NMR studies of chiral lithium amides with phosphine chelating groups reveal strong Li-P-interactions in ethereal solvents

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Dedicated to Professor William Bailey on the occasion of his 65th birthday

Abstract

Chiral lithium amides with a chelating diphenylphosphine group have previously been found to mediate excellent enantioselectivity in the asymmetric addition of alkyllithiums to benzaldehyde. NMR studies reveal for the first time that chiral lithium amides can form chelating dimeric complexes with P-Li interactions in both diethyl ether and THF. The two lithium atoms in the dimer are found to be non-equivalent, one of them is coordinated to two phosphines, detected by ^{6}Li,^{31}P-couplings, while the other lithium is only solvent bound. Slow ethereal ligand exchange on the NMR time scale below –50 °C has been detected by ^{13}C NMR. Excess of *n*-butyllithium generates mixed dimeric complexes in both diethyl ether and THF.

Keywords: Chiral, lithium amide, NMR, ^{6}Li,^{31}P coupling, aggregate

Introduction

The 1,2-addition of organolithiums to aldehydes or ketones is one of the most straightforward ways for carbon-carbon bond formation, and the development of asymmetric versions of the reaction is of fundamental interest.[1] Ever since the first reports nearly thirty years ago, chiral complexing agents have been used to control the enantiofacial selectivity of nucleophilic addition reactions.[2] We and others we have for some time now been involved in the development and exploration of the use of various chiral chelating lithium amides, derived from amino acids, to induce asymmetry in the addition of alkyllithiums to benzaldehyde.[3] Until recently, these amides have been designed to form strong 5-membered chelates between the amide nitrogen and a hard Lewis base such as an ether group. However, we have found that chiral amino sulfides give surprisingly high asymmetric induction, in fact even higher than with the ether analogues.[4] NMR studies and computational studies have shown that the sulfur-lithium interaction within the thioether amides are substantially weaker than the corresponding lithium-oxygen interaction.[5] Continuing this work involving weaker

Lewis bases we became very interested in the corresponding chiral phosphino lithium amides and developed an efficient and general route for the preparation of multigram quantities of chiral secondary amino phosphines.[6] Indeed these amino phosphines gave very high enantiomeric excesses (96–98%) of 1-phenyl pentanol in the addition of butyllithium to benzaldehyde.

An important component of our research is the ability to study structures and dynamics by NMR spectroscopy at low temperatures and over the years we have studied a substantial number of chiral lithium amides and their mixed complexes with e.g. alkyllithium reagents.[7] Detailed NMR studies on the dynamic processes, e.g. lithium-lithium and ligand-ligand exchange[8] and the magnitude of the $^{15}N,^6Li$ coupling constant[9] have revealed important facts towards a better understanding of these synthetically important reagents.[10]

To the best of our knowledge there are only a handful of reports of lithium chelating phosphine groups, were direct $^7Li,^{31}P$ couplings have been observed.[11] Interestingly some of these chelates are also observed in tetrahydrofuran (THF) solution but these structures also exhibit substantial sterical hinderance that may force them to yield short lithium-phosphine distances, which are reflected in the observation of $^7Li,^{31}P$ couplings. Herein we now report detailed NMR studies of the structures and dynamics of chiral N,P-lithium amides by low temperature NMR.

Results and Discussion

The NMR studies were performed at −78 °C in special NMR tubes equipped with an airtight Teflon valve system that allows sequential additions via gas-tight syringes under a protecting nitrogen atmosphere. Pre-dried and per-deuterated toluene (toluene-d_8), diethyl ether (Et$_2$O-d_{10}), THF (THF-d_8) and isotopically enriched n-[^6Li]-BuLi were used in all NMR studies, described herein.[12]
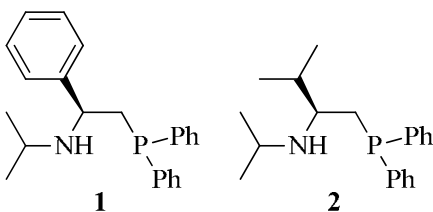

Scheme 1

Two different lithium amines **1** and **2** (Scheme 1) were synthesized and their corresponding lithium salts, e.g. the lithium amides Li-**1** and Li-**2** were studied by NMR spectroscopic techniques. The study of these amides were motivated since Li-**1** and Li-**2** are lithium amides with *N*-isopropyl groups with the possibility to form N-Li-P chelates that have been found to induce very high enantioselectivity in asymmetric alkylation reactions.[6] Compounds Li-**1** and Li-**2** are structurally similar and their NMR spectra also show great similarity. In the result section we have excluded any duplicate observation and thus mainly one of the complexes are described in detail. However,

the coupling constants and chemical shifts for the various complexes involving Li-**1** and Li-**2** are reported.

## NMR studies of the amides in non-coordinating solvents

Chelating lithium amides are known to form trimeric and ladder like tetrameric structures in a non-coordinating solvent such as toluene.[13] Indeed, addition of *n*-BuLi (1.5 equivalents) into a toluene-d_8 solution of the aminophosphine **1** (0.3 M) in an NMR tube revealed two lithium-6 signals in a 2:1 ratio, a singlet at 1.80 ppm and a doublet ($^1J_{6Li,31P}$ 16 Hz) at 2.25 ppm in the ^6Li NMR spectra at −78 °C, Figure 1.
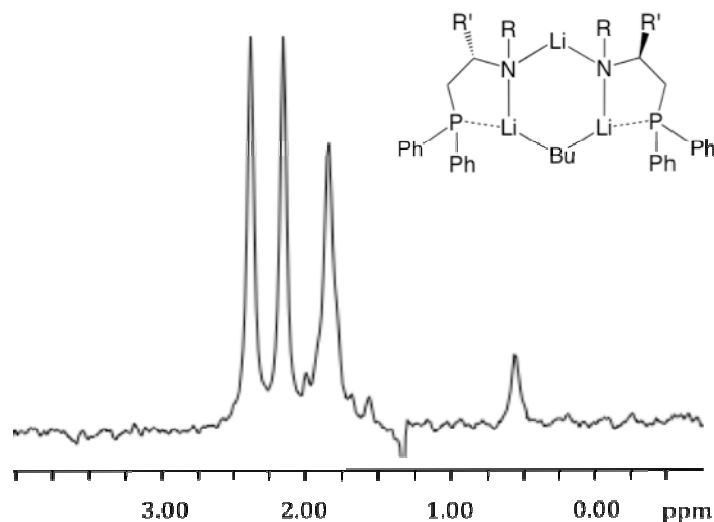

Figure 1. ^6Li NMR of Li-**1** and *n*-BuLi in toluene solution, along with the proposed mixed complex that forms in solution (R=i-Pr and R'=Ph). The minor peak at 0.45 ppm is due to an un-assigned lithium signal, possibly arising from a larger aggregate of the amide.

In both the ^1H and the ^{13}C NMR spectra there is only one set of signals for the amide and for the *n*-BuLi, respectively. The shifts of the NMR signals are significantly different from those of pure *n*-BuLi and the amine precursor **1** in toluene. Based on these results and on the result of previously studies of lithium amides with NO or NS chelates, we assigned these signals to a 2:1 cyclic and mixed complex containing one *n*-BuLi and two amides, Figure 1.[5]

Upon further addition of amine **1**, several new ^6Li NMR signals are observed, i.e. two overlapping multiplets at 1.9 ppm and an apparent singlet at 0.7 ppm. Careful inspection of the spectra reveals one ^6Li NMR doublet signal at 1.86 ppm ($^1J_{6Li,31P}$ 18 Hz), assigned to arise from a cyclic trimer of the amide, Figure 2 and 3. Similar trimers of lithium amides have previously been observed with chiral chelating NO and NS amides.[14,15] Since the lithiums are coordinated by one phosphine each they are chemically equivalent and give rise to a single doublet signal in the ^6Li NMR spectrum.
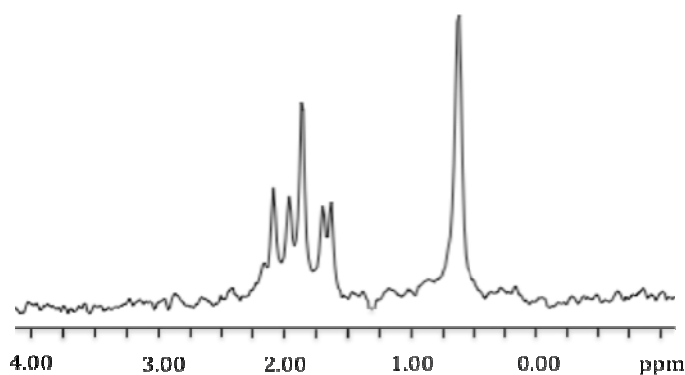
Figure 2. ^{6}Li NMR of Li-**1** in toluene solution.
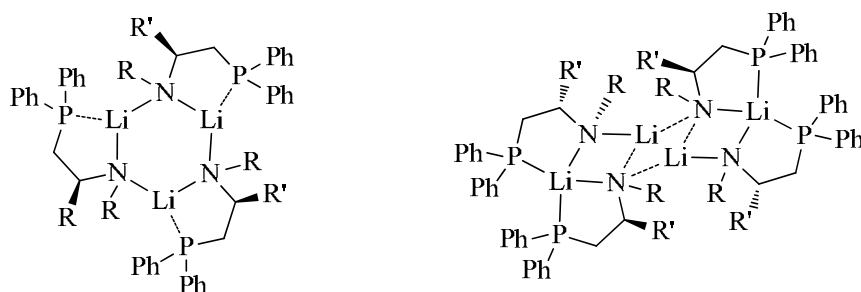
Figure 3. The proposed cyclic trimer a) and ladder–type tetramer b) of Li-**1** (R = i-Pr and R' = Ph).

It is suggested that the other two signals, a singlet at 0.67 ppm and a triplet ($^1J_{6Li,31P}$ 15 Hz) at 1.88 ppm with an intensity ratio of 1:1, are from a complex with two different lithiums. These are assigned to a complex in which one of the lithiums is coordinated by two phosphines while the other lithium is unsolvated. These signals could tentatively be assigned to a dimer with two non-equivalent lithiums. However, such dimers have not been observed previously in non-coordinating solvents. Alternatively, these signals are from a ladder-type tetrameric structure (Figure 3). Such ladder-type structures have also been observed previously for NN-chelating lithium amides.[16] The presence of two different types of aggregates is also supported by ^{13}C NMR spectra, which shows two sets of signals for the lithium amide, i.e. the cyclic trimer and the ladder-type tetramer of the lithium amide.

NMR studies of the amides in coordinating solvents (i.e. Et$_2$O and THF)
Adding one equivalent of *n*-BuLi, to solutions (approx. 0.2 M) of the respective amines **1** or **2** in Et$_2$O results in the formation of a single specie, a lithium amide, according to the ^{1}H and ^{13}C NMR spectra at −78 °C. The ^{6}Li NMR spectra of these amides display two signals for the two non-equivalent lithiums, a singlet and a triplet ($^1J_{6Li,31P}$ 13-15 Hz) respectively in a 1:1 ratio, Table 1. The NMR data indicate that these lithio-phosphine amides form dimers with one of the lithiums

chelated by the two PPh$_2$ groups while the other lithium is coordinated with the solvent, i.e. Et$_2$O. (Table 1 and Figure 4 below).
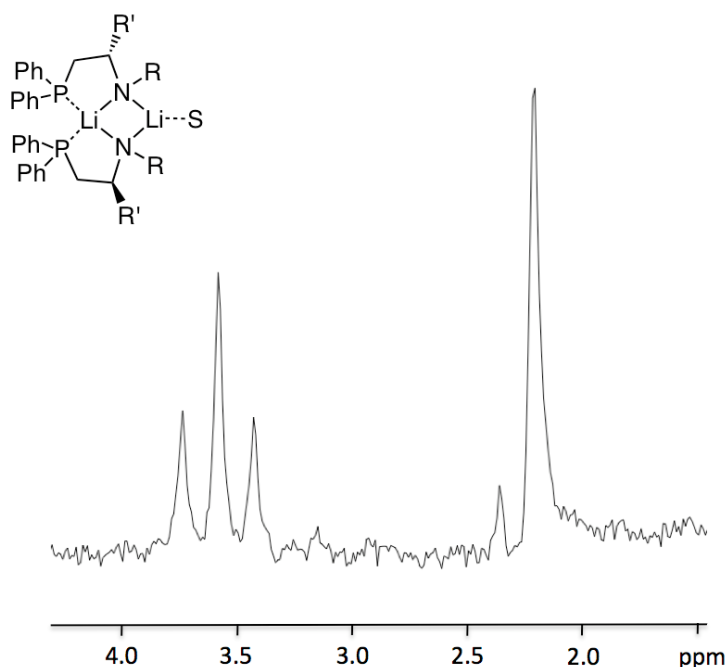

Figure 4. ^{6}Li NMR spectrum of (Li-**2**)$_2$ (0.3 M) obtained at −78 °C in Et$_2$O solution.

When these lithium amides were prepared in toluene-d_8 solution containing one equivalent of Et$_2$O the ^{6}Li NMR spectra displayed the two characteristic signals for the dimer with non-equivalent lithium, a singlet for the lithium solvated by Et$_2$O and a triplet for the lithium coordinated by two phosphines. In addition, the ^{13}C NMR spectrum shows two signals for the coordinated Et$_2$O at a slightly different chemical shift compared to that of free Et$_2$O, Figure 5. The ^{13}C NMR spectrum also shows one set of resonances for the amide. Upon further additions of Et$_2$O both resonances for free uncomplexed and coordinated Et$_2$O are observed simultaneously. The signals for the free Et$_2$O are also observed to increase upon further additions while those for the complexed Et$_2$O are unaffected. This shows that the dimer is only solvated by one Et$_2$O molecule.

The ^{6}Li,^{31}P coupling should be lost upon addition of THF if THF is capable of replacing phosphine in the coordination sphere of lithium. The common knowledge about lithium solvation is that the Li-P interaction should be substantially weaker than that of Li-THF. Based on previous finding on various chelating amides the addition of THF to Et$_2$O solutions should result in significant chemical shift changes in the ^{6}Li NMR.[17] Thus, we were surprised to observe that the ^{6}Li NMR spectra are unaffected by addition of THF to an Et$_2$O solution of Li-**2**. This result also indicates that THF does not replace Et$_2$O as ligand to lithium. This unexpected result was reproduced multiple times with different THF and Et$_2$O sources. However, upon analysis of the ^{13}C NMR spectra we could conclude that THF indeed replaces Et$_2$O as ligand to lithium in these

amides. The ^{13}C NMR spectrum of the THF solvate of Li-**2** displays two sets of signals for THF, one for free THF and one for complexed THF, Figure 6. These set of signals are observed to coalesce at higher temperature indicating slow THF exchange between free and complexed THF on the NMR time scale below –60 °C.
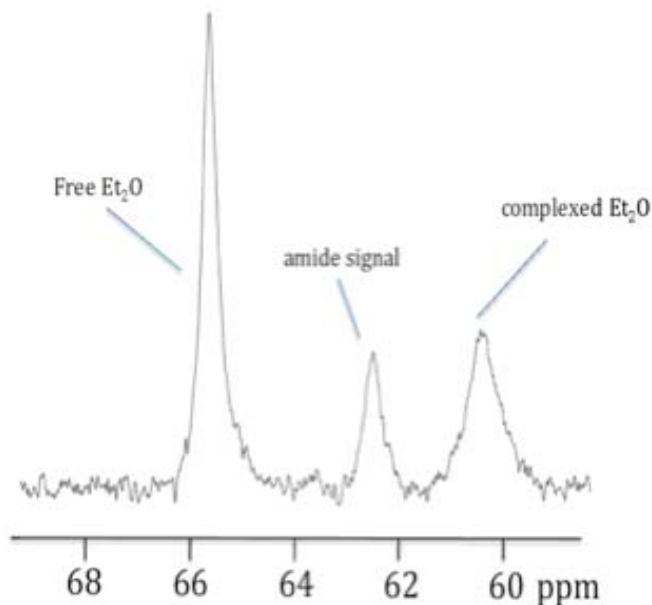
Figure 5. A Selected region (the CH$_2$ carbons of Et$_2$O) of the ^{13}C NMR spectra with approx. 2 equivalents of Et$_2$O added to the toluene-d_8 solution of Li-**1**. Both free uncoordinated and coordinated Et$_2$O ether signals appear as separate signals due to slow ethereal ligand exchange on the NMR time scale –80 °C.
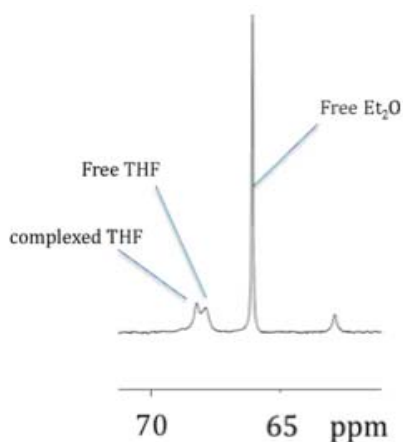
Figure 6. A Selected region (the OCH$_2$ carbons of THF) of the ^{13}C NMR spectra with approx. 2 equivalents of THF added to the Et$_2$O-d_{10} solution of Li-**1**. Both free uncoordinated and coordinated THF ether signals appear as separate signals due to slow ethereal ligand exchange on the NMR time scale –80 °C. The high field signal at 62 ppm is from the lithium amide.

This shows that THF indeed replaces Et_2O as ligand to the lithium in the amide dimer, and the absence of any observable changes in the ^6Li NMR must be due to accidental chemical shift equivalence.

The directly observed $^6Li,^{31}P$ couplings in both Et_2O and THF solutions indicate that there is a strong Li-P interaction. The analogue Li-S interactions are lost upon addition of THF, while the Li-P interaction is strong enough to resist addition of the much better ligand THF.

New signals appear in the ^6Li NMR spectra upon further addition of n-BuLi to the Et_2O solutions of the amides. The signal at 1.9 ppm corresponds to the excess of tetrameric n-BuLi. Two other signals, one doublet ($^1J_{6Li,31P}$ = 8–9 Hz) and one singlet were assigned to lithiums in a mixed complex between n-BuLi and the respective lithium amide, see Table 1.

Table 1. ^6Li NMR chemical shifts and $^6Li,^{31}P$ coupling constants for the dimer with non-equivalent lithiums and for the respectively mixed complexes with n-BuLi in Et_2O and THF solutions

| R:	ether	dimer	ppm (multiplicitiy, coupling constant in Hz)	
Ph	Et_2O	homo	2.22 (s)	4.04 (t 15.6)
		mixed	3.10 (d 9.1)	3.51 (s)
	THF	homo	2.22 (s)	4.04 (t 16.0)
		mixed	2.65 (s)	3.32 (d 7.8)
i-Pr	Et_2O	homo	2.20 (s)	3.80 (t 14.5)
		mixed	3.10 (d 9.2)	3.40 (s)
	THF	homo	2.20 (s)	3.80 (t 14.5)
		mixed	2.50 (d 8.7)	3.40 (s)

The ^{13}C NMR spectra display two sets of resonances for the chiral lithium amides and two sets of resonances for n-BuLi, one for each homo complex (i.e. n-BuLi and lithium amides) and one for the mixed complex between n-BuLi and the lithium amide. The ^{13}C NMR spectra displays quintets ($^1J_{13C,6Li}$ ≈ 8 Hz) for the α-carbons of the complexed n-BuLi. This splitting shows that the carbanionic carbon of an n-butyl is connected to two different lithiums, i.e. formation of a 1:1 mixed complex between n-BuLi and a lithium amide. Typically the solutions contain tetrameric n-BuLi (a), chiral lithium amide dimers with non-symmetrically solvated lithiums (b) and 1:1 mixed complexes between the amide and n-BuLi (c), Figure 6.

The ^6Li NMR spectrum of mixtures of **2** and n-BuLi in Et_2O solution shows several signals (Figure 7). The signal labeled with a are from free n-BuLi, the signals labeled with b are from the two lithiums of the Et_2O solvated (Li-**2**)$_2$ and the signals labeled with c are from the two lithiums of the mixed complex n-BuLi/Li-**2**. Addition of THF to the Et_2O solution results in significant shift changes of the ^6Li signals for the mixed complex. At less than 5% THF (30 μL THF vs 700 μL Et_2O) added the singlet from the mixed dimer shifts upfield by approx 1 ppm while the doublet only undergoes a slight downfield shift (less than 0.2 ppm). This indicates that the lithium coordinated by Et_2O becomes solvated by THF, while the chelated lithium appears practically

unaffected (Figure 8, the signal labeled with c). The coupling constant for the doublet is only slightly affected (Table 1).
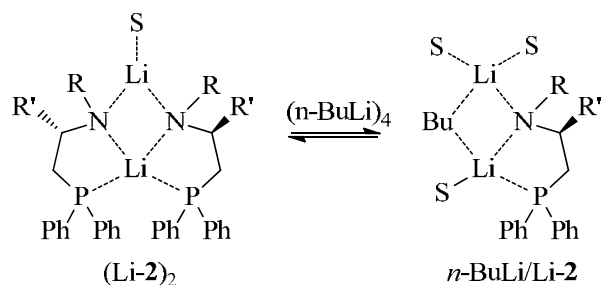
Figure 7. The equilibrium between (Li-**2**)$_2$, (*n*-BuLi)$_4$, and mixed complexes *n*-BuLi/(Li-**2**), R= R'= i-Pr.
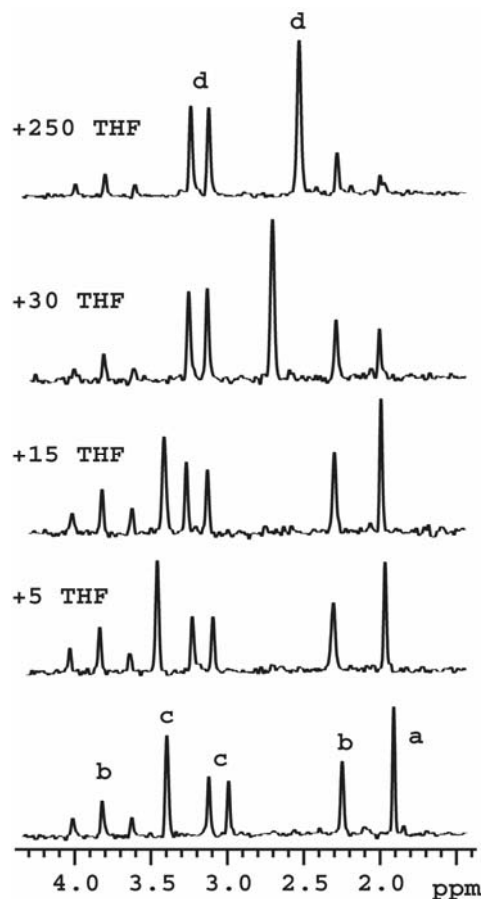
Figure 8. ^{6}Li NMR spectrum of Li-**2** (0.3 M) obtained at −78 °C in 700 μL Et$_2$O-d_{10} and varying amounts of THF added. Signal a is from tetrameric *n*-BuLi, the two signals labeled b is from the two lithiums in the dimer and the two labeled c is for the signals for the two lithiums in the mixed complex solvated by Et$_2$O. The two signals labeled d is from the two lithiums of the THF solvated mixed complex.

However, the addition of THF appears to have a strong effect on the equilibrium between the homo-aggregates (Li-**2**)$_2$ and the mixed complex, i.e. *n*-BuLi/Li-**2**, Figure 7. At higher THF concentrations (250 μL THF vs 700 μL Et$_2$O) practically all lithium amide is complexed with *n*-BuLi, i.e. in the mixed complex *n*-BuLi/Li-**2** (Figure 8, the signal labeled with d). This shows that THF solutions favor the mixed complex between *n*-BuLi and the chiral amide, a prerequisite for asymmetric induction.

Conclusions

In summary the ^{6}Li NMR spectra of the lithium amides with expected weakly chelating groups have revealed several interesting facts. Lithiation of chiral N,P-amines with *N*-isopropyl substitution in ethereal solvents shows typically two signals, a triplet and a singlet, which have been assigned to the two non-equivalent lithiums in the dimers. The splitting of one of the signals into a triplet shows that one of the lithiums is coordinated by two phosphines ($I = 1/2$). These structures also prevail in THF solution. Thus THF is not capable of competing with the intramolecular N-Li-P interaction. In contrast THF additions have large impact the structure of lithium amides with chelating ether groups. To the best of our knowledge, chelates of the Li-P type described herein has not been observed before, although there have been a few reports on X-ray structures of organolithium species crystallized from THF solutions with short Li-P distances.[11] The coordination of phosphorous to lithium persists even in THF solution. Although, we cannot fully exclude some influence of steric effects. This surprising result shows that the intra molecular Li-P interaction appears to be stronger than the corresponding solvation by either Et$_2$O or THF. Based on this we propose that Li-P interactions may provide an attractive structural motif that has not been explored in e.g. asymmetric organometallic chemistry.

Experimental Section

Synthesis of the studied chiral amines. The amines used in this study have been prepared previously in our laboratory.[6]

NMR studies. Glassware and syringes were dried at 50 °C in a vacuum oven before transfer into a glove box (equipped with a gas purification system that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture and oxygen content was less than 3 ppm. All manipulations concerning the NMR studies were carried out using gas-tight syringes. Ethereal solvents, distilled under nitrogen from sodium and benzophenone, were kept over 4 Å molecular sieves in septum sealed flasks inside the glove box.

n-Bu[⁶Li] was prepared from [⁶Li] and 1-chlorobutane as described previously.[18] The respective amide and *n*-Bu[⁶Li] was added to an NMR tube, sealed with a septum and a Teflon valve, loaded with 700 μL of solvent, toluene-d₈, Et₂O-d_{10} or THF-d_8.

All NMR spectra were recorded using a Varian Unity 500 spectrometer equipped with three channels using a custom made 5 mm ¹H, ¹³C, ⁶Li triple resonance probe head. Measuring frequencies were 500 MHz (¹H), 125 MHz (¹³C) and 73 MHz (⁶Li). The ¹H and ¹³C NMR spectra were referenced to the respective solvent signals (toluene-d_8 at 2.05 ppm (¹H, CHD₂) and 20.4 ppm (¹³C, CD₃); Et₂O-d_8 at 1.06 ppm (¹H, CHD) and at 20.4 ppm (¹³C, CD₃) THF-d_8 at 1.72 ppm (¹H, CHD) and 67.6 ppm (¹³C, CD₂) respectively).

Acknowledgements

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