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A Lithiomethyl Trimethylammonium Reagent as Methylene Donor

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Straightforward deprotonation of soluble tetramethylammonium salts with alkyllithium 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.
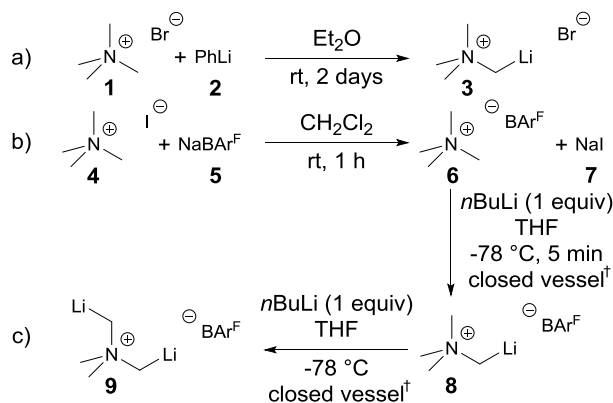
Ever since the pioneering work of Nobel laureate George Wittig in the 1960s, ylides have become versatile reagents in organic synthesis.[1] Although N–C ylides[2] were the first to be discovered, P–C ylides[3] are the most widely used ylides. The lack of application of N–C ylides is likely due to the lower stability of those reagents, compared to their P–C analogues.[4,5] In 1947 Wittig and coworkers reported[6a] the synthesis of 'trimethylammonium methylide' (**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 lithiomethyl 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 SI), 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 prepared[9] anhydrous NMe$_4$ BAr^F (Scheme 1b, **6**), which is soluble in anhydrous Et$_2$O and THF. Deprotonation of **6** in THF-D$_8$ at −78 °C gave the corresponding 'N–C ylide' **8** within 5 minutes. ^{1}H, ^{1}H,^{6}Li HMBC, and ^{1}H,^{15}N HMBC NMR experiments at low temperature confirmed the structure of the lithiomethyl trimethylammonium BAr^F reagent **8** (Figure 1; also see SI). Further deprotonation of **8** gave dilithiomethyl dimethylammonium BAr^F **9** (Scheme 1c; see SI). At low temperature, **9** slowly deprotonates the BAr^F anion, reforming **8** (see SI). 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 SI). The stability of this 'N–C ylide' is remarkable, especially since no electron withdrawing or aromatic

Scheme 1. Synthesis of lithium-coordinated N–C ylides. BAr^F: tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.
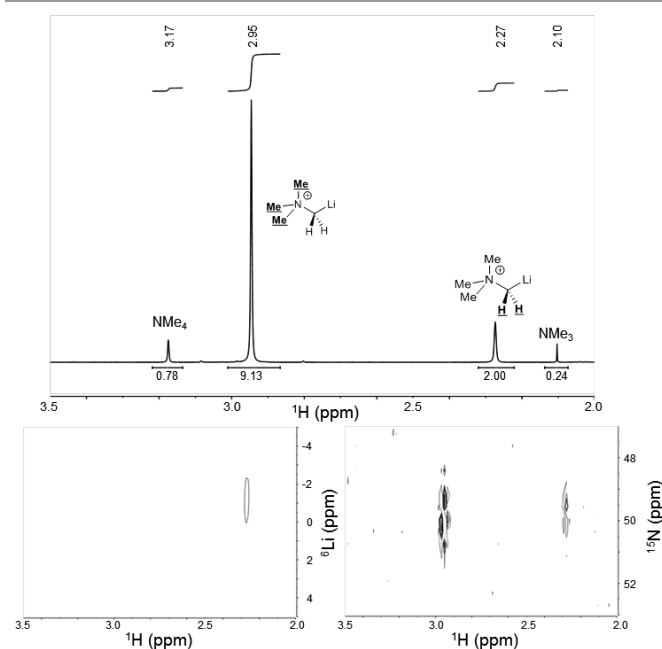
Figure 1. NMR spectra of the lithiomethyl trimethylammonium BAr^F species **8**.

Table 1. Stabilisation of ylides by a Li cation

Environment	Reaction energy (kcal mol^{-1})
in vacuo	-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 SI for other solvation treatments).

densities. These steps afford the preparation energy, the Pauli repulsion and electrostatic attraction, 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$_3$CH$_2$ (**10**) and NMe$_3$CH$_2$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 PMe$_3$CH$_2$Li$^+$ (**11**) there are less stabilising orbital interactions as compared to PMe$_3$CH$_2$ (**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 (Figure 2). In NMe$_3$CH$_2$ (**10**) the methylide moiety adopts a tetrahedral geometry, while in PMe$_3$CH$_2$ (**13**) the geometry of the methylide is closer to trigonal planar. In contrast, in both NMe$_3$CH$_2$Li$^+$ (**12**) and PMe$_3$CH$_2$Li$^+$ (**11**) the lithiomethyl moiety adopts a tetrahedral geometry.[17] Furthermore, in PMe$_3$CH$_2$ (**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 PMe$_3$CH$_2$Li$^+$ (**11**) these bonds are affected to a smaller degree. Conversely, in NMe$_3$CH$_2$ (**10**) as well as NMe$_3$CH$_2$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 NMe$_3$CH$_2$Li$^+$ (**12**) will give a localised high electron density at the methylene of NMe$_3$CH$_2$ (**10**). In contrast, when the Li cation is removed from PMe$_3$CH$_2$Li$^+$ (**11**) the resulting electron density around the methylene will be partly dispersed over the PMe$_3$CH$_2$ 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

groups are present to stabilise the reagent by charge delocalisation. P–C ylides, including trimethylphosphonium methylide,[6b,10] can be isolated at room temperature after deprotonation of their corresponding phosphonium salts,[10c] 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 Gaussian09.[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 analysis[15] of the bond between the N or P atom and the (lithiated) methylene with ADF2010[16] at the BP86/TZP level (see SI). 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$_2$Li$^+$). The individual fragments are altered into the structures they have in the total molecule, brought together, and allowed to mix their electron

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 XMe$_3$CH$_2$Li$^+$ but omitting the Li cation.

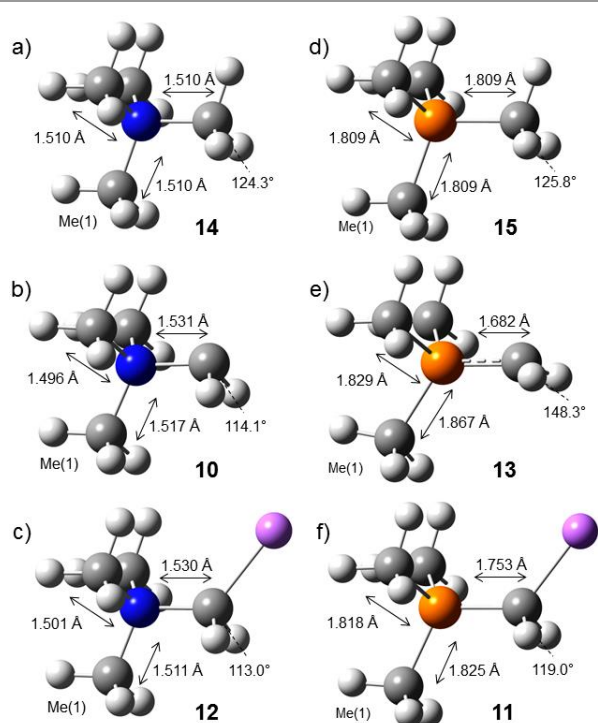*Figure 2.* Selected bond lengths and angles of a) NMe_4^+ (**14**); b) NMe_3CH_2 (**10**); c) $NMe_3CH_2Li^+$ (**12**); d) PMe_4^+ (**15**); e) PMe_3CH_2 (**13**); f) $PMe_3CH_2Li^+$ (**11**).

PMe_3CH_2 compared to this region in the PMe_3 or NMe_3 fragments of the other molecules (see Table S1); 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 lithiomethyl trimethylammonium BAr^F reagent **8** is further confirmed by two NMR experiments (see SI). 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 strong Li-coordinating reagent 12-crown-4[19] 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 'ylide' lithiomethyl trimethylammonium triflate (**17**) is fully soluble. 'Ylide' **17** is thus a convenient reagent for the methylenation of ketones,[20] imines,[21] aldehydes[20] 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 NMe_3. 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 NMe_3. 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 products (*e.g.* **24**) and 'ylide' addition products (generated before NMe_3 elimination), no side products have been observed.
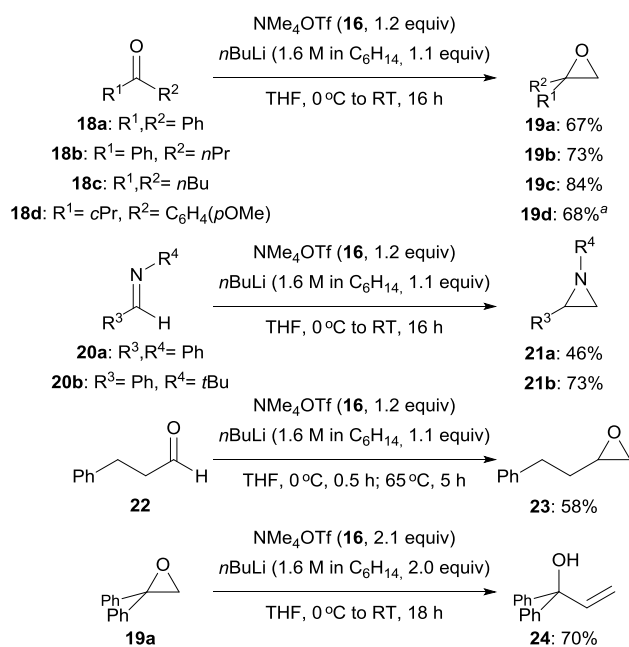
Scheme 2. Methylenation of ketones, imines, aldehydes and epoxides.[b,c] [a] Crude yield. [b] For full experimental details see SI. [c] Isolated yields after column chromatography.

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 discussions[5] 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.

Notes and references

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1   a) G. Wittig, *Science*, 1980, **210**, 600; b) R. W. Hoffmann, *Angew. Chem. Int. Ed.*, 2001, **40**, 1411.

2   For selected reviews see: a) *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, ed. J. S. Clark, Oxford University Press, Oxford, 2002; b) G. Wittig, *J. Organomet. Chem.*, 1975, **100**, 279; c) E. P. Urriolabeitia, *Top. Organomet. Chem.*, 2010, **30**, 15; d) M. Nyerges, J. Tóth and P. W. Groundwater, *Synlett*, 2008, 1269; e) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.*, 2006, 2873.

3   *Phosphorus Ylides: Chemistry and Application in Organic Synthesis*, ed. O. I. Kolodiazhnyi, WILEY-VCH, Weinheim, 1999.

4   For common rearrangements of N-C ylides, see: a) T. S. Stevens, E. M. Creighton, A. B. Gordon and M. MacNicol, *J. Chem. Soc.*, 1928, 3193; b) J. A. Vanecko, H. Wan and F. G. West, *Tetrahedron*, 2006, **62**, 1043; c) M. Sommelet, *C. R. Hebd. Seances Acad. Sci.*, 1937, **205**, 56; d) J. Clayden, M. Donnard, J. Lefranc and D. J. Tetlow, *Chem. Commun.*, 2011, **47**, 4624.

5   For theoretical discussion, see: a) J. A. Dobado, H. Martínez-García, J. M. Molina Molina and M. R. Sundburg, *J. Am. Chem. Soc.*, 2000, **122**, 1144; b) I. A. Koppel, R. Schwesinger, T. Breuer, P. Burk, K. Herodes, I. Koppel, I. Leito and M. Mishima, *J. Phys. Chem. A*, 2001, **105**, 9575; c) V. K. Aggarwal, J. N. Harvey and R. Robiette, *Angew. Chem. Int. Ed.*, 2005, **44**, 5468; d) M. J. Calhorda, A. Krapp and G. Frenking, *J. Phys. Chem. A*, 2007, **111**, 2859; b) Y. Fu, H.-J. Wang, S.-S. Chong, Q.-X Guo and L. Liu, *J. Org. Chem.*, 2009, **74**, 810.

6   a) G. Wittig and M.-H. Wetterling, *Justus Liebigs Ann. Chem.*, 1947, **557**, 193; b) G. Wittig and M. Rieber, *Justus Liebigs Ann. Chem.*, 1949, **562**, 177; c) G. Wittig and R. Polster, *Justus Liebigs Ann. Chem.*, 1956, **599**, 1; d) V. Franzen and G. Wittig, *Angew. Chem.*, 1960, **72**, 417; e) F. Weygand and H. Daniel, *Chem. Ber.*, 1961, **94**, 3147; f) G. Wittig and D. Krauss, *Justus Liebigs Ann. Chem.*, 1964, **97**, 34; g) F. Weygand, H. Daniel and J. Paetsch, *Chem. Ber.*, 1964, **97**, 1217; h) H. Daniel and J. Paetsch, *Chem. Ber.*, 1965, **98**, 1915; i) H.-J. Cristau, F. Plénat and S. Bayssade, *J. Organomet. Chem.*, 1999, **592**, 29.

7   For gas-phase synthesis of lithium trimethyl ammonium methylide, see: R. A. J. O'Hair, T. Waters and B. Cao, *Angew. Chem. Int. Ed.*, 2007, **46**, 7048.

8   H. Daniel and J. Paetsch, *Chem. Ber.*, 1968, **101**, 1445.

9   a) K. Fujiki, M. Kashiwagi, H. Miyamoto, A. Sonoda, J. Ichikawa, H. Kobayashi and T. Sonoda, *J. Fluorine Chem.*, 1992, **57**, 307; b) P. N. Bartlett, D. C. Cook, M. W. George, J. Ke, W. Levason, G. Reid, W. Su and W. Zhang, *Phys. Chem. Chem. Phys.*, 2010, **12**, 492.

10 a) H. Schmidbaur and W. Tronich, *Angew. Chem. Int. Ed.*, 1967, **6**, 448; b) R. Köster, D. Simić and M. A. Grassberger, *Liebigs Ann. Chem.*, 1970, **739**, 211.

11 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215.

12 B. Ramachandran, P. Kharidehal, L. M. Pratt, S. Voit, F. N. Okeke and M. Ewan, *J. Phys. Chem. A*, 2010, **114**, 8423.

13 L. M. Pratt, D. G. Truhlar, C. J. Cramer, S. R. Kass, J. D. Thompson and J. D. Xidos, *J. Org. Chem.*, 2007, **72**, 2962.

14 Gaussian 09, Revision A.1, M. J. Frisch et al., see SI.

15 a) T. Ziegler and A. Rauk, *Inorg. Chem.*, 1979, **18**, 1558; b) T. Ziegler and A. Rauk, *Inorg. Chem.*, 1979, **18**, 1755; c) F. M. Bickelhaupt and E. J. Baerends, in *Rev. Comput. Chem.*, ed. K. B. Lipkowitz and D. B. Boyd, Wiley, New York, 2000, vol. 15, pp. 1.

16 a) ADF2010, SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, http://www.scm.com; b) C. Fonseca Guerra, J. G. Snijders, G. te Velde and E. J. Baerends, *Theor. Chem. Acc.*, 1998, **99**, 391; c) G. te Velde, F. M. Bickelhaupt, S. J. A. van Gisbergen, C. Fonseca Guerra, E. J. Baerends, J. G. Snijders and T. Ziegler, *J. Comput. Chem.*, 2001, **22**, 931.

17 Similar structural differences have been seen before for methylide *vs.* lithiomethyl groups in S–C and O–C ylides: K. B. Wiberg and H. Castejon, *J. Am. Chem. Soc.*, 1994, **116**, 10489.

18 T. Leyssens and D. Peeters, *J. Org. Chem.*, 2008, **73**, 2725.

19 F. A. L. Anet, J. Krane, J. Dale, K. Daasvatn and P. O. Kristiansen, *Acta Chem. Scand.* 1973, **27**, 3395.

20 a) A. W. Johnson and R. B. LaCount, *J. Am. Chem. Soc.*, 1961, **83**, 417; b) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 867; c) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 3782; d) V. Franzen and H.-E. Driesen, *Chem. Ber.* 1963, **96**, 1881.

21 C. R. Johnson, M. Haake and C. W. Schroeck, *J. Am. Chem. Soc.*, 1970, **92**, 6594.

22 L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin and J. R. Falck, *Tetrahedron Lett.*, 1994, **35**, 5449.

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