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Spontaneous Resolution and Carbonation of Chiral Benzyllithium Complexes

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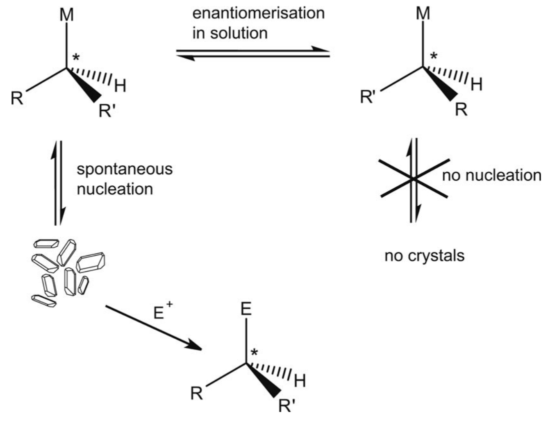
In search for new examples of absolute asymmetric synthesis (AAS), chiral α-substituted benzyllithium complexes have been prepared. While [Li(phet)(pmdta)] (**1**) (phet = 1-phenylethyl, pmdta = *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine) affords only racemic crystals, a promising candidate for AAS was indeed found: [Li(phet)(tmpda)], α-**2**, (tmpda = *N*,*N*,*N*′,*N*′-tetramethylpropylenediamine) crystallises as a conglomerate. Although concomitant polymorphism was not observed, a racemic phase (β-**2**) could also be isolated. Chiral crystals of α-**2** gave 2-phenylpropionic acid in high yield on reaction with gaseous CO_2, but the bulk product was racemic. It is unclear whether the lack of selectivity originates during crystallisation or carbonation. In order to investigate this, similar complexes displaying Si or S atoms in the α-position were prepared and structurally characterized: [Li(tmsb)(tmpda)] (tmsb = 1-trimetylsilylbenzyl) (**3**), [Li{C(CH_3)(Ph)(SPh)}(pmdta)] (**4**), [Li{C(CH_3)(Ph)(SPh)}(tmeda)] (**5**), and [Li(tmeda)$_2$][C(CH_3)(Ph)(SPh)] (**6**). The introduction of heavy atoms should allow determination of absolute configuration and enantiopurity, but so far only racemic crystals have been obtained.

Introduction

Stereochemically labile organometallic reagents that crystallise in a Sohncke space group[1] may undergo total spontaneous resolution (also known as crystallisation-induced asymmetric transformation).[2] This constitutes absolute asymmetric synthesis (AAS), since optically active products are created from achiral or racemic starting materials.[3] A substance that crystallises in a Sohncke space group may form a conglomerate of chiral crystals and is said to undergo spontaneous resolution, since the two enantiomers separate spontaneously during crystallisation. The bulk crystalline product will remain racemic unless the substance is configurationally labile in solution and crystallisation is initiated by one single crystal nucleus. In such a case, all crystals can be of the same enantiomorph, and since the solution will remain racemic during crystallisation, an excess of one enantiomorph may be obtained. Ideally, a racemate may be converted to a pure enantiomer in quantitative yield by slow crystallisation.[4] The product will, of course, racemise if dissolved in a solvent. In some rare cases, however, a stereochemically labile substance may be transformed into a stereochemically inert organic compound through a chemical reaction. This requires conditions where racemisation is slow compared to the rate of reaction (e.g., solvent-free reaction). We have reported that octahedral Grignard reagents displaying chirogenic Mg atoms[5] may crystallise as conglomerates and give chiral secondary alcohols with up to 22% *ee* on reaction with prochiral aldehydes.[6] The need to generate a new chirogenic centre in the product by asymmetric induction from the reagent probably explains the low enantiomeric excesses. Nevertheless, this was the first report of absolute asymmetric synthesis of an organometallic reagent; previous work on absolute asymmetric synthesis through total spontaneous resolution generally relies on photochemical rearrangement in chiral crystals or total spontaneous resolution of prochiral substrates, such as keto-compounds or alkenes.[7–11] We have more recently studied organometallic reagents displaying chirogenic α-carbon atoms (Scheme 1), since subsequent reaction with an electrophile may trap the configuration at the α-carbon atom and generate a configurationally inert organic product. We recently published the absolute



Scheme 1.

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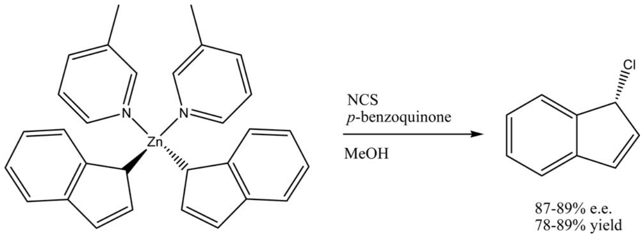
asymmetric synthesis of such a reagent, bis(1-η^1-indenyl)bis(3-picoline)zinc (Scheme 2).[12] This complex displays two indenyl groups of the same configuration, and optically active bulk samples may be obtained on slow crystallisation. Treating selected crystals of bis(1-η^1-indenyl)bis(3-picoline)zinc with *N*-chlorosuccinimide and *p*-benzoquinone in methanol gave essentially pure 1-chloroindene with an enantiomeric excess of 82–89 %. Bulk samples gave up to 71 % *ee* without optimisation of the crystallisation conditions.



Scheme 2.

Beside bis(indenyl)zinc complexes, other groups of organometallic reagents may be considered for absolute asymmetric synthesis. α-Substituted benzyllithium complexes, such as (1-phenylethyl)lithium, have a number of attractive properties. They should be relatively easy to prepare, they can be expected to racemise rapidly in solution, and they display a high reactivity towards electrophiles. Benzyllithium compounds may be prepared by lithiation of the corresponding hydrocarbon by alkyllithium reagents, at least in the presence of a Lewis base.[13] Toluene is readily transformed to benzyllithium by *n*BuLi in THF and the product is easily purified by crystallisation.[14] Often, however, considerable amounts of ring metalation and polymetalation products are obtained as well. When an excess of ethylbenzene was added to *n*BuLi/TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) at 30 °C, the reaction product consisted of 38 % (1-phenylethyl)lithium, 9 % 2-ethylphenyllithium, 36 % 3-ethylphenyllithium and 17 % 4-ethylphenyllithium.[15] The composition of the reaction mixture was the same after 0.5 h and 6.5 h, with no indication of shifting towards (1-phenylethyl)lithium. Alternative methods for the preparation of (1-phenylethyl)lithium involves reductive lithiation of phenyl 1-phenylethyl sulfide by lithium and a catalytic amount of naphthalene in diethyl ether, which gives (1-phenylethyl)lithium in 54–68 % yield[16,17] or transmetalation of tributyl(1-phenylethyl)stannane with *n*BuLi.[18]

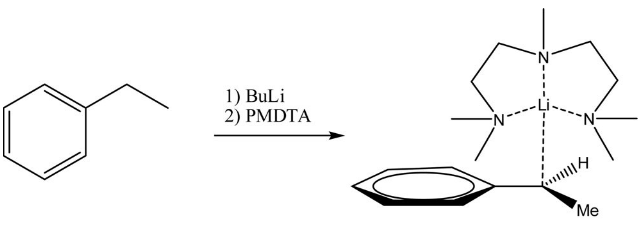
The rate of enantiomerisation in solution is a factor of importance, since this will determine the possibility of total spontaneous resolution. The enantiomerisation rate of (1-phenylethyl)lithium in THF has been studied through the reaction with chiral electrophiles. Even at –78 °C, using the most reactive aldehydes, the diastereomeric ratios were the same for the racemic and the enantiomerically pure electrophiles, indicating a fast enantiomerisation in solution.[18] Several reagents displaying a heteroatom in α-position, like (1-trimethylsilylbenzyl)lithium and (1-phenylthiobenzyl)lithium alos enantiomerises faster than the rate of addition to the aldehyde.[19] On the other hand, {1-(*N*,*N*-diisopropylcarbamato)-1-methyl-benzyl}lithium was found to be configurationally inert in THF at –78 °C.[19] A number of organolithium reagents displaying chirogenic α-carbon atoms have been obtained in optically active form by conventional asymmetric synthesis. Optically active *s*BuLi complexes have been prepared at low temperature from (±)-2-octyllithium and (–)-di-*sec*-butylmercury in pentane.[20] Carbonation of the product gave optically active 2-methylbutyric acid. 2-Octyllithium is known to largely retain the configuration at low temperature: optically active 2-methyloctanoic acid was obtained by carbonation of a mixture of (–)-2-iodooctane and sBuLi in petroleum ether/diethyl ether (17:1) at –70 °C. If the reaction mixture was heated to 0 °C before carbonation, only a racemic product was obtained.[21] Reaction between menthylchloride and lithium metal in hydrocarbon solution gave menthyllithium, which on carbonation yielded 3-*p*-menthanecarboxylic acid with only traces of the enantiomeric form.[22] In hydrocarbon solution 1-menthyllithium appears to be configurationally inert up to at least 50 °C as indicated by ^{1}H-NMR spectroscopy. Menthyllithium racemises in diethyl ether at 0 °C and racemisation is indicated at –40 °C in dimethyl ether.[21]

For a reagent to be useful in absolute asymmetric synthesis, it must crystallise as a conglomerate, which is rather rare; this has been estimated to occur for 5–10 % of crystalline racemates.[23] A trial and error search for a conglomerate may therefore be very time consuming. Nevertheless, in this work we set out to isolate an α-substituted benzyllithium complex crystallising as a conglomerate, in order to be able to trap the chirality of such a complex by reaction with carbon dioxide.

Results and Discussion

[Li(phet)(pmdta)] (1)

Ethylbenzene is readily lithiated by neat *n*BuLi in the presence of PMDTA (*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine). The reaction proceeds with evolution of gas and heat, and results in a red microcrystalline product (Scheme 3). Reaction in hexane solution proceeds more smoothly and affords red crystals of [Li(phet)(pmdta)] (phet = 1-phenylethyl), **1**, which were analysed by single-crystal X-ray diffraction; compound **1** exhibits chiral mononuclear molecules (Figure 1). Several excellent reviews concerning organolithium crystal structures have been published;[24a–24d] a lithium cation usually coordinates a benzyl anion in a η^1- or η^2-mode, but the bonding may also approach a η^3-mode through interactions with one of the *ortho* carbon atoms.[24e] The borders between the three modes are floating, but one could perhaps use 2.50 Å as an upper limit for a Li–C bond.[24f] The potential-energy surface above a delocalised carbanionic system is probably shallow, meaning that the hapticity of the lithium complex will be determined by the steric requirements of the neutral ligands and/or by crystal packing effects.[24g] All Li–C distances in **1** exceed 2.5 Å except the Li1–C2 distance, and **1** is therefore probably best described as a η^1-coordinate complex (Table 1). Similar η^1-coordination is exhibited by [Li(Bn)(tmeda)(thf)],[25] while η^2-coordination was found in [Li(Bn){O(*t*Bu)(Me)}]$_n$.[26] A structure close to a η^3-coordination mode is exhibited by $[Li_2\{C(Ph)_2(CH_2)_2C(Ph)_2\}(Et_2O)_4]$ with a lithium to *ortho*-carbon distance of 2.58 Å.[27] There are no previous reports of (1-phenylethyl)lithium complexes in the Cambridge Structural Database (CSD, version 5.30 of May 2009).[28] It is noteworthy that the ^{13}C-NMR spectrum of **1** in C_6D_6 displays two signals (at δ = 111 and 115 ppm) for the two *ortho*-carbons, indicating that they have significantly different chemical environment. Although the aromatic ring may rotate, the observation of two *ortho*-carbons indicate that this dynamic process is slow on the NMR time scale. The NMR spectrum corresponds well to the crystal structure of **1**, where the Li1–C4 distance of 2.742(2) Å is almost a full ångström shorter than the distance from the lithium cation to the other *ortho*-carbon, Li1–C8 = 3.684(2) Å, and thus indicates that the solid-state structure may be retained in solution.



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Scheme 3.

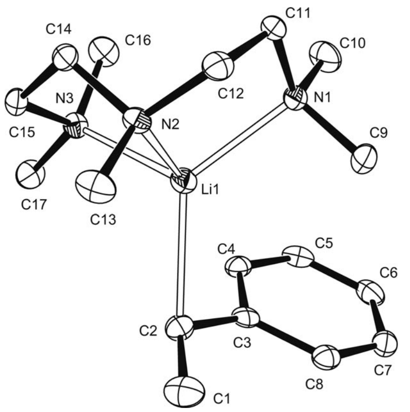


Figure 1. ORTEP plot of **1** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. Only Li–C interactions shorter or equal to 2.5 Å have been indicated as bonds.

Compound **1** crystallises in the centrosymmetric space group $P2_1/n$, and crystals of **1** will contain equal amounts of both enantiomers. Repeated crystallisation of **1** always gave the same crystalline phase, and **1** is therefore not useful in absolute asymmetric synthesis. However, if a racemic Li(phet) complex is required as a precursor complex or for other synthetic purposes, **1** should be quite useful. It is cheap and easy to prepare, and since it readily crystallises, it can conveniently be separated from any by-products.

Table 1. Selected bond lengths and bond angles for **1**.

Bond lengths [Å]		Bond angles [°]	
Li(1)–C(2)	2.271(2)	N(2)–Li(1)–N(1)	85.11(7)
Li(1)–C(3)	2.572(2)	N(2)–Li(1)–N(3)	87.12(7)
Li(1)–C(4)	2.742(2)	N(1)–Li(1)–N(3)	116.68(8)
Li(1)–N(1)	2.150(2)	N(2)–Li(1)–C(2)	113.11(8)
Li(1)–N(2)	2.122(2)	N(1)–Li(1)–C(2)	127.76(8)
Li(1)–N(3)	2.164(2)	N(3)–Li(1)–C(2)	112.91(8)

[Li(phet)(tmpda)] (2)

Although lithiation of ethylbenzene is an attractive route to [Li(phet)(pmdta)] it may not be generally useful for preparing [Li(phet)L$_n$] complexes with other neutral ligands. For example, when TMEDA was used as ligand only low quality crystals could be obtained. Moreover, the lithiation of ethylbenzene using ligands such as TMPDA (*N*,*N*,*N*′,*N*′-tetramethylpropylenediamine) appear to proceed at a much lower rate than lithiation in the presence of PMDTA. The reaction mixtures turned red rather slowly, and no crystalline product could be isolated. Instead, we prepared [Li(phet)(tmpda)] (**2**) by transmetallation of tributyl(1-phenylethyl)stannane with *n*BuLi and TMPDA in hexane. Actually, two polymorphs, α-**2** and β-**2**, could be isolated. When a hexane solution of **2** was cooled to –35 °C, red crystals of α-**2** were isolated. Compound α-**2** crystallises in the Sohncke space group $P2_1$, but the asymmetric unit consists of four molecules, designated **I**–**IV** (Figure 2). The four molecules in the asymmetric unit have the same configuration at the α-carbon, but differ with respect to the conformations of the chelate ring systems. Molecules **I** and **IV** have the same conformation of the chelate rings, but the opposite conformation is found in molecules **II** and **III**. The Li–C distances are significantly different in the four molecules (Table 2). Molecule **I** and **IV** display shorter distances to the *ipso*- and nearest *ortho*-carbon atoms than molecules **II**–**III**, and thus approaches a η^3-coordination mode. All molecules are, however, probably best described as η^2-coordinate. Refinement of α-**2** in the centrosymmetric space group $P2_1/n$ reduces the number of molecules in the asymmetric unit to two. The result is a disordered structure where phet-ligands of opposite configuration are superimposed and refinement gives high values of *R*1 and *wR*2. Also, refinement in $P2_1$ does not give rise to the distorted geometries that typically results due to matrix-singularity when refining equivalent molecules as non-equivalent.[29] The molecules in the asymmetric unit are connected by CH-π interactions (Figure 3).[30] The distance between H13b and the centroid of the C18–C23 phenyl ring is 2.76 Å. Also, H14c appears to interact with the π system of the C17–C18 bond, the H14c–C17 and H14c–C18 distances being 2.81 and 2.71 Å, respectively. A similar (but not identical) set of interactions appears between molecules **II** and **IV**. The distance between H58b and the centroid of the C33–C38 phenyl ring is 2.77 Å and the distance between H59c and C33 is 2.66 Å. The H59c–C32 distance is considerably longer, 2.95 Å. There are two sets of CH-π interactions between the asymmetric units: the distance between

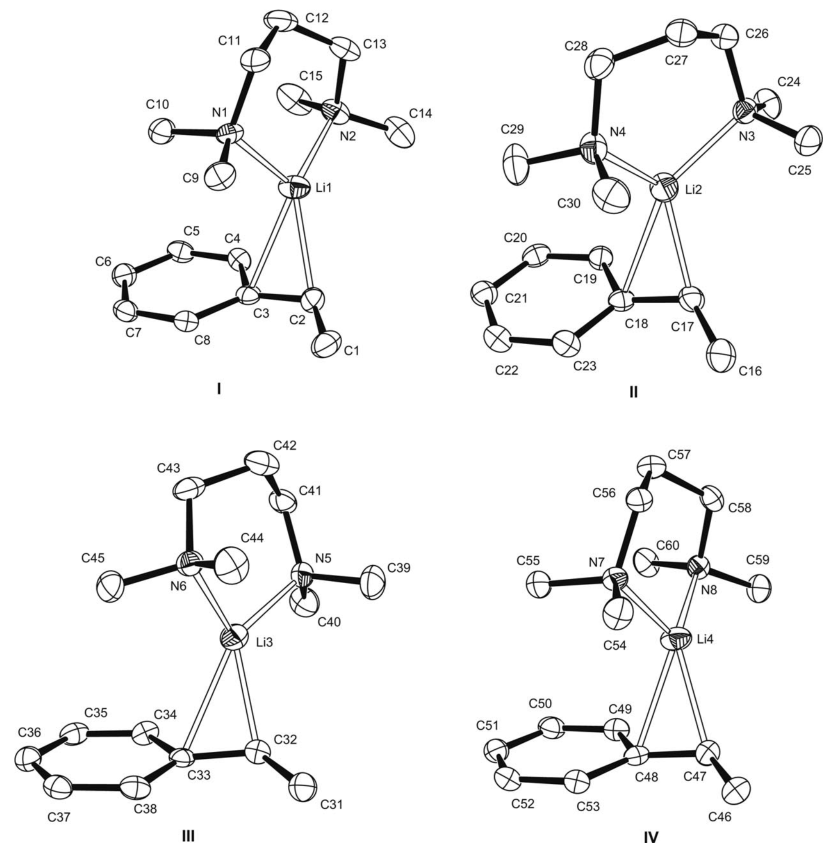


Figure 2. ORTEP plot of α-**2** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. Li–C distances shorter or equal to 2.5 Å have been indicated as bonds.

H24b and the centroid of the C3^i–C8^i phenyl ring is 2.80 Å and the distance between H40b and the centroid of the C48^i–C53^i phenyl ring is 2.94 Å [Symmetry code: (i) $1 + x$, y, z]. The structure can be described as being built up by stacks of equivalent molecules along the *b*-axis.

Table 2. Selected bond lengths [Å] for α-**2**.

Li(1)–C(2)	2.236(5)	Li(3)–C(32)	2.195(5)
Li(1)–C(3)	2.370(5)	Li(3)–C(33)	2.455(5)
Li(1)–C(4)	2.547(5)	Li(3)–C(34)	2.685(5)
Li(1)–N(1)	2.018(5)	Li(3)–N(5)	2.072(5)
Li(1)–N(2)	2.083(5)	Li(3)–N(6)	2.030(5)
Li(2)–C(17)	2.209(5)	Li(4)–C(47)	2.231(5)
Li(2)–C(18)	2.463(5)	Li(4)–C(48)	2.345(5)
Li(2)–C(19)	2.736(5)	Li(4)–C(49)	2.606(5)
Li(2)–N(3)	2.071(5)	Li(4)–N(7)	2.037(5)
Li(2)–N(4)	2.040(5)	Li(4)–N(8)	2.068(5)

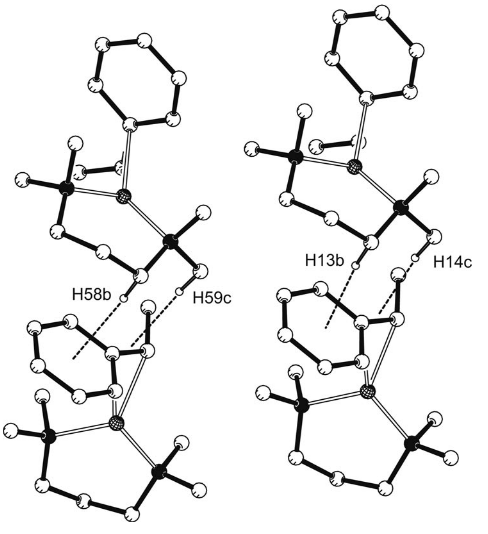


Figure 3. The asymmetric unit of α-**2** viewed along the b axis, displaying intermolecular interactions. All H atoms except those involved in interactions have been omitted for clarity.

If a hexane solution of **2** obtained by transmetallation is kept at ambient temperature, a red oil separates. When this oil was isolated and stirred at ambient temperature, it formed a precipitate, which melted on gentle heating, and red crystals grew on cooling to ambient temperature. These crystals were found to consist of a racemic phase, β-**2**, which crystallises in the centrosymmetric space group $P2_1/n$. The two phases, α-**2** and β-**2**, have similar densities but differ in melting points. Crystals of α-**2** melts immediately at ambient temperature, while the melting point of β-**2** lies slightly above ambient temperature. The occurrence of a competing racemic phase is not uncommon. In the case of the chiral reagents *cis*-[(*p*-$CH_3C_6H_4$)MgBr(dme)$_2$] and *cis*-[Mg(CH_3)(thf)(dme)$_2$]I, we found that conglomerates crystallise at ambient temperature, while racemic phases were obtained at –60 °C.[6] In the case of 10-nitro-phenantren-9-yl sulfide,[31a] bis(2,6-dimethylpyridine)dichloro-

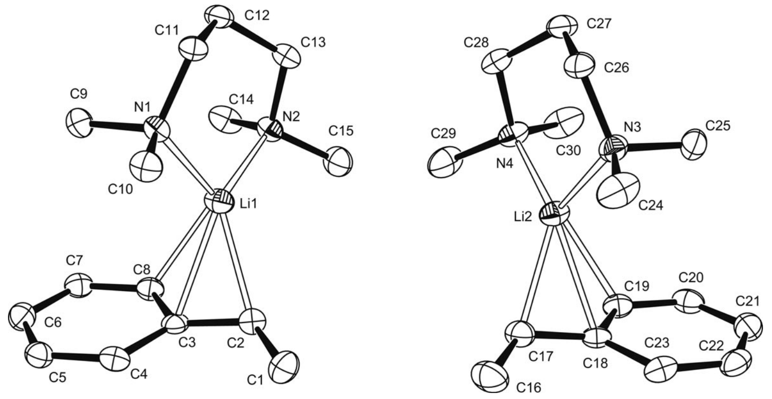


Figure 4. ORTEP plot of β-**2** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. Li–C distances shorter or equal to 2.5 Å have been indicated as bonds.

zinc[31b] and bis(1-η^1-indenyl)bis(3-picoline)zinc[12] we have reported the concomitant crystallisation[32–33] of chiral and racemic phases. In the case of **2**, we have not yet observed any concomitant crystallisation of the two phases; the bulk products have either been pure α-**2** or pure β-**2**. The asymmetric unit of β-**2** consist of two independent molecules (Figure 4). These two molecules have opposite configuration at the α-carbon atom and they have the same conformation of the chelate ring system. A difference between the molecules in α-**2** and β-**2** is found in the interactions between Li and the phet-moiety: the distances to the nearest *ortho*-carbon is significantly shorter in β-**2** compared to the molecules in α-**2**, or most other benzyllithium derivatives, and the coordination is probably best described as η^3 for both Li1 and Li2 (Table 3). The *ortho*-carbons of **2** give rise to only one signal in the ^{13}C-NMR spectrum, which is consistent with rapid exchange between the many conformations displayed in the crystal structures of α- and β-**2**. This also illustrates how the didentate TMPDA ligand gives a less rigid complex, as compared to **1** that has the tridentate PMDTA ligand. There is one set of CH-π interactions within the asymmetric unit of β-**2**: the distance between H27a and the centroid of the C3–C8 phenyl ring is 2.63 Å (Figure 5).

Table 3. Selected bond lengths [Å] for β-**2**.

Li(1)–C(2)	2.196(4)	Li(2)–C(17)	2.180(4)
Li(1)–C(3)	2.307(4)	Li(2)C–(18)	2.296(4)
Li(1)–C(8)	2.460(4)	Li(2)–C(19)	2.503(4)
Li(1)–N(1)	2.022(4)	Li(2)–N(3)	2.017(4)
Li(1)–N(2)	2.068(4)	Li(2)–N(4)	2.061(4)

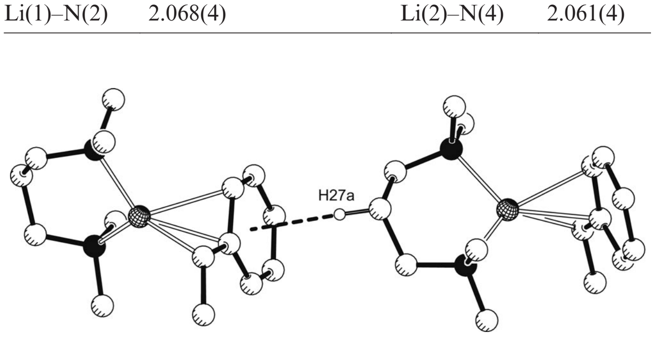
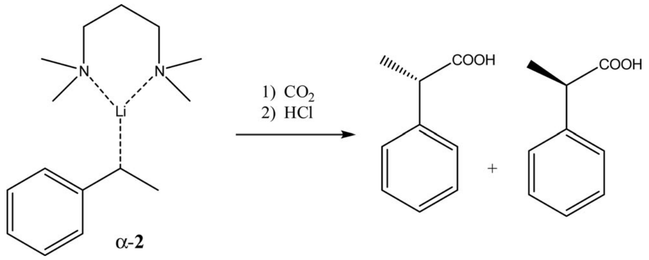


Figure 5. The asymmetric unit of β-**2** displaying intermolecular CH-π interactions. All H atoms except H27a have been omitted for clarity.

Carbonation of [Li(phet)(tmpda)]

Since carbonation of optically active organolithium reagents can give optically active carboxylic acids, as described in the introduction, carbon dioxide appeared to be a suitable electrophile for reactions with the chiral crystal of α-**2**. Carbon dioxide would allow a solid-gas reaction, which may proceed faster than a solid-solid reaction. We found that crystals of α-**2** indeed react with carbon dioxide to give chiral 2-phenylpropionic acid as the major product (Scheme 4). Reactions were performed at –78 °C by exposing crystals of α-**2** (dried in vacuo) to an atmosphere of dry carbon dioxide in a Schlenk tube. The progress of the reaction could be followed visually by decolouration of the crystals; the reactions were generally completed in 1–2 h. The reaction product was quenched with dilute hydrochloric acid and injected on an enantioselective HPLC column, but we were unfortunately never able to observe any enantiomeric excess in the product. The failure to obtain an optically active product could be due to low optical purity of the reagent crystals. A crystal batch could in principle consist of (i) homochiral and enantiomerically pure α-**2**, (ii) a racemic mixture of enantiomerically pure α-**2** crystals, or (iii) crystals of α-**2** twinned by inversion. There is also a risk of obtaining a mixture of α-**2** and β-**2**, or even pure β-**2**. Unfortunately, there is no easy way to establish the enantiomeric composition of the highly air-sensitive crystal batches of α-**2**. Since α-**2** does not contain any atom heavier than N, a reliable Flack parameter[34–36] could not be obtained, so it is not known if crystals of α-**2** are enantiomerically pure; even crystals of a chiral phase may be essentially racemic due to twinning-by-inversion. The crystals were generally small, and of poor quality, and we did not succeed in performing reactions on selected single crystals. Even if single crystals are enantiomerically pure, the bulk samples may be racemic. Some substances will only give an optically active bulk product when crystallised whilst stirring.[37,38]

Attempts to crystallise **2** in a cooling bath whilst stirring resulted in a precipitate, but since it remained solid at ambient temperature, the precipitate probably consisted of β-**2**. The only reliable method of obtaining pure α-**2** is rapid cooling of the solution to low temperature, but the chances of performing total spontaneous resolution under such conditions should be affected by fast primary nucleation. It is, in conclusion, not known to what degree total spontaneous resolution of bulk samples of α-**2** was obtained.



Scheme 4.

The carbonation conditions are another probable source of low enantioselectivity. The carbonation product often had an oily appearance, which may have affected the outcome of the reaction. Formation of an oil may lead to dissolution of the reagent crystals and subsequent racemisation. The carbonation could take place in a liquid film surrounding the crystals rather than in the solid state, with possible loss of enantioselectivity. Quenching the reactions before completion did not give rise to any detectable enantiomeric excess. The low melting point of α-**2** is another potential problem. Heat generated in the reaction could perhaps fuse the crystal surface and cause racemisation. Reaction between solid CO_2 and a suspension of α-**2** in hexane gave no enantiomeric excess. The matter is further complicated by the high degree of air-sensitivity displayed by α-**2**. When crystals of α-**2**, initially at –100 °C, are exposed to ambient atmosphere they melt within a few seconds first giving a red oil under evolution of heat and smoke, the oil then decolourises within one or two seconds, and finally solidifies.

Lithiation of Benzyltrimethylsilane

With the hope of finding a conglomerate more suited for absolute asymmetric synthesis, a number of new complexes were prepared. Benzyllithium complexes displaying a heavy heteroatom in α-position were prepared, since the heteroatom would allow the determination of the absolute structure when non-centrosymmetric crystals were isolated. It would then be possible to establish whether individual single crystals are enantiomerically pure or not, and picking several crystals from a single batch would give an indication of the enantiomeric purity of the bulk samples. One of the simplest routes to such complexes would be lithiation of benzyltrimethylsilane, which is commercially available or can be easily prepared.[39] Indeed, lithiation of benzyltrimethylsilane by *n*BuLi in presence of TMPDA afforded yellow crystals of [Li(tmsb)(tmpda)] (tmsb = 1-trimetylsilylbenzyl), **3** (Figure 6). Compound **3** could, as seen from Table 4, be described as a η^2-coordinate complex, but is also close to a η^1 coordination mode. The ^{13}C-NMR spectrum of **3** in C_6D_6 displays only one signal (at $\delta = 119$ ppm) from the *ortho*-carbons. Thus there must be a fast exchange of the two *ortho*-carbons on the NMR time scale, consistent with longer and weaker interactions between lithium and the *ortho*-carbons. These distances in the crystal structure of **3** are similar (and long): the Li1–C7 distance is 2.991(3) Å and the Li1–C3 distance is 3.286(3) Å. The indication is that the solid-state structure is retained in solution. There is one crystal structure of a (1-trimethylsilylbenzyl)-lithium complex, [Li(tmsb)(tmeda)], previously reported in the CSD.[24] This compound displays smaller deviations from the η^2 coordination mode: the corresponding Li1–C1 and Li1–C2 distances are 2.128(6) and 2.277(6) Å, respectively. Complex **3** crystallises in the centrosymmetric space group $P2_1/c$ with one molecule in the asymmetric unit. The molecules are assembled by weak CH-π interactions that results in chains along the *c*-axis. The distance from H13b to the centroid of the C2^{ii}–C7^{ii} phenyl ring is 2.54 Å [symmetry code: (ii) *x*, 1/2 – *y*, –1/2 + *z*].

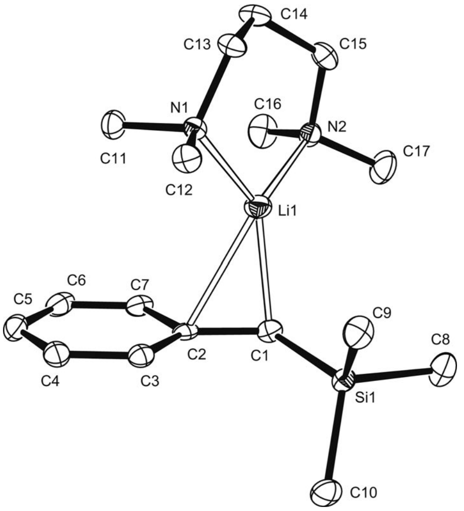


Figure 6. ORTEP plot of **3** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. Li–C distances shorter or equal to 2.5 Å have been indicated as bonds.

Table 4. Selected bond lengths [Å] for **3**.

Li(1)–C(1)	2.154(3)
Li(1)–C(2)	2.463(3)
Li(1)–C(3)	3.286(3)
Li(1)–C(7)	2.991(3)
Li(1)–N(1)	2.043(3)
Li(1)–N(2)	2.063(3)

Lithiation of Phenyl 1-Phenylethyl Sulfide

Further complexes could be synthesised by lithiation of phenyl 1-phenylethyl sulfide by *n*BuLi in the presence of chelating ligands. Complexation with many neutral ligands yielded oils rather than crystals, but crystalline complexes were obtained in the case of PMDTA and TMEDA. Additional complexes could probably be obtained by transmetallation of the corresponding 1-(tributylstannyl) derivative with *n*BuLi. Phenyl 1-phenylethyl sulfide is easily synthesised by condensation of thiophenol and 1-phenylethanol in the presence of perchloric acid, the water being continuously removed azeotropically.[40] Lithiated phenyl 1-phenylethyl sulfide complexes are attractive not only due to the heavy S atom which allows absolute structure determination, but also due to the lack of an α-hydrogen atom. Such compounds would give rise to a chiral product upon reaction with an acid, such as water. Lithiation of phenyl 1-phenylethyl sulfide by *n*BuLi/PMDTA gave crystals of [Li{C(CH$_3$)(Ph)(SPh)}(pmdta)] (**4**). Compound **4** forms chiral mononuclear molecules (Figure 7), and like **1**, the complex is best described as η^1-coordinate (Table 5). The α-carbon is only slightly pyramidised; the distance from C2 to the least-squares plane formed by C1, C3 and S1 is 0.246(2) Å. The ^{13}C-NMR spectrum of **4** in C_6D_6 displays only one signal (at δ = 117 ppm) from the *ortho*-carbon atoms, which is consistent with the crystal structure of **4**: the Li1–C4 distance is 3.299(4) Å and the Li1–C8 distance is 3.531(4) Å. Complex **4** crystallises in the polar space group $Pc2_1n$, with a reasonably low Flack parameter, –0.06(6). There is no evidence of any CH–π or π–π interactions in **4**, and the S atoms do not participate in hydrogen bonding.

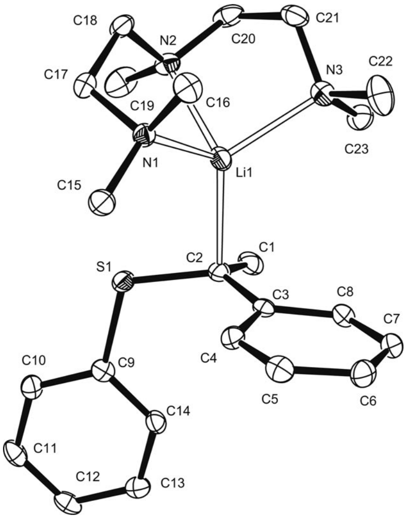


Figure 7. ORTEP plot of **4** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. Li–C distances shorter or equal to 2.5 Å have been indicated as bonds.

Table 5. Selected bond lengths [Å] for **4**.

Li(1)–C(2)	2.318(4)
Li(1)–C(3)	2.740(4)
Li(1)–C(4)	3.299(4)
Li(1)–C(8)	3.531(4)
S(1)–Li(1)	3.030(3)
Li(1)–N(1)	2.218(4)
Li(1)–N(2)	2.142(4)
Li(1)–N(3)	2.157(4)

Using TMEDA as a ligand, two different complexes could be isolated: [Li{C(CH$_3$)(Ph)(SPh)}(tmeda)] (**5**) and [Li(tmeda)$_2$][C(CH$_3$)(Ph)(SPh)] (**6**). Compound **5** was obtained by addition of *n*BuLi and TMEDA to the sulfide, yielding a red oil, which was dissolved in diethyl ether and cooled to –35 °C, whereupon crystals deposited. Compound **5** is closely related to **1**–**4**; it is probably best described as η^2-coordinate and forms chiral mononuclear molecules (Figure 8, Table 6). The ^{13}C-NMR spectrum of **5** in C_6D_6 displays a very broad signal (at δ = 114 ppm) from the *ortho*-carbons, indicating an intermediate exchange rate on the NMR time scale. This is consistent with that the distances from lithium to the *ortho*-carbons in the crystal structure of **5** differ somewhat: the Li1–C4 distance is 2.727(3) Å and the Li1–C8 is 3.459(3) Å. Again, the indication is that the solid-state structure is retained in solution, since the didentate TMEDA ligand will furnish a less rigid complex than **1**, which excludes a spectrum with two fully resolved *ortho*-carbon signals. Since the analysed crystals were found to belong to the centrosymmetric space group $P2_1/n$, they are not useful in absolute asymmetric synthesis. During one attempted synthesis of **5**, the oil suddenly solidified, and the solids could only be partly dissolved on gentle heating with diethyl ether. When placing the mixture at +4 °C, crystals of [Li(tmeda)$_2$][C(CH$_3$)(Ph)(SPh)] (**6**) grew from the precipitate. Compound **6** forms an SSIP, a solvent

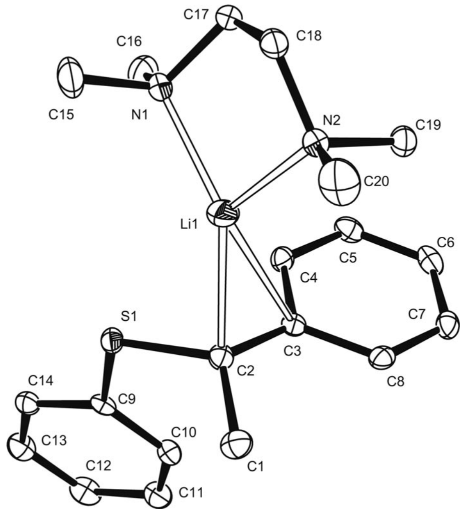


Figure 8. ORTEP plot of **5** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. Li–C distances shorter or equal to 2.5 Å have been indicated as bonds.

Table 6. Selected bond lengths [Å] for **5**.

Li(1)–C(2)	2.195(2)
Li(1)–C(3)	2.453(2)
Li(1)–C(4)	2.727(3)
Li(1)–S(1)	2.795(2)
Li(1)–N(1)	2.095(2)
Li(1)–N(2)	2.052(2)

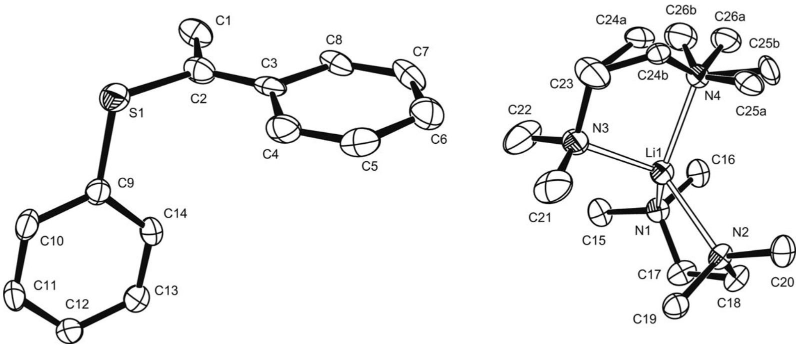


Figure 9. ORTEP plot of the anion (left) and cation (right) of **6** displaying the crystallographic numbering scheme with displacement ellipsoids drawn at the 50% probability level. All H atoms have been omitted for clarity. One of the TMEDA ligands is partly disordered over two positions.

separated ion pair (Figure 9, Table 7). Similar SSIP's have been reported for $[Li(tmeda)_2][C(Ph)_2(SiMe_3)]$[41] and $[Li(tmeda)_2][C(3,5\text{-dimethylphenyl})(PMe_2)(SiMe_3)]$.[42] Since there are no short Li–C distances, C2 cannot be considered as a chirogenic centre (although the thiophenyl group shields C2 from one side) but an *ee* would perhaps still be possible to obtain upon carbonation, if only **6** would have crystallised as a conglomerate. Like **4**, complex **6** crystallises in the polar space group $Pc2_1n$, and the crystals are therefore racemic. The structure displays disorder in one of the TMEDA ligands, which exhibits two different conformations. The isolation of **6** may give a clue to possible enantiomerisation processes in solution. As pointed out by Hoffmann et al.,[18] the structure of $[Li(Bn)(OEt_2)_2]_n$[43] is a model for such a process where the benzyl anion is equidistant to two Li^+ ions. The structure of **6** shows another possible pathway, namely the formation of solvent separated ion pairs. Several mechanisms may operate simultaneously, and species like $[Li(thf)_4]^+$ $[Li\{C(SiMe_3)(Ph)_2\}_2]^-$ have been isolated.[41] In this complex one Li^+ ion is sandwiched between two anions, the second Li^+ ion being solvated by THF molecules.

Table 7. Selected bond lengths [Å] for **6**.

Li(1)–N(1)	2.108(3)
Li(1)–N(2)	2.145(4)
Li(1)–N(3)	2.134(4)
Li(1)–N(4)	2.123(4)

Conclusions

Several α-substituted benzyllithium compounds have been synthesised and characterised by single-crystal X-ray diffraction. NMR spectroscopic data confirm that the PMDTA ligand provides rigid complexes and indicate that the solid-state structures may be retained in benzene solution. One of the complexes, [Li(phet)(tmpda)] (**2**), was found to crystallise as a conglomerate (α-**2**), and therefore appeared to be suitable for absolute asymmetric synthesis. However, when the crystals were treated with carbon dioxide, only racemic 2-phenylpropionic acid was isolated, although in high yield. One problem was the possible intervention of the racemic phase (β-**2**); another problem was that we could not determine the enantiomerical purity of the crystals. Crystals of [Li(phet)(tmpda)] are extremely air-sensitive and the low melting point infer restrictions on the handling of the crystals. In order to find a conglomerate which would enable absolute structure determination, similar complexes displaying a Si or S atom in α-position were prepared. Although no chiral crystals were found (other than α-**2**) it is likely that more α-substituted conglomerates will be identified in the future, since neutral ligands and α-substituents can be varied to a large extent.

Experimental Section

General: Experiments were performed under nitrogen atmosphere using Schlenk technique. Glass equipment was dried at 130 °C overnight. Toluene, ethylbenzene, THF, and diethyl ether were distilled from sodium/benzophenone shortly prior to use; hexane was distilled from sodium/benzophenone/tetraglyme. Commercial TMEDA (Aldrich), PMDTA (Aldrich), and TMPDA (Aldrich) were distilled from CaH_2 prior to use. Carbon dioxide (AGA) and *n*BuLi (2.5 M in hexane, Acros Organics) were used as received. Tributyl(1-phenylethyl)stannane,[44] phenyl 1-phenylethyl sulfide[40] and benzyltrimethylsilane[39] were prepared according to published procedures. NMR spectra were recorded using a Varian Unity 400 MHz spectrometer. HPLC analyses were carried out on a Varian system with a 9010 Solvent Delivery System and a 9065 Polychrom UV-DAD detector coupled with a PDR-Chiral Inc. Advanced Laser Polarimeter. Separation was achieved using a Daicel Chiracel OD column with a mobile phase consisting of hexane/2-propanol (95:5) with 0.1% trifluoroacetic acid at 0.5 mL min^{-1}. Commercial 2-phenylpropionic acid (Aldrich) was used as a standard.

[Li(phet)(pmdta)] (1): *n*BuLi (2.5 M in hexane, 1.0 mL, 2.5 mmol) was added to ethylbenzene (0.30 mL, 2.5 mmol) followed by dropwise addition of PMDTA (0.52 mL, 2.5 mmol). The mixture was kept at ambient temperature overnight whereupon crystals formed. The mixture was cooled to –80 °C for 24 h; the mother liquor was withdrawn, the crystals washed with hexane (2 × 0.5 mL) and dried in vacuo; yield 0.49 g (68%). ^1H NMR (400 MHz, C_6D_6): $\delta = 7.03$ (br. s, 1 H, *o*-CH), 6.83 (br. s, 1 H, *o*-CH), 6.22 (s, 2 H, *m*-CH), 5.92 (s, 1 H, *p*-CH), 2.38 (q, $J_{HH} = 5.7$ Hz, 1 H, CH-Li), 1.70–2.00 (m, 26 H, N-CH_3 + C-CH_3 + CH_2) ppm. ^{13}C NMR (125 MHz,

C_6D_6): *δ* = 157 (*ipso*-C), 130 (*m*-C), 115 (*o*-C), 111 (*o*-C), 103 (*p*-C), 58.0 (CH_2), 54.3 (CH_2), 46.0 [$N(CH_3)_2$], 45.4 (N-CH_3), 44.5 (C-Li), 16.6 (C-CH_3) ppm.

[Li(phet)(tmpda)] (2): *n*BuLi (2.5 M in hexane, 1.0 mL 2.5 mmol) was added dropwise to a solution of tributyl(1-phenylethyl)stannane (0.80 mL, 2.5 mmol) and TMPDA (0.40 mL, 2.5 mmol) in hexane (2.0 mL) at 0 °C. The solution was slowly warmed up and then kept at ambient temperature overnight, and subsequently cooled to –35 °C. Red crystals of α-2 or β-**2** started to grow after a few hours. The mother liquor was withdrawn, the crystals washed with hexane (2 × 1 mL) at –78 °C and dried in vacuo; yield 0.54 g (89 %). ^1H NMR (400 MHz, C_6D_6): *δ* = 6.85 (br. s, 2 H, *m*-CH), 6.09 (br. s, 1 H, *o*-CH), 5.94 (br. s, 1 H, *o*-CH), 5.78 (t, J_{HH} = 6.6 Hz, 1 H, *p*-CH), 2.58 (q, J_{HH} = 5.8 Hz, 1 H, CH-Li), 1.90 (d, J_{HH} = 5.9 Hz, 3 H, C-CH_3), 1.81 (m, 16 H, CH_2N, N-CH_3), 1.00 (m, 2 H, CH_2-CH_2-CH_2) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* = 153 (*ipso*-C), 131 (*m*-C), 110 (*o*-C), 103 (*p*-CH), 62.0 (N-CH_2), 48.4 (C-Li), 46.0 (N-CH_3), 23.3 (CH_2-CH_2-CH_2), 15.2 (C-CH_3) ppm.

Carbonation of α-2. Method 1: Crystals of α-**2** (0.60 g, 2.5 mmol) were isolated and washed with hexane (2 × 1 mL) at –78 °C in a Schlenk tube under nitrogen atmosphere. The tube was evacuated and filled with carbon dioxide. After 5 h, the tube was disconnected from the CO_2, allowed to return to ambient temperature and the reaction was quenched by the addition of NaOH (0.3 g) in H_2O (1 mL). The mixture was washed with diethyl ether (5 × 0.5 mL) and acidified by addition of 6 M HCl (3 mL). The mixture was extracted with diethyl ether (5 × 1 mL), the combined organic phases were dried with sodium sulfate and the solvents evaporated in vacuo; yield of 2-phenylpropionic acid: 0.26 g (70 %) ^1H NMR ($CDCl_3$): *δ* = 7.40–7.20 (m, 5 H, Ph), 3.74 (q, 1 H, CH), 1.52 (d, 3 H, CH_3) ppm.

Carbonation of α-2. Method 2: Crystals of α-**2** were isolated and washed with hexane (2 × 1 mL) at –78 °C. Hexane (1–3 mL) was added followed by an excess of dry ice (*c.* 1 g). After *c.* 3 h, the mixture was allowed to return to ambient temperature and the reaction was quenched by the addition of dilute hydrochloric acid (5 mL). The resulting slurry was extracted with hexane (4 × 5 mL) and the combined organic phases were dried with magnesium sulfate. The solvent was removed in vacuo.

[Li(tsmb)(tmpda)] (3): *n*BuLi (2.5 M in hexane, 1 mL, 2.5 mmol) and TMPDA (0.40 mL, 2.5 mmol) was added dropwise to benzyltrimethylsilane (0.50 mL, 2.5 mmol). The mixture was allowed to stand at ambient temperature for 5 h and was cooled to +4 °C, which afforded yellow crystals of **3**. The mother liquor was withdrawn, the crystals washed with hexane (3 × 0.5 mL) and dried in vacuo; yield 0.67 g (89 %). ^1H NMR (400 MHz, C_6D_6): *δ* = 7.00 (t, J_{HH} = 7.7 Hz, 2 H, *m*-CH), 6.66 (br. s, 2 H, *o*-CH), 6.31 (t, J_{HH} = 7.7 Hz, 1 H, *p*-CH), 1.60–1.76 (m, 17 H, N-CH_2, N-CH_3, CH-Li), 0.80 (apparent quintett, J_{HH} = 5.2 Hz, 2 H, CH_2-CH_2-CH_2), 0.45 (s, 9 H, Si-CH_3) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* = 157 (*ipso*-C), 130 (*m*-CH), 119 (*o*-CH), 110 (*p*-C), 61.8 (N-CH_2), 46.2 (N-CH_3), 42.8 (C-Li), 23.1 (CH_2-CH_2-CH_2), 3.41 (CH_3-Si) ppm.

[Li{C(CH$_3$)(Ph)(SPh)}(pmdta)] (4): *n*BuLi (2.5 M in hexane, 1.0 mL, 2.5 mmol) was added dropwise to a solution of phenyl 1-phenylethyl sulfide (0.51 mL, 2.5 mmol) and PMDTA (0.52 mL, 2.5 mmol) in diethyl ether (5 mL). After a few minutes orange-red crystals of **4** started to grow. The mixture was allowed to stand for 1 h. The crystals were washed with diethyl ether (4 × 1 mL) and dried in vacuo; yield 0.97 g (99 %). ^1H NMR (400 MHz, C_6D_6): *δ* = 7.48 (d, J_{HH} = 7.5 Hz, 2 H, Ph), 6.91–7.41 (m, 6 H, Ph), 6.86 (t, J_{HH} = 7.2 Hz, 1 H, Ph), 6.51 (t, J_{HH} = 7.1 Hz, 1 H, Ph), 2.52 (s, 3 H, C-CH_3), 2.11 (m, 2 H, N-CH_2), 2.06 (s, 3 H, N-CH_3), 1.44–1.84 (m, 20 H, $N(CH_3)_2$ + CH_2-CH_2) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* = 155 (Ph), 147 (Ph), 129.3 (Ph), 129.0 (Ph), 126 (Ph), 123 (Ph), 117 (Ph), 111 (Ph), 58.1 (N-CH_2), 54.5 (N-CH_2), 46.3 ($N(CH_3)_2$), 46.1 (N-CH_3), 38.9 (C-Li), 25.1 (C-CH_3) ppm.

Table 8. Crystal and refinement data for **1**–**6**.

Parameter	**1**	**α-2**	**β-2**	**3**	**4**	**5**	**6**
Empirical formula	$LiC_{17}H_{32}N_3$	$LiC_{15}H_{27}N_2$	$LiC_{15}H_{27}N_2$	$LiC_{17}H_{33}N_2Si$	$LiC_{23}H_{36}SN_3$	$LiC_{20}H_{29}SN_2$	$LiC_{26}H_{45}SN_4$
M	285.40	242.33	242.33	300.48	393.55	336.45	452.66
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic	monoclinic	orthorhombic
Space group	$P2_1/n$	$P2_1$	$P2_1/n$	$P2_1/c$	$Pc2_1n$	$P2_1/n$	$Pc2_1n$
a /Å	8.4887(14)	12.9922(17)	16.093(3)	13.051(2)	9.0435(15)	9.0920(15)	10.2741(17)
b /Å	14.884(2)	18.456(2)	11.7374(16)	9.6627(15)	12.993(2)	14.859(2)	16.372(2)
c /Å	14.588(2)	13.1855(17)	18.086(3)	15.928(3)	19.848(3)	14.933(3)	16.820(2)
α /°	90	90	90	90	90	90	90
β /°	96.039(7)	96.163(5)	113.467(5)	101.091(6)	90	101.148(5)	90
γ /°	90	90	90	90	90	90	90
V /Å^3	1832.9(5)	3143.4(7)	3133.7(9)	1971.1(6)	2332.3(6)	1979.4(6)	2829.3(7)
Z	4	8	8	4	4	4	4
D_c /g cm^{-3}	1.034	1.024	1.027	1.013	1.121	1.129	1.063
μ(Mo-K_α) /mm^{-1}	0.060	0.059	0.059	0.115	0.151	0.166	0.133
T /K	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
Crystal size /mm	0.3 × 0.3 × 0.3	0.4 × 0.4 × 0.3	0.3 × 0.3 × 0.3	0.3 × 0.3 × 0.1	0.3 × 0.2 × 0.2	0.4 × 0.4 × 0.1	0.3 × 0.1 × 0.1
θ Range /°	1.96 to 25.00	1.92 to 25.00	1.44 to 25.00	1.59 to 25.00	2.05 to 25.00	2.78 to 25.00	2.32 to 25.00
Reflections collected	10945	19612	19181	12082	14204	11953	16983
Unique reflections, R_{int}	3112 (0.0308)	5564 (0.0257)	5430 (0.0521)	3448 (0.0361)	4030 (0.0549)	3349 (0.0218)	4928 (0.0508)
Number of parameters	200	685	541	322	259	333	328
Flack *x* parameter	–	–	–	–	–0.06(6)	–	–0.01(7)
GOF on F^2	1.033	1.103	1.198	1.152	1.060	1.049	1.085
Final $R_1(F)$[a] $[I > 2\sigma(I)]/wR_2(F^2)$[b]	0.0362/0.0949	0.0426/0.0969	0.0661/0.1222	0.0480/0.0919	0.0351/0.0754	0.0285/0.0708	0.0423/0.0886
R_1[a]/$wR_2(F^2)$[b] (all data)	0.0410/ 0.0974	0.0448/0.0981	0.0750/0.1259	0.0538/0.0944	0.0379/0.0766	0.0329/0.0732	0.0462/0.0902

[a] $R_1(F) = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$. [b] $wR_2(F^2) = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma\,[w(F_o^2)^2]\}1/2$.

[Li{C(CH_3)(Ph)(SPh)}(tmeda)] (5): *n*BuLi (2.5 M in hexane, 1 mL, 2.5 mmol) was added dropwise to phenyl 1-phenylethyl sulfide (0.51 mL, 2.5 mmol). TMEDA (0.38 mL, 2.5 mmol) was added dropwise, resulting in a red oil. The oil was dissolved in diethyl ether (7 mL). Cooling to –35 °C afforded orange crystals of **5** overnight. The mother liquor was withdrawn, the crystals washed with diethyl ether (2 × 0.5 mL) and dried in vacuo; yield 0.71 g (84%). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.39 (d, J_{HH} = 7.7 Hz, 2 H, Ph), 6.40–7.25 (br. s, 4 H, Ph), 7.05 (t, J_{HH} = 7.5 Hz, 2 H, Ph), 6.86 (t, J_{HH} = 7.2 Hz, 1 H, Ph), 6.22 (t, J_{HH} = 7.3 Hz, 1 H, Ph), 2.50 (s, 3 H, C-CH_3), 1.66 (s, 12 H, N-CH_3), 1.48 (s, 4 H, CH_2-CH_2) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 152 (Ph), 146 (Ph), 131 (Ph), 129 (Ph), 128 (Ph), 126 (Ph), 123 (Ph), 114 (Ph), 109 (Ph), 56.3 (CH_2-CH_2), 45.0 (N-CH_3), 41.9 (C-Li), 24.0 (CH_3-C) ppm.

[Li(tmeda)$_2$][C(CH_3)(Ph)(SPh)] (6): *n*BuLi (2.5 M in hexane, 0.5 mL, 1.2 mmol) was added dropwise to phenyl 1-phenylethyl sulfide. TMEDA (0.2 mL, 1.2 mmol) was added dropwise, resulting in a red oil. The oil solidified within a few minutes, and the solids where heated in diethyl ether (10 mL) to reflux. A large portion of the solids remained undissolved. The mixture was placed at +4 °C. Crystals of **6** had grown from the solid residue overnight.

X-ray Crystallography: Crystals of **1**–**6** were selected using microscope at low-temperature.[45] Data were recorded at 100 K using a Rigaku R-AXIS IIc area detector with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) from a Rigaku RU-H3R rotating anode, operating at 50 kV and 90 mA. 90 oscillation photos with a rotation angle of 2° were collected. Data were processed using the CrystalClear software package,[46] and an empirical absorption correction was applied using the REQAB program (**3**–**6**). The structures were solved using the program SIR-92[47] and refined using full-matrix least-squares calculations on F^2 using the SHELXL-97 program.[48] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included in calculated positions and refined using a riding model (**1**, α-**2**, **4**, and **6**) or located from a difference Fourier map and refined without constraints (β-**2**, **3** and **5**). Structures were drawn using ORTEP3[49] for Windows and Pluton.[50] SIR-92, SHELXL-97, Pluton and ORTEP3 were enclosed in the WinGX software package.[51] Crystal and refinement data are given in Table 8.

CCDC-745839 (for **1**), -745840 (for α-**2**), -745841 (for β-**2**), -745842 (for **3**), -745843 (for **4**), -745844 (for **5**), and -745845 (for **6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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