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A lithiomethyl trimethylammonium reagent as a methylene donor†

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Straightforward deprotonation of soluble tetramethylammonium salts with alkyl lithium reagents gives lithiomethyl trimethylammonium reagents. Coordination of the Li cation is crucial to the stability of these 'N–C ylides'. These reagents were used to prepare epoxides, aziridines and allylic alcohols.

Ever since the pioneering work of Nobel laureate George Wittig in the 1960s, ylides have become versatile reagents in organic synthesis.¹ Although N–C ylides² were the first to be discovered, P–C ylides³ are the most widely used ylides. The lack of application of N–C ylides is likely due to the lower stability of those reagents, compared to their P–C analogues.^{4,5} In 1947 Wittig and coworkers reported^{6a} the synthesis of 'trimethylammonium methyllide' (**3**)⁷ by the deprotonation of tetramethylammonium bromide (**1**) with 1 equiv. of PhLi for 2 days (Scheme 1a).

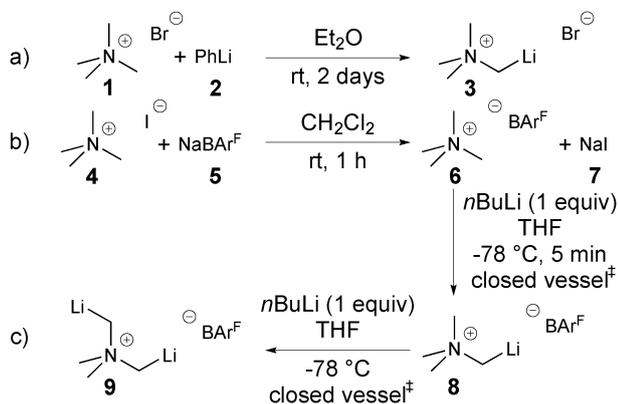
The structure of **3** had so far never been established,^{6c,8} and the long deprotonation time complicated application of **3**.

Our interest in N–C ylides as potential methylene donors prompted us to gain further insight into the stability of these reagents in solution. Here, we report the synthesis of lithio-methyl trimethylammonium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAR^F) (**8**, Scheme 1b), a 'N–C ylide' that is reasonably stable and soluble in common organic solvents. Furthermore, we present an NMR study to explore the structure of this lithium-coordinated ylide **8** and show, both by density functional theory (DFT) calculations and experimentally, that the Li cation is essential for the stability of this reagent. Finally, we illustrate that soluble lithiomethyl trimethylammonium reagents can be used as methylene donors in organic synthesis, providing an alternative to S–C ylides.

Tetramethylammonium salts are notoriously hard to solubilise in common organic solvents.⁶ We reasoned that the previously reported^{6a–c,e} long deprotonation time of tetramethylammonium bromide (**1**) is not due to the inherent low acidity of the salt (see ESI†), but rather due to its poor solubility.

Solubility of cations in low-polarity solvents can be enhanced by exchanging the counterion for a more hydrophobic one. We have prepared⁹ anhydrous NMe₄ BAR^F (Scheme 1b, **6**), which is soluble in anhydrous Et₂O and THF. Deprotonation of **6** in THF-D₈ at –78 °C gave the corresponding 'N–C ylide' **8** within 5 minutes. ¹H, ¹H,⁶Li HMBC, and ¹H,¹⁵N HMBC NMR experiments at low temperature confirmed the structure of the lithio-methyl trimethylammonium BAR^F reagent **8** (Fig. 1; also see ESI†). Further deprotonation of **8** gave dilithiomethyl dimethylammonium BAR^F **9** (Scheme 1c; see ESI†). At low temperature, **9** slowly deprotonates the BAR^F anion, reforming **8** (see ESI†). In subsequent NMR experiments, lithiomethyl trimethylammonium BAR^F species **8** proved to be quite stable in a closed vessel‡ up to ca. 0 °C (see ESI†). The stability of this 'N–C ylide' is remarkable, especially since no electron withdrawing or aromatic groups are present to stabilise the reagent by charge delocalisation.

P–C ylides, including trimethylphosphonium methyllide,^{6b,10} can be isolated at room temperature after deprotonation of



Scheme 1 Synthesis of lithium-coordinated N–C ylides. BAR^F: tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

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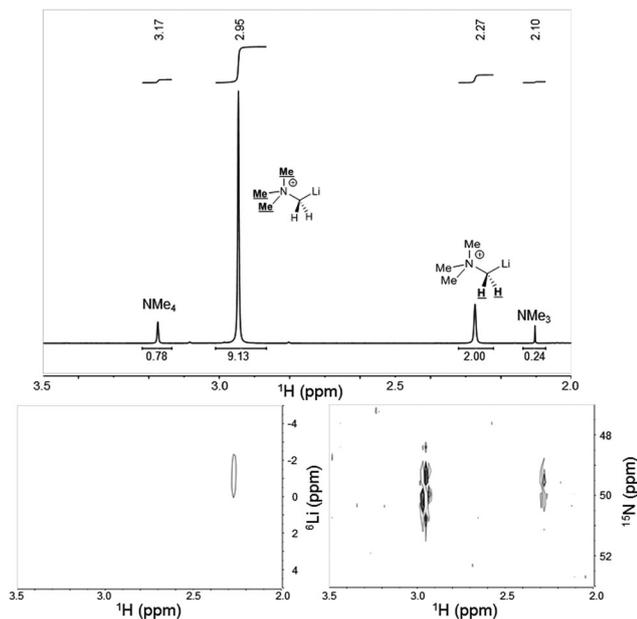


Fig. 1 NMR spectra of the lithiomethyl trimethylammonium BARF^{F} species **8**.

their corresponding phosphonium salts,^{10b} indicating that the Li cation is not essential for the stability of P–C ylides. To explore whether or not the cation has a more profound influence on the stability of N–C ylides, we studied the electronic structure of several N–C and P–C ylides and Li-coordinated analogues using DFT calculations. We selected the M06 functional for its good performance for organometallic chemistry,¹¹ noncovalent interactions,¹¹ and organolithium reagents.¹²

First, we studied the thermodynamics of the isodesmic reaction displayed in Table 1 both *in vacuo* and using a solvent model and microsolvation^{12,13} in Gaussian 09.¹⁴ The results indicate that the Li cation stabilises the N–C ylide by 8.1 kcal mol^{−1} more than the P–C ylide *in vacuo*, and by 3.6 kcal mol^{−1} more in solution.

Furthermore, we performed an Extended Transition State (ETS) bond analysis¹⁵ of the bond between the N or P atom and the (lithiated) methylene with ADF2010¹⁶ at the BP86/TZP level (see ESI†). For this analysis we divided the structures into a NMe_3 or PMe_3 fragment and either a singlet carbene (CH_2) or a carbocation (CH_2Li^+). The individual fragments are altered into the structures they have in the total molecule, brought together, and allowed to mix their electron densities. These steps afford the preparation energy, the Pauli repulsion and electrostatic attraction,

Table 1 Stabilisation of ylides by a Li cation

Environment	Reaction energy (kcal mol ^{−1})
<i>In vacuo</i>	−8.1 ^a
Solution	−3.6 ^b

^a M06/aug-cc-pVTZ zero-point corrected energies. ^b M06/aug-cc-pVTZ/SMD(THF)//aug-cc-pVDZ/SMD(THF) Gibbs-corrected energies (298.15 K) with two explicit THF molecules (see ESI for other solvation treatments).

and the orbital interactions that together constitute the net bonding between the two fragments.¹⁵ With this strategy we have also studied the Li-free ylides using the atomic coordinates of the lithium-coordinated species. The bond energy decompositions (Table 2) show that for NMe_3CH_2 (**10**) and $\text{NMe}_3\text{CH}_2\text{Li}^+$ (**12**) the orbital interactions and steric repulsion (*i.e.* total steric interactions) remain relatively constant whether or not there is a Li cation present (compare bold entries in columns 2 and 3). In contrast, for $\text{PMe}_3\text{CH}_2\text{Li}^+$ (**11**) there are less stabilising orbital interactions as compared to PMe_3CH_2 (**13**), while the ylide **13** suffers from a much larger destabilisation by steric interactions than lithium-coordinated ylide **11** (compare bold entries in columns 5 and 6).

These effects are also observable when the optimised geometries of **10–13** are compared (Fig. 2). In NMe_3CH_2 (**10**) the methylene moiety adopts a tetrahedral geometry, while in PMe_3CH_2 (**13**) the geometry of the methylene is closer to trigonal planar. In contrast, in both $\text{NMe}_3\text{CH}_2\text{Li}^+$ (**12**) and $\text{PMe}_3\text{CH}_2\text{Li}^+$ (**11**) the lithiomethyl moiety adopts a tetrahedral geometry.¹⁷ Furthermore, in PMe_3CH_2 (**13**) the P–methylene bond is shortened and the P–Me(1) bond is elongated compared to the P–Me bonds in tetramethylphosphonium (**15**). In $\text{PMe}_3\text{CH}_2\text{Li}^+$ (**11**) these bonds are affected to a smaller degree. Conversely, in NMe_3CH_2 (**10**) as well as $\text{NMe}_3\text{CH}_2\text{Li}^+$ (**12**) the N–(lithium-coordinated) methylene bonds and the N–Me(1) bond are both slightly elongated compared to the N–Me bonds in tetramethylammonium (**14**).

To summarise, removal of the Li cation from $\text{NMe}_3\text{CH}_2\text{Li}^+$ (**12**) will give a localised high electron density at the methylene of NMe_3CH_2 (**10**). In contrast, when the Li cation is removed from $\text{PMe}_3\text{CH}_2\text{Li}^+$ (**11**) the resulting electron density around the methylene will be partly dispersed over the PMe_3CH_2 molecule (**13**). This redistribution of electron density is possible due to^{5a,18} (1) enhanced negative p,σ^* -hyperconjugation which can be deduced from the higher electron redistribution into the σ^* orbital region of the PMe_3 fragment in PMe_3CH_2 compared to this region in the PMe_3 or NMe_3 fragments of the other molecules (see Table S1, ESI†); (2) enhanced electron dispersion towards P due to the lower polarisation of P–C bonds as compared to N–C bonds; and (3) enhanced overlap of the methylene orbitals with the diffuse 3p-P orbitals. Consequently, lithium coordination is more beneficial for the stabilisation of N–C ylides than for P–C ylides.

The importance of the Li cation for the stability of lithio-methyl trimethylammonium BARF^{F} reagent **8** is further confirmed by two NMR experiments (see ESI†). In THF-D_8 at -30°C reagent **8** is quite stable. Opening of the NMR tube under an Ar counterflow at low temperature and addition of THF-D_8 causes partial degradation of **8**. However, when the NMR tube is closed again and cooled to -30°C , **8** is quite stable. When instead a THF-D_8 solution of the strongly Li-coordinating reagent 12-crown-4¹⁹ is added at low temperature a larger portion of **8** decays, compared to the previous experiment. Furthermore, after closure of the NMR tube, **8** continues to decay at -30°C , indicating that the Li cation is essential for the stability of **8**.

While an analogue of **6**, tetramethylammonium triflate (**16**, Scheme 2), is sparingly soluble in anhydrous THF, the corresponding

Table 2 ETS analysis of P–C and N–C ylides and lithium-coordinated analogues^a

Parameter ^b	NMe ₃ –CH ₂ (10)	NMe ₃ –CH ₂ ^c	NMe ₃ –CH ₂ Li ⁺ (12)	PMe ₃ –CH ₂ (13)	PMe ₃ –CH ₂ ^c	PMe ₃ –CH ₂ Li ⁺ (11)
Pauli repulsion	327.12	325.06	231.72	614.99	387.61	283.51
Electrostatic attraction	–172.51	–168.50	–139.81	–310.57	–199.38	–154.88
Total steric interactions	154.61	156.55	91.91	304.41	188.22	128.63
Orbital interaction	–210.41	–210.98	–199.39	–398.28	–277.62	–268.41
Total interaction energy	–55.79	–54.43	–107.48	–93.87	–89.40	–139.77
Deformation energy	3.01		22.67	5.78		29.19
Net bonding energy	–52.77		–84.81	–88.08		–110.58

^a BP86/TZP, energies in kcal mol^{–1}. ^b See ref. 15. ^c Atomic coordinates of XMe₃CH₂Li⁺ but omitting the Li cation.

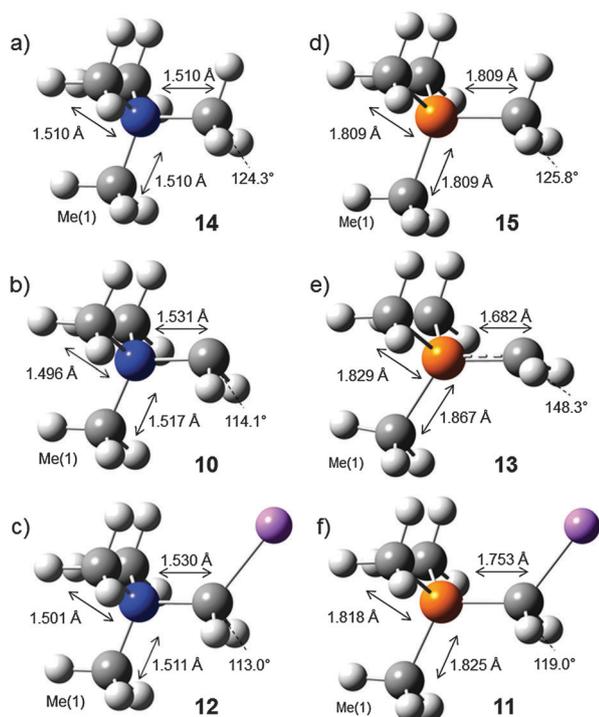
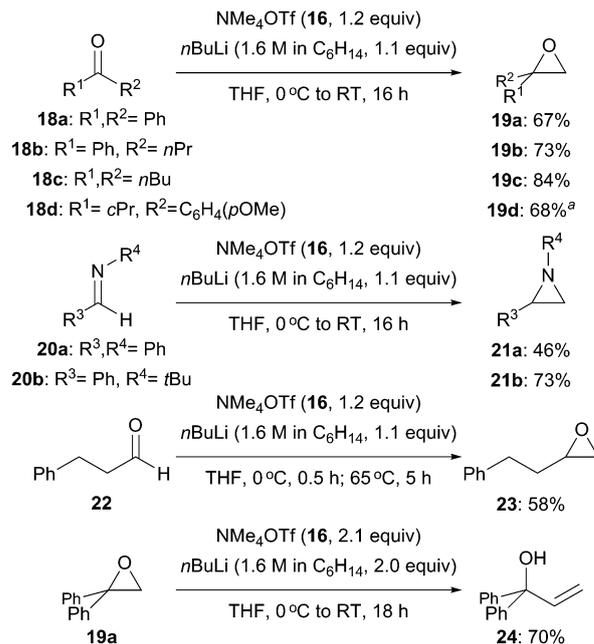


Fig. 2 Selected bond lengths and angles of (a) NMe₄⁺ (**14**); (b) NMe₃CH₂ (**10**); (c) NMe₃CH₂Li⁺ (**12**); (d) PMe₄⁺ (**15**); (e) PMe₃CH₂ (**13**); (f) PMe₃CH₂Li⁺ (**11**).

'ylide' lithiomethyl trimethylammonium triflate (**17**) is fully soluble. 'Ylide' **17** is thus a convenient reagent for the methylenation of ketones,²⁰ imines,²¹ aldehydes²⁰ and epoxides.²² Methylenation of bisaryl- (**18a**), aryl,alkyl- (**18b**) and bisalkyl-substituted (**18c**) ketones gives the corresponding oxiranes (**19a–c**) in fair to good yields *via* consecutive 1,2-addition of reagent **17** to ketone **18** and ring-closure with concomitant elimination of NMe₃. The sensitive cyclopropyl-substituted ketone **18d** is converted to the corresponding oxirane **19d** in fair yield as well. Furthermore, using **16** aziridines **21a** and **21b** can be formed in acceptable and good yield, respectively, by methylenation of the corresponding imines (**20a,b**). However, methylenation of the less electron-rich aldehyde **22** to give oxirane **23** in fair yield required heating to force elimination^{5c} of NMe₃. Finally, epoxide **19a** could be methylenated to give the allylic alcohol **24** in fair yield. The displayed reactivity of the lithiomethyl trimethylammonium reagents is identical to the reactivity of S–C ylides in the Corey–Chaykovsky reaction.^{20–22} The somewhat lower yields using our method are due to the extensive purification and the small scale; *i.e.* except for traces of remaining starting material, allylic alcohol



Scheme 2 Methylenation of ketones, imines, aldehydes and epoxides.^{b,c} ^aCrude yield. ^bFor full experimental details see ESI.† ^cIsolated yields after column chromatography.

products (*e.g.* **24**) and 'ylide' addition products (generated before NMe₃ elimination), no side products have been observed.

In conclusion, we have prepared lithiomethyl trimethylammonium reagents. The Li cation plays a major role in the stabilisation of these 'N–C ylides', and this effect has previously been overlooked in theoretical discussions⁵ on the stability of ylides. Finally, the lithiomethyl trimethylammonium reagents can be used as alternative for S–C ylides,^{20–22} when it is desired to avoid the use of sulfur-containing reagents.

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Notes and references

‡ The lithiomethyl trimethylammonium reagent is only stable in closed vessels. When the vessel is open to the Ar line the reagent degrades even at

low temperature. This degradation is presumably due to rapid formation of ethylene, catalysed by trace metals (ppt-level). The presence of NMe₃ might inhibit this degradation.

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