Figure 3). The THF protons and the OCH_2 and OCH_3 protons of **1** had similar shifts, but careful examination revealed that the cross-peaks were resolved. In comparison, strong NOEs appeared in the ^{6}Li,^{1}H-HOESY spectrum between the downfield signal of lithium in Li-**1** and the protons of THF at $\delta = 3.44$ ppm. If the lithium cation occupies the chelated position it should not show any NOE to the protons of the THF, but under fast lithium–sodium exchange, one would also expect a strong NOE between the lithium and protons of THF.

To ensure that not all of the added THF molecules were coordinated to the lithium amide, an additional three equivalents of THF were added per Li. This made no difference to the ^{6}Li NMR spectrum, or to the cross-peaks observed for the mixed-metal amide in the corresponding ^{6}Li,^{1}H-HOESY spectrum. These observations showed that the mixed-metal amide in Et_2O must be an asymmetric dimer with methoxy coordinated to lithium, leaving sodium exposed to THF solvent coordination.

Upon further addition of THF, some of the C_2-symmetric Li-**1**/Na-**1** turned into a complex in which both metals were exposed to the solvent (Scheme 5). The lithium signal of the dimeric mixed-metal amide shifted continuously upfield with increasing THF concentration. With 12 equivalents of THF (per lithium) added, the ^{6}Li,^{1}H HOESY spectrum revealed strong cross-peaks between the lithium atom of the mixed-metal amide at $\delta = 1.1$ ppm and the THF protons at $\delta = 3.58$ ppm, as well as the protons of the methoxy group of **1** at $\delta = 3.36$ ppm. In the THF-solvated mixed-metal dimer both lithium and sodium atoms were coordinated by methoxy groups, in agreement with our previous studies of chiral lithium amides derived from α-amino acids.[17] The possible formation of a mixed-metal amide with methoxy coordination at only the lithium atom was excluded, since such a complex would not produce the observed NOE between the lithium atom and the THF protons in the ^{6}Li,^{1}H HOESY spectrum. This is most likely to be the reactive complex that coordinates to cyclohexene oxide in THF, with possible reaction sites both at lithium and sodium atoms.



Scheme 5. Addition of more than four equivalents of THF (per lithium) to the Et_2O-solvated (Li-**1**/Na-**1**) complex results in a complex in which both metals are coordinated by solvent.

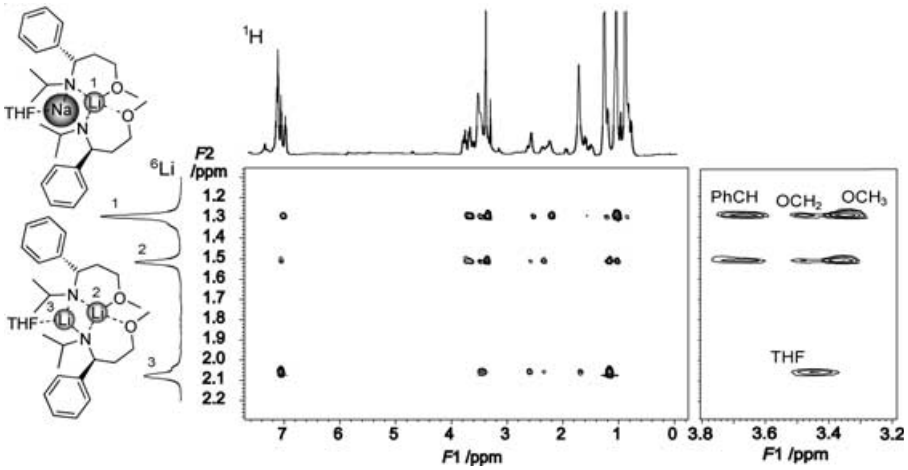


Figure 3. ^{6}Li,^{1}H HOESY spectrum of **1** (0.18 mmol), *n*BuNa (0.07 mmol), *n*BuLi (0.11 mmol), and THF (0.11 mmol) in [D_{10}]Et_2O (0.6 mL) at −88 °C, with scale expansion of the ^{1}H spectral region ($\delta = 3.2$–3.8 ppm) shown on the right.

Further addition of *n*BuLi (0.05 mmol) resulted in the formation of a mixed *n*BuLi/Na-**1** complex, indicated by a signal at $\delta = 1.7$ ppm in the ^{6}Li NMR spectrum and a new set of sig-

nals in the ^{13}C spectrum (Figure 4). The *n*BuLi α-carbon signal at $\delta = 12.6$ ppm was split into a 1:1:1 triplet with $^{1}J(^{13}C,^{6}Li) = 7.7$ Hz. Further addition of *n*BuLi resulted in the formation of the mixed *n*BuLi/Li-**1** complex, dimeric (Li-**1**)$_2$, and more mixed *n*BuLi/Na-**1** complex.

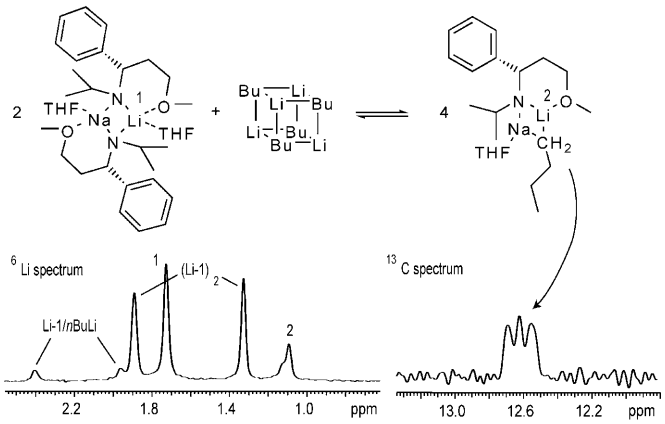


Figure 4. The ^{6}Li NMR spectrum of the Li-**1**/Na-**1** complex in equilibrium with the mixed complex *n*BuLi/Na-**1** in Et_2O/THF (0.6/0.1 mL) at −87 °C (left), and the region of the ^{13}C NMR spectrum showing the α-carbon of the *n*BuLi/Na-**1** complex (right).

In pure [D_8]THF, the spectral line of the mixed lithium/sodium amide appeared at $\delta = 1.0$ ppm in the ^{6}Li spectrum at −87 °C. This signal was split into two (2:3 intensity ratio) upon lowering the temperature below −95 °C. This suggests that both symmetrical and asymmetrical mixed-metal dimers are formed in THF.

Conclusion

We have shown that the mixed-metal amides generated from chiral γ-amino ethers are potentially useful chiral amides for enantioselective synthesis. The sodium and mixed-metal amides exhibit a significantly higher reactivity in the asymmetric deprotonation of cyclohexene oxide than the corresponding lithium amides in either Et_2O or THF. Surprisingly, the mixed-metal amides are even more reactive than the sodium amides. In THF, the increased reactivity of the sodium and mixed-metal amides occurs at the expense of a decreased enantioselectivity, but in Et_2O some of the enantioselectivities increase upon replacing the lithium amide with a sodium amide.

Mixing Na-**1** with Li-**1** leads to the complete formation of a mixed amide dimer as shown by the NMR experiments. However, our attempts to form dimers with the sodium atom internally chelated and the lithium atom exposed to the solvent were unsuccessful, as indicated by the $^{6}Li,^{1}H$-HOESY NMR spectra. In Et_2O a dimeric mixed-metal complex with sodium exposed to solvent is formed, while both lithium and sodium are coordinated by the solvent in the mixed-metal amide in THF. It appears that the ether chelation to lithium is much stronger than that to sodium, and this is suggested to be the reason for the reported structure.

These complexes significantly increased the reactivity in the deprotonation of cyclohexene oxide. They are therefore promising precursors for the development of dimers with the sodium atom internally chelated and the lithium atom exposed to the solvent. Diamines are better chiral bases for the asymmetric deprotonation of cyclohexene oxide than amino ethers. We therefore aim to develop such mixed-metal amides with amine chelates. Such mixed amides are potentially more reactive than the lithium analogue, while they also mediate the reactions with high enantioselectivity.

Experimental Section

Synthesis of chiral amino ethers: NMR spectra were recorded on a Varian 400 MHz spectrometer by using $CDCl_3$ as solvent. Optical rotations were measured using a Perkin–Elmer 341 LC polarimeter. IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrometer. Melting points were determined using a Büchi Melting Point B-545 and are uncorrected. Dried solvents were distilled from sodium/benzophenone. High-resolution mass spectroscopy was carried out on a Micromass LCT spectrometer.

The chiral amino acids used as starting materials, (*R*)-phenylglycine and (*S*)-valine, were purchased from Sigma–Aldrich and their reduction to amino alcohols,[18] protection as *t*BOC amido alcohols,[19] and conversion to tosylates[20] were made according to literature procedures. The synthesis of the chiral β-amino ether (*S*)-2-isopropylamino-1-methoxy-3-methylbutane (**3**) has been described previously.[15]

(*S*)-3-(*N-tert*-Butoxycarbonylamino)-3-phenylpropanenitrile: A mixture of (*R*)-2-(*N-tert*-butoxycarbonylamino)-2-phenylethyl tosylate (18.87 g, 45.3 mmol, 1.0 equiv) dissolved in DMF (125 mL) was added to a suspension of finely ground NaCN (6.66 g, 136 mmol, 3.0 equiv) in DMF (125 mL) and the mixture stirred overnight at room temperature. A solution of NaOH (2.0 M, 200 mL) was added and the mixture extracted with dichloromethane (3 × 100 mL). The combined organic extract was washed with water (3 × 100 mL) and concentrated in vacuo. The residue was dissolved in ethyl acetate/hexane (1:1, 200 mL), washed again with water (3 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo yielding a pale yellow oil that quickly crystallized (10.59 g, 95 %). Spectral data were consistent with those reported in the literature.[14]

(*R*)-3-(*N-tert*-Butoxycarbonylamino)-4-methylpentanenitrile: The same procedure was used as for the preparation of (*S*)-3-(*N-tert*-butoxycarbonylamino)-3-phenylpropanenitrile, but with (*R*)-2-(*N-tert*-butoxycarbinolamino)-3-methylbutyl tosylate. Yield 72 % as a white solid. The spectral data were consistent with those reported in the literature.[14]

(*S*)-3-Amino-3-phenylpropanol: The nitrile, (*S*)-3-(*N-tert*-butoxycarbonylamino)-3-phenylpropanenitrile (8.68 g, 35.2 mmol, 1.0 equiv) was added to hydrochloric acid (6 M, 200 mL, 1.23 mol, 35 equiv), and the mixture was refluxed overnight. The solution was cooled to 0 °C, washed with dichloromethane (2 × 100 mL) and concentrated in vacuo. The residue was dissolved in water, made basic with a solution of NaOH (5 M), washed with dichloromethane (2 × 50 mL), and concentrated in vacuo. The resulting white powder was dried using benzene. The dry sodium carboxylate salt of the γ-amino acid was added to an ice-cooled suspension of $LiAlH_4$ (4.01 g, 105 mmol, 3.0 equiv) in dry THF (250 mL). The mixture was allowed to reach room temperature and then refluxed overnight. The mixture was cooled to 0 °C and the excess $LiAlH_4$ was quenched with a solution of NaOH (2 M, 30 mL). The precipitate was filtered off and extracted with THF (4 × 25 mL). The combined organic extract was concentrated in vacuo, and the residue was dissolved in a solution of NaOH (2 M, 70 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extract was washed with brine (50 mL), dried over Na_2SO_4, and concen-

trated in vacuo yielding a clear, colorless oil (2.77 g, 52%). The spectral data were consistent with those reported in the literature.[21]

(*R*)-3-Amino-4-methylpentanol: The same procedure as for the preparation of (*S*)-3-amino-3-phenylpropanol was used, but with (*R*)-3-(*N*-*tert*-butoxycarbonylamino)-4-methylpentanenitrile. Yield 64% as a pale yellow oil. Spectral data were consistent with those reported in the literature.[22]

(*S*)-3-Isopropylamino-3-phenylpropanol: The amino alcohol (*S*)-3-amino-3-phenylpropanol (2.77 g, 18.3 mmol, 1.0 equiv) and acetone (10.63 g, 13.44 mL, 183 mmol, 10 equiv) were dissolved in benzene (125 mL) and refluxed for six hours. The solution was allowed to cool to room temperature and concentrated in vacuo. The residue was dissolved in dry ethanol (125 mL) and $NaBH_4$ (1.38 g, 36.6 mmol, 2.0 equiv) was added. The mixture was stirred overnight at room temperature. Water (50 mL) was added and the ethanol removed under reduced pressure. The remaining aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic extract was washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo resulting in a white solid (3.48 g, 98%). M.p. 85°C; $[\alpha]_D^{20} = -77.3°$ ($c = 0.99$ in dichloromethane); IR (KBr): $\tilde{\nu}$ = 3262, 3196, 2971, 2926, 2864, 1490, 1452, 1384, 1178, 1055, 1035, 892, 761, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (d, $J = 6.3$ Hz, 3H; (CH_3)$_2$CH), 1.09 (d, $J = 6.3$ Hz, 3H; (CH_3)$_2$CH), 1.76 (m, 1H; CH_2CH$_2$OH), 1.94 (m, 1H; CH_2CH$_2$OH), 2.63 (septet, $J = 6.3$ Hz, 1H; (CH$_3$)$_2$CH), 3.81 (m, 1H; PhCH), 3.91 (m, 2H; CH_2OH), 7.23–7.38 ppm (m, 5H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$ ((CH_3)$_2$CH), 24.4 ((CH_3)$_2$CH), 39.1 (CH_2CH$_2$OH), 45.5 ((CH$_3$)$_2$CH), 61.6 (PhCH), 63.5 (CH_2OH), 126.4 (*o*-Ar), 127.5 (*p*-Ar), 128.9 (*m*-Ar), 143.5 ppm (*i*-Ar); HRMS (ESI+): *m/z* calcd for $C_{12}H_{20}NO$: 194.1545; found: 194.1544.

(*R*)-3-Isopropylamino-4-methylpentanol: The same procedure as for the preparation of (*S*)-3-isopropylamino-3-phenylpropanol was used, but with (*S*)-3-amino-4-methylpentanol. Yield 86% as a clear colorless oil. B.p. 60°C, 0.05 mbar; $[\alpha]_D^{20} = +60.5°$ ($c = 1.01$ in dichloromethane); IR (thin film): $\tilde{\nu}$ = 3274, 2961, 2870, 1466, 1382, 1370, 1171, 1076, 855, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.9$ Hz, 3H; (CH_3)$_2$CH), 0.93 (d, $J = 6.9$ Hz, 3H; (CH_3)$_2$CH), 1.07 (d, $J = 6.1$ Hz, 6H; (CH_3)CHN), 1.42 (m, 1H; CH_2CH$_2$OH), 1.52 (m, 1H; CH_2CH$_2$OH), 1.95 (m, $J = 4.2$, 6.9 Hz, 1H; (CH$_3$)$_2$CH), 2.70 (m, 1H; CHCH$_2$CH$_2$OH), 2.96 (septet, $J = 6.1$ Hz, 1H; (CH$_3$)CHN), 3.79 (m, 1H; CH_2OH), 3.86 ppm (m, 1H; CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.3$ ((CH_3)$_2$CH), 20.4 ((CH_3)$_2$CH), 22.4 ((CH_3)$_2$CHN), 22.5 ((CH_3)$_2$CHN), 28.9 ((CH$_3$)$_2$CH), 29.7 (CH_2CH$_2$OH), 45.2 ((CH$_3$)$_2$CHN), 61.8 (CHCH$_2$CH$_2$OH), 63.8 ppm (CH_2OH); HRMS (ESI+): *m/z* calcd for $C_9H_{22}NO$: 160.1701; found: 160.1703.

(*S*)-1-Isopropylamino-3-methoxy-1-phenylpropane (1): The amino alcohol (*S*)-3-isopropylamino-3-phenylpropanol (3.48 g, 18.0 mmol, 1.0 equiv) dissolved in dry THF (50 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 0.94 g, 23.4 mmol, 1.3 equiv) in dry THF (50 mL). The mixture was warmed at 50°C for 1 h before being cooled to room temperature. Methyl iodide (3.32 g, 1.46 mL, 23.4 mmol, 1.3 equiv) dissolved in dry THF (10 mL) was added dropwise and the mixture allowed to react overnight at room temperature. Water (50 mL) was added and the mixture concentrated in vacuo. The remaining aqueous phase was extracted with dichloromethane (3×50 mL) and the combined organic extract was washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo yielding a clear yellow oil. The product was purified using flash chromatography on Al_2O_3 with ethyl acetate/hexane 1:4 as eluent, followed by short-path distillation, yielding a clear colorless oil (1.28 g, 34%). B.p. 75°C, 0.07 mbar; $[\alpha]_D^{20} = -33.4°$ ($c = 1.00$ in dichloromethane); IR (thin film): $\tilde{\nu}$ = 3337, 2964, 2927, 2869, 1453, 1380, 1174, 1119, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (d, $J = 6.3$ Hz, 3H; (CH_3)$_2$CH), 1.02 (d, $J = 6.3$ Hz, 3H; (CH_3)$_2$CH), 1.79 (m, 1H; CH_2CH$_2$O), 2.00 (m, 1H; CH_2CH$_2$O), 2.59 (septet, $J = 6.3$ Hz, 1H; (CH$_3$)$_2$CH), 3.23 (m, 1H; CH_2O), 3.29 (s, 3H; CH_3O), 3.34 (m, 1H; CH_2O), 3.87 (t, $J = 7.0$ Hz, 1H; PhCH), 7.23–7.35 ppm (m, 5H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.3$ ((CH_3)$_2$CH), 24.5 ((CH_3)$_2$CH), 38.6 (CH_2CH$_2$O), 45.8 (CH$_3$)$_2$CH), 57.8 (PhCH), 58.8 (CH_3O), 70.4 (CH_2O), 127.1 (*p*-Ar), 127.3 (Ar), 128.6 (Ar), 144.5 ppm (*i*-Ar); HRMS (ESI+): *m/z* calcd for $C_{13}H_{22}NO$: 208.1701; found: 208.1699.

(*R*)-2-Isopropylamino-4-methoxy-1-methylpentane (2): Same procedure as for the preparation of (*S*)-1-isopropylamino-3-methoxy-1-phenylpropane, but with (*R*)-3-isopropylamino-4-methylpentanol. Yield 40% as a clear colorless oil. B.p. 35°C, 0.02 mbar; $[\alpha]_D^{20} = +14.0°$ ($c = 1.03$ in dichloromethane); IR (thin film): $\tilde{\nu}$ = 3340, 2959, 2931, 2872, 1465, 1380, 1171, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.6$ Hz, 3H; (CH_3)$_2$CH), 0.88 (d, $J = 6.6$ Hz, 3H; (CH_3)$_2$CH), 1.01 (d, $J = 6.1$ Hz, 3H; (CH_3)$_2$CHN), 1.03 (d, $J = 6.1$ Hz, 3H; (CH_3)$_2$CHN), 1.42 (m, 1H; (CH$_3$)$_2$CH), 1.67 (m, 1H; CH_2CH$_2$O), 1.77 (m, 1H; CH_2CH$_2$O), 2.47 (m, 1H; CHCH$_2$CH$_2$O), 2.82 (septet, $J = 6.1$ Hz, 1H; (CH$_3$)$_2$CHN), 3.33 (s, 3H; CH_3O), 3.47 ppm (m, 2H; CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.8$ ((CH_3)$_2$CH), 19.0 ((CH_3)$_2$CH), 23.5 ((CH_3)$_2$CHN), 24.1 ((CH_3)$_2$CHN), 30.9 ((CH$_3$)$_2$CH), 31.7 (CH_2CH$_2$O), 46.7 ((CH$_3$)$_2$CHN), 57.5 (CHCH$_2$CH$_2$O), 58.8 (CH_3O), 71.2 ppm (CH_2O); HRMS (ESI+): *m/z* calcd for $C_{10}H_{24}NO$: 174.1858; found: 174.1850.

Kinetics: Reaction vessels and syringes were thoroughly oven-dried before use. THF, Et_2O, hexane, and toluene were distilled from sodium benzophenone and kept inside a glovebox. *n*-Decane, 1-hexanol and cyclohexene oxide were distilled from calcium hydride and kept inside a glovebox. Stock solutions of cyclohexene oxide in *n*-decane (2.00 M) and 1-hexanol in toluene (3.53 mM) were prepared inside the glovebox and used in the experiments. The concentrations of the *n*BuLi (2.45 M in hexane) and the *n*BuNa suspension (0.53 M in hexane) were determined by employing double Gilman titrations.[23] GC analyses were carried out by using a Varian Star 3400 CX gas chromatograph equipped with a chiral stationary-phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack. Analyses were performed using He (1.5 mL min^{-1}) as carrier gas (injector 225°C, detector 250°C).

Synthesis of *n*-butylsodium: Inside the glovebox sodium *tert*-butoxide (1.5 g, 15.6 mmol, 1.0 equiv) was added to the reaction vessel equipped with a magnetic stirring bar. Dry hexane (10 mL) was added and the vessel sealed and taken out of the glovebox and cooled to 0°C in an ice bath. *n*-Butyllithium (2.45 M in hexane, 12.49 mL, 31.2 mmol, 2.0 equiv) was added dropwise through a septum, and the suspension was stirred for one hour at 0°C before being allowed to warm up to room temperature and was then stirred for an additional 6 h. The resulting suspension was centrifuged and the precipitate was washed with dry hexane (5×10 mL). The precipitate was then suspended in hexane (10 mL) and transferred to another airtight vessel and stored at −20°C. The concentration of the *n*NaBu suspension was determined to be 0.53 M as evidenced from a double Gilman titration.

Typical kinetic procedure: The chiral amine (0.20 mmol) was dissolved in dry solvent (THF or Et_2O), in amounts making the total volume of the reaction 1 mL, in an airtight reaction vessel inside the glovebox. The reaction vessel was sealed and taken out of the glovebox, placed under a nitrogen atmosphere and the solution cooled to −78°C in a dry ice/acetone cooling bath. The *n*BuNa suspension was sonicated briefly in order to make it homogenous and a portion (0.53 M, 0.10 mmol) was withdrawn by syringe. This homogenous suspension was then added dropwise to the reaction vessel. The mixture was allowed to react for 5 min before *n*BuLi (2.45 M, 0.10 mmol) was added dropwise using a syringe. The mixture was allowed to react for a further 5 min and then allowed to reach room temperature, and was placed in a thermostat bath and equilibrated to 20.0°C for 5 min. The reaction was started by addition of a solution of cyclohexene oxide (2.0 M, 0.10 mmol) in *n*-decane (0.050 mL) with a syringe. Samples of the reaction mixture were quenched in hydrochloric acid (0.64 M, 100 μl) at even intervals with a syringe and extracted with toluene (500 μl) containing an internal standard of 1-hexanol (3.53 mM). The organic phases were transferred to vials and analysed by capillary gas chromatography.

NMR sample preparation: The solution studies of the lithium amides and the mixed sodium/lithium amides were performed in deuterated Et_2O and THF solvents using ^{6}Li-labeled *n*BuLi. The *n*BuNa suspension in hexane (0.53 M) was transferred to an NMR tube under N_2 atmosphere. The hexane was removed under reduced pressure and deuterated solvent was added followed by rapid cooling of the sample at −78°C.

NMR studies: All NMR spectra were recorded using a Varian Unity 500 spectrometer equipped with three channels using 5 mm ^{13}C, ^{6}Li, or ^{1}H

triple-resonance probe-heads, built by the Nalorac Company. We used measuring frequencies of 500 MHz (^{1}H), 125 MHz (^{13}C), and 73 MHz (^{6}Li). The ^{1}H and ^{13}C NMR spectra were referenced to the solvent [D_{10}]Et_2O signals at $\delta = 1.33$ ppm (^{1}H $-CH_2$) and $\delta = 65.5$ ppm (^{13}C $-CH_2$), and the [D_8]THF signals at $\delta = 1.72$ ppm (^{1}H $-CH_2$) and $\delta = 67.6$ ppm (^{13}C $-CH_2$), respectively. Probe temperatures were measured after more than one hour of temperature equilibrium with both a calibrated methanol–freon NMR spectroscopy thermometer and the standard methanol thermometer supplied by Varian instruments.[24] ^{6}Li,^{1}H-HOESY experiments were performed with $t_M = 1.0$ s in both THF and Et_2O. For further data of the ^{6}Li,^{1}H HOESY experiments, see previous studies.[17,25]

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