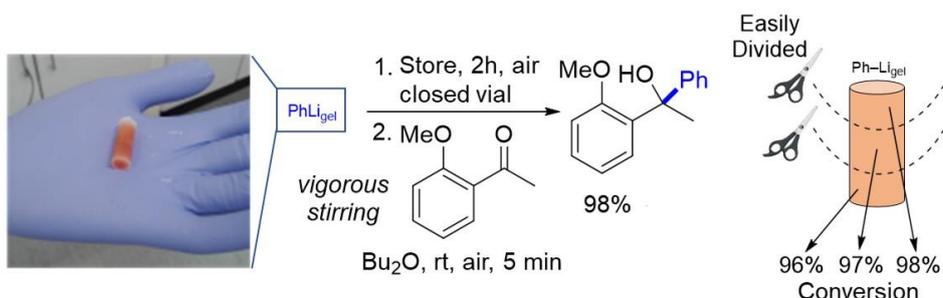


Organolithium Gels – Simple Easily Divided Delivery Vehicles for Highly Reactive Species

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Graphical Abstract



Organolithium reagents are a vital tool in modern organic chemistry allowing the synthesis of new carbon-carbon bonds. However, due to the high reactivity of organolithiums, the use of low temperatures, inert atmospheres and strictly dried solvents are usually necessary. Here, we report a new encapsulating method for the stabilisation of the sensitive organolithium reagents, PhLi and BuLi (*n*-BuLi), within a low-cost hexatriacontane (C₃₆H₇₄) organogel. The use of this technology is showcased in nucleophilic addition reactions under ambient conditions, low-temperature bromine-lithium exchange and CH functionalisation reactions. The gel significantly enhances the stability of these organolithiums, allows simple handling, delivery and storage, and enables reproducible reagent portioning. The use of gels as easily divided delivery vehicles for hazardous organometallic reagents has the potential to revolutionise this area of synthetic chemistry, making these powerful reactions safer and more accessible to non-specialist researchers, enabling the more widespread use of these common synthetic methods.

A wide range of reactions in synthetic organic chemistry utilise hazardous reagents, many of which are unstable or pyrophoric in water or air and require handling under inert conditions. Organolithium reagents constitute one of the most important classes of such reagents, and are widely used for the construction of carbon-carbon bonds.^{1,2} Most notably, they are industrially applied in the synthesis of a range of pharmaceuticals,^{3,4} as well as in the production of elastomer polymers.⁵ There has been significant development of these simple but reactive systems in asymmetric synthesis,^{2,3,6,7,8} which has added significantly to their synthetic value. However, it remains necessary to store and use these reagents under inert conditions – there are problems associated with reagent decomposition on extended storage, and reactions must be set up under rigorously inert conditions.^{9,10} These issues introduce additional costs and safety hazards into the use of organolithium chemistry in an industrial setting, and also limit the extent to which non-specialist researchers choose to make use of these powerful methods. A simple and effective way of storing organolithiums for extended periods, and dosing reactions with them on demand, would be highly desirable – indeed, there is considerable interest in general in innovating the chemistry laboratory bench to empower the next generation of synthetic chemists.¹¹

Consideration has previously been given to the stabilisation of other reactive species. In this context, one of the most significant contributions was described by Buchwald and co-workers who produced

paraffin capsules in which they mechanically removed the core, loaded the capsule with air- and moisture-sensitive palladium (pre-)catalysts and metal salts and then sealed them again.¹² The capsules could then be removed from the glove box, safely handled in ambient conditions, and subsequently used to dose the reagents into a range of cross-coupling reactions (Figure 1A). Other researchers have applied this general approach to a variety of reactions¹³⁻¹⁶ including potassium hydride.¹⁷ Paraffin reagent capsules have also been reported to have the benefit of protecting other species in multi-step reactions from processes such as catalyst poisoning and undesired side reactions, making product purification easier.¹⁸ In related work, but with a focus on toxic and malodorous reagents, Richert and co-workers reported a crystalline coating for reagents based on tetrakis(dimethoxyphenyl)adamantane.¹⁹ Xu and co-workers used a tableting approach based on mixing poly(tetrafluoroethylene) and cross-linked poly(styrene) with solid reagents, and then coating them with the same polymer mix to enhance stability.²⁰ Braje, Jolit and co-workers very recently made use of hydroxypropyl methylcellulose capsules of the type used for drug delivery to stabilise and simultaneously deliver catalyst, ligand and base into cross-coupling reactions.²¹ With specific regard to organolithium reagents, the Hevia group has reported that deep eutectic solvents (DESs) can be used for the delivery of organolithiums into a range of reactions, and play a role in minimising hydrolysis and other side reactions (Figure 1B).²²⁻²⁵ Capriati and co-workers have performed Pd-catalysed cross-coupling reactions using organolithiums in aqueous conditions, albeit the reactions were very fast (<1 min reaction times).²⁶

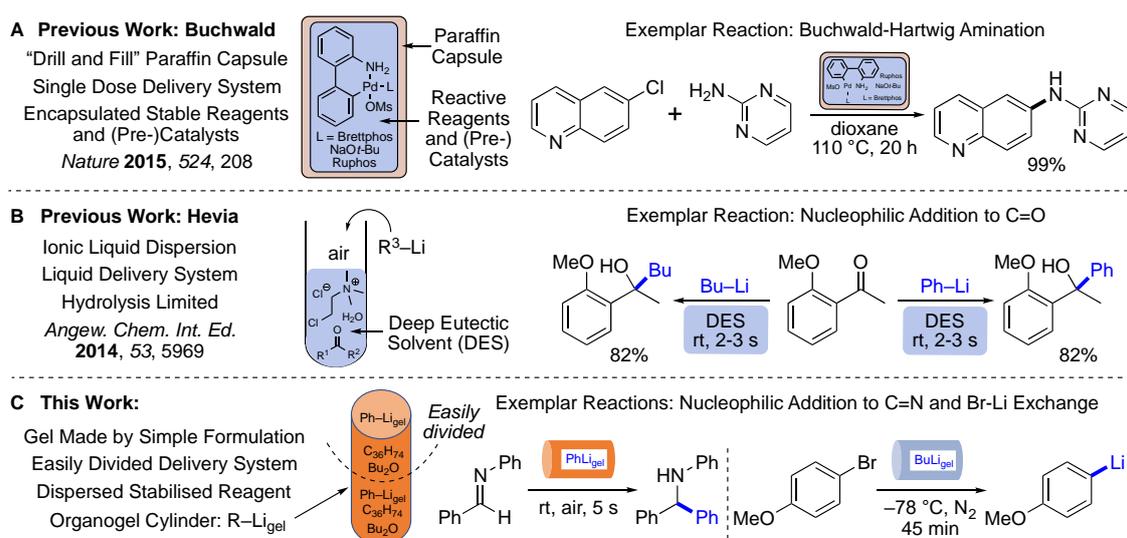


Figure 1. Schematic of selected relevant technologies for delivery of reactive species, including paraffin capsules (Buchwald and co-workers¹²) and ionic liquids (Hevia and co-workers²²).

In the search for alternative ways of handling and dosing widely-used organolithium reagents, we reasoned that low-molecular-weight organogelators (LMWGs) could be utilised to facilitate the generation of a gel-encapsulated organolithium that could be handled without the need for special working procedures. Such organogelators can self-assemble into nanostructured materials at relatively low loadings in organic solvents as a result of non-covalent interactions.²⁷⁻²⁹ The resulting gels combine the solid-like behaviour of the nanostructured network with the liquid-like characteristics of the solvent phase.³⁰ Gels allow effective diffusion of soluble small molecules and hence are interesting media to support catalysts and other types of reaction processes.³¹⁻³⁴ Incorporating an organolithium reagent into a gel could provide it with solid-like handling characteristics, and the possibility that the

reactive species could be protected from the influence of air and water, offering stabilisation and the ability to dramatically improve ease-of-handling. Furthermore, it should be possible to subdivide such gels, which is not an option with the previously developed capsules or tablets.

To develop such a reagent dosing system, it would be necessary to use a gelator that would be stable in the presence of an organolithium reagent and is compatible with the organic solvents in which they are typically used. Clearly, the gelator should not contain acidic protons, but since many LMWGs self-assemble as a result of hydrogen bond interactions,³⁵ this is a considerable design constraint. Therefore, we focussed our attention on a low cost, linear alkane LMWG consisting of 36 carbon atoms, C₃₆H₇₄ – hexatriacontane. Organogels comprising such long chain alkanes have previously been described – they form networks of lamellar platelet-type aggregates.^{36,37} However, such organogels have not been exploited in applications other than the design of superhydrophobic surfaces³⁸ or coatings³⁹ – indeed, they are best-known as the troublesome gel-phase aggregates that can form in oil pipelines as a result of the presence of small quantities of these higher alkanes.⁴⁰ Our key design principle was to repurpose these higher alkanes such as C₃₆H₇₄ as simple delivery vehicles for highly reactive organolithium reagents. Herein, we report the successful implementation of hexatriacontane (C₃₆H₇₄) as an organogelator for commercial solutions of PhLi and BuLi (*n*-BuLi) and the use of these novel, easily divided, easy-to-handle and air-/moisture-stable organolithium gels in synthetic organolithium reactions of industrial and academic relevance (Figure 1C).

To start, we studied the minimum gelation concentration of C₃₆H₇₄ in dibutyl ether and hexane, as these are the solvents that are most commonly used for the storage of organolithium reagents. In both cases, stable gels were obtained after a simple heat-cool cycle at concentrations of ca. 3% wt/vol. The T_{gel} values of these gels were 35–55 °C depending on the concentration of the gelator. These relatively low T_{gel} values are desirable for organolithium delivery vehicles as they enable easy thermal processing to form (and break-down) the gels. As expected, the gels exhibited lamellar platelet-type aggregates when imaged by scanning electron microscopy (see ESI).^{36,37}

In order to prepare an organolithium-loaded gel, a simple procedure, combining C₃₆H₇₄ gelator, organolithium reagent (from a commercial solution) and additional solvent, was developed (Fig. 2A and 2B). Thus, an oven-dried vial (7 mL, 2 cm diameter, 4.2 cm height) with stirrer bar was charged with the C₃₆H₇₄ gelator, closed with a rubber septum and flushed with nitrogen. Anhydrous, degassed solvent (dibutyl ether for PhLi or hexane for BuLi, <50 ppm of H₂O) was added, followed by the organolithium reagent (PhLi in dibutyl ether or BuLi in hexane). The vial was gently heated under a nitrogen atmosphere until all of the gelator had dissolved, and it was then immediately placed in an ice-water bath until the organogel formed. In each case, using 2.7-2.8% wt/vol of C₃₆H₇₄ gelator, a stable gel with an incorporated organolithium reagent (PhLi_{gel} and BuLi_{gel}) in a vial was obtained.

Encouraged by the successful formation of organolithium gels in vials, their stability and reactivity under ambient conditions were evaluated. Initially, PhLi_{gel} (2 equiv.) was prepared and used in a nucleophilic addition reaction with 2'-methoxyacetophenone **1** (Fig. 2A), the reaction chosen by Hevia et al.²³ to study the reactivity of organolithium reagents in deep eutectic solvents. In all examples, the gel was exposed to the air for the specified time, after which the reagent was placed on the top of the gel in the vial. After rapid stirring for only 5 s, which led to the mechanical breakdown of the gel, the mixture was extracted, worked-up and analysed by ¹H NMR spectroscopy to determine conversion to product. The gel network provides the incorporated organolithium reagents with significant additional

stability in ambient conditions. Exposure of the gel to air at ambient conditions for 30 min and subsequent reaction with 2'-methoxyacetophenone **1** resulted in 92% conversion to **2** (Entry 1). In contrast, when commercial PhLi solution in dibutyl ether (1.9 M) was placed in the vial and exposed to ambient air (in the fumehood, room temperature) for 30 min, only traces of **2** were observed. Prolonging the gel exposure time to 120 min did not cause any significant loss in PhLi activity (Entries 2 and 3). However, overnight (19 h) exposure resulted in partial evaporation of the solvent (dibutyl ether) and subsequent damage to the gel network (see ESI) together with the decomposition of PhLi as evidenced by <5% conversion to **2** (Entry 4). This evaporation problem was easily addressed by closing the vial with a lid. As a result, PhLi_{gel} that was exposed to ambient air for 30 min and then stored in a closed vial overnight (18 h) still showed excellent activity: 95% conversion to **2** (Entry 5). Pleasingly, after a much longer storage time in a closed vial (25 days) under ambient conditions, the degradation of PhLi inside the gel was still negligible and 92% conversion to **2** was obtained (Entry 6). This highlights that the gel formulation can provide long term stabilisation of PhLi, even without storage under inert atmosphere.

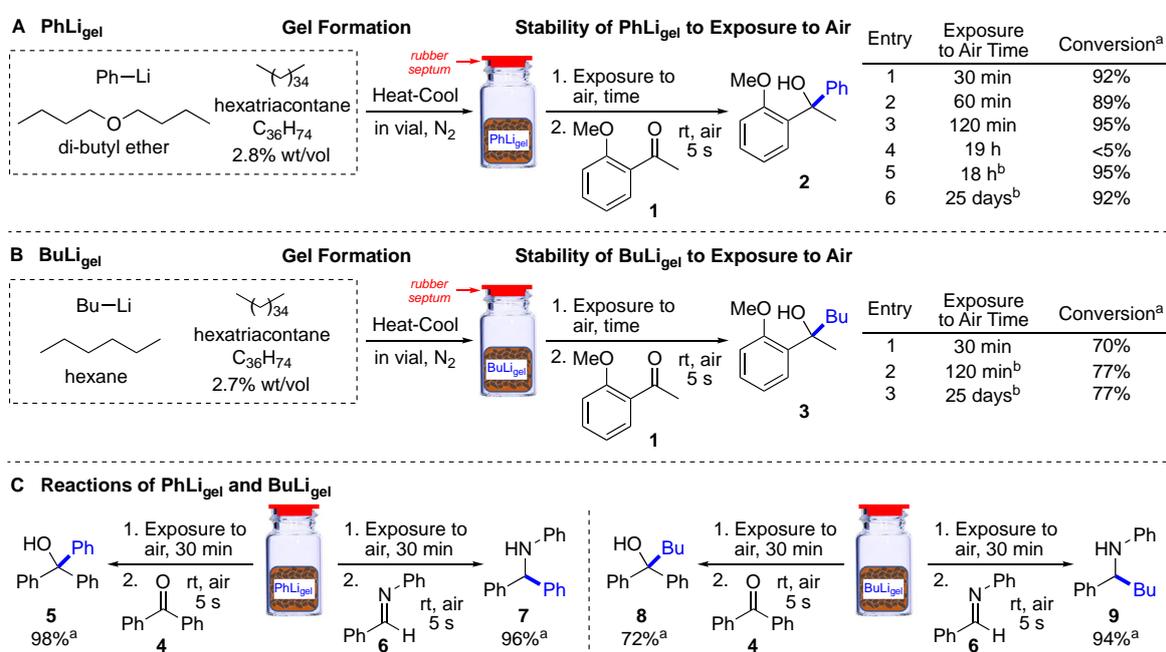


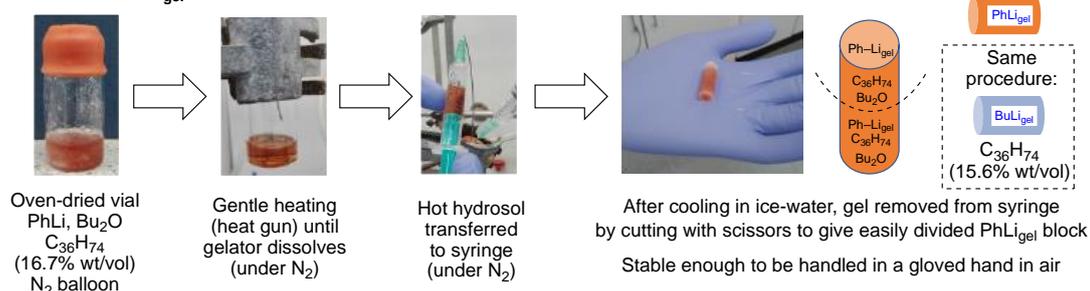
Figure 2. A/B Formation of PhLi_{gel}/BuLi_{gel} and screening of PhLi_{gel}/BuLi_{gel} stability under ambient conditions using reactivity in a nucleophilic addition reaction as the probe. ^a Conversions determined by ¹H NMR spectroscopy using the relative integrals of key signals in product and starting material. ^b The vial was closed with a lid after 5 min exposure to air – this significantly extended the lifetime of the gel. **C Nucleophilic addition reactions of PhLi_{gel} and BuLi_{gel} with a ketone and an imine.**

Using a similar approach, BuLi was incorporated into a gel with C₃₆H₇₄. The stability and reactivity of BuLi_{gel} (2 equiv.) under ambient conditions was also evaluated by reaction with 2'-methoxyacetophenone **1** (Fig. 2B). The results obtained suggest that, like PhLi, the BuLi is highly stabilised within the gel and decomposition is limited (see ESI). Indeed, the conversion to **2** after 25 days storage in a closed vial under ambient conditions (77%, entry 3) was in fact slightly higher than the reaction using commercial BuLi solution under an inert atmosphere (70%). It was also shown that

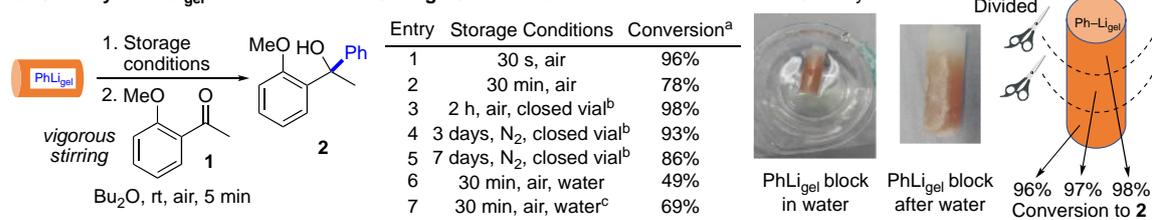
PhLi and BuLi organogels in vials could be successfully used for nucleophilic additions to benzophenone **4** and *N*-benzylideneaniline **6** (Fig. 2C).

In each of the synthetic reactions in Fig. 2, the reagents were placed on the top of the organolithium gel which had been formed within a vial. The obtained results demonstrate that under this experimental set-up, the organolithium reagents within the gel are highly stabilised. However, for general and practical use, we next prepared gel 'blocks' loaded with a specified amount of organolithium reagent that could be directly and easily transferred under ambient conditions to another reaction vessel (such as a round-bottomed flask) containing the other reagents. To achieve this, the original organolithium gel formation procedure was modified enabling us to prepare the gel inside a plastic syringe (Fig. 3A for PhLi_{gel}). In particular, it was necessary to modify the concentration of gelator and organolithium reagent within the gel in order to produce an organolithium gel block that was stable after exposure to air (see ESI). Ultimately, increasing the concentration of the C₃₆H₇₄ gelator from 2.8% wt/vol to 16.7% wt/vol and diluting the commercial PhLi solution to 0.6 M concentration in dibutyl ether resulted in the formation of a PhLi_{gel} block that was mechanically stable under ambient conditions and could be easily transferred using gloves. Based on titration experiments, it was evident that decomposition of the organolithium reagent during gel preparation was negligible (see ESI). It was also possible to incorporate BuLi into a gel block using a similar procedure and concentration of the reagents (15.6% wt/vol C₃₆H₇₄ gelator) (see ESI).

A Formation of PhLi_{gel} Block



B Stability of PhLi_{gel} Block to Different Storage Conditions



C Reactions of PhLi_{gel} and BuLi_{gel} Blocks

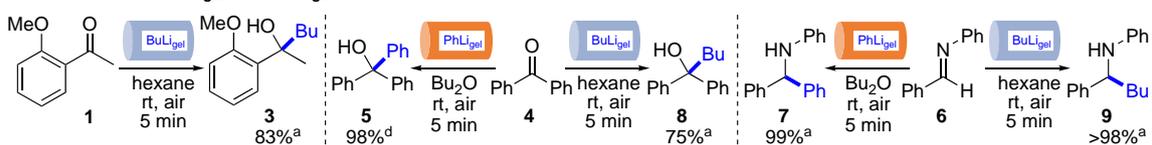


Figure 3. A Formation of PhLi_{gel} block. B Stability of PhLi_{gel} block under different storage conditions using reactivity in a nucleophilic addition reaction as the probe, including assessing the divisibility of the PhLi_{gel} block. C Nucleophilic addition reactions of PhLi_{gel} and BuLi_{gel} blocks with ketones and an imine. ^a Conversions determined by ¹H NMR spectroscopy using the relative integrals of key signals in product and starting material. ^b The PhLi_{gel} block was transferred to a vial flushed with N₂ and closed with a lid. ^c PhLi_{gel} block formed using 33% wt/vol C₃₆H₇₄ gelator. ^d % Yield after purification by chromatography.

With a successful method for the preparation of a PhLi_{gel} block in place, the stability and reactivity with 2'-methoxyacetophenone **1** under a variety of storage conditions were explored (Fig. 2B). After preparing the PhLi_{gel} block (2 equiv.) and storing for 30 s under ambient conditions in air, it was added to the 2'-methoxyacetophenone **1** in solvent. Upon stirring, the gel block broke down to release the PhLi into the solution and a 96% conversion to **2** was obtained (Entry 1). Storing for 30 min before reaction led to a lower conversion to **2** (78%) (Entry 2). The PhLi_{gel} blocks were more sensitive to storage than the gels in vials, presumably due to their greater surface area, with surface-located PhLi being more able to react with moisture in the ambient air. However, a 2 h storage time in air in a closed vial restored a high conversion to **2** (98%) (Entry 3) which was essentially maintained over 7 days under nitrogen in a closed vial (Entries 4 and 5). Alternatively, storage of the PhLi_{gel} block in an inert atmosphere, by leaving it in the syringe with the needle blocked in a rubber stopper, was an effective way of maintaining the activity. A similar profile of stability was also observed with the BuLi_{gel} block (see ESI).

To further demonstrate the protective ability of the gel network, the PhLi_{gel} block was immersed in a beaker of water for 30 min (Fig. 3B). After that time, the PhLi_{gel} block was removed from the water, dried with a paper towel and directly used in a reaction with 2'-methoxyacetophenone **1**. The conversion to **2** (49%) (Entry 6) was lower than the standard reaction presumably since PhLi located at the surface of the block partly decomposes upon contact with water (as noted visually, Fig. 3B). However, the fact that the reaction still proceeds in reasonable yield is strong evidence of the very high stability of the PhLi that is inside the gel block and the protective effect of encapsulation within the gel. Obviously PhLi added to water in the absence of gel protection is all very rapidly destroyed. Increasing the loading of the C₃₆H₇₄ gelator to 33% wt/vol and performing the same experiment led to a more robust gel and improved conversion to **2** (69%) (Entry 7). Clearly, the PhLi_{gel} block could potentially be further stabilised by coating it with an inert layer, to prevent decomposition at the surface. Indeed, coating the PhLi_{gel} block in paraffin led to a filled capsule that gave an 83% conversion to **2** after exposure to water (see ESI). However, we reason that there are significant advantages of working with a gel block rather than a filled capsule as described in the Introduction.

One of the key design principles of our organolithium gels is that they have an even distribution of the reagent through the gel which is distinct to the 'drill and fill' capsule technology originally reported by Buchwald and co-workers (Fig. 1A).¹² To prove the equal distribution of reagent through the organolithium gels, a PhLi_{gel} block was cut into three equivalent pieces using a razor blade. Each of these pieces was used in a separate reaction with 2'-methoxyacetophenone **1** to give **2** in conversions of 96%, 97% and 98% (Fig. 3B), clearly demonstrating that it will be possible to subdivide the organolithium gel blocks to facilitate accurate dosing of the organolithium reagent into the desired reaction. In terms of application of the technology, this is crucial as it demonstrates that a single large batch of an organolithium gel could be produced in-house (or by a chemical supply company), packaged and stored (and shipped) in an appropriate way, and then subdivided into the precise amounts required by the end-user and used in multiple different reactions.

The PhLi_{gel} and BuLi_{gel} blocks also performed very well in other nucleophilic addition reactions. For these reactions, the organolithium gels were prepared and then stored for 10-30 s before use in the reactions shown – good conversions to products **3**, **5** and **7-9** (75-79%) were obtained from reactions with 2'-methoxyacetophenone **1**, benzophenone **4** and *N*-benzylideneaniline **6** (Fig. 3C). It was important to show that the C₃₆H₇₄ gelator can be readily separated from the products. In general, most

of the C₃₆H₇₄ gelator can be removed in the work-up by precipitation and filtration. Standard flash column chromatography can then be used to remove the final traces of the C₃₆H₇₄ gelator, eluting first with hexane to remove C₃₆H₇₄ and then with 1:1 hexane-dichloromethane to elute the product. Using this method, a 98% isolated yield of alcohol **5** was obtained from a PhLi_{gel} block and benzophenone **4** (Fig. 3C). The same approach was used by Buchwald and co-workers to remove the residual paraffin from reactions using their paraffin capsules.¹²

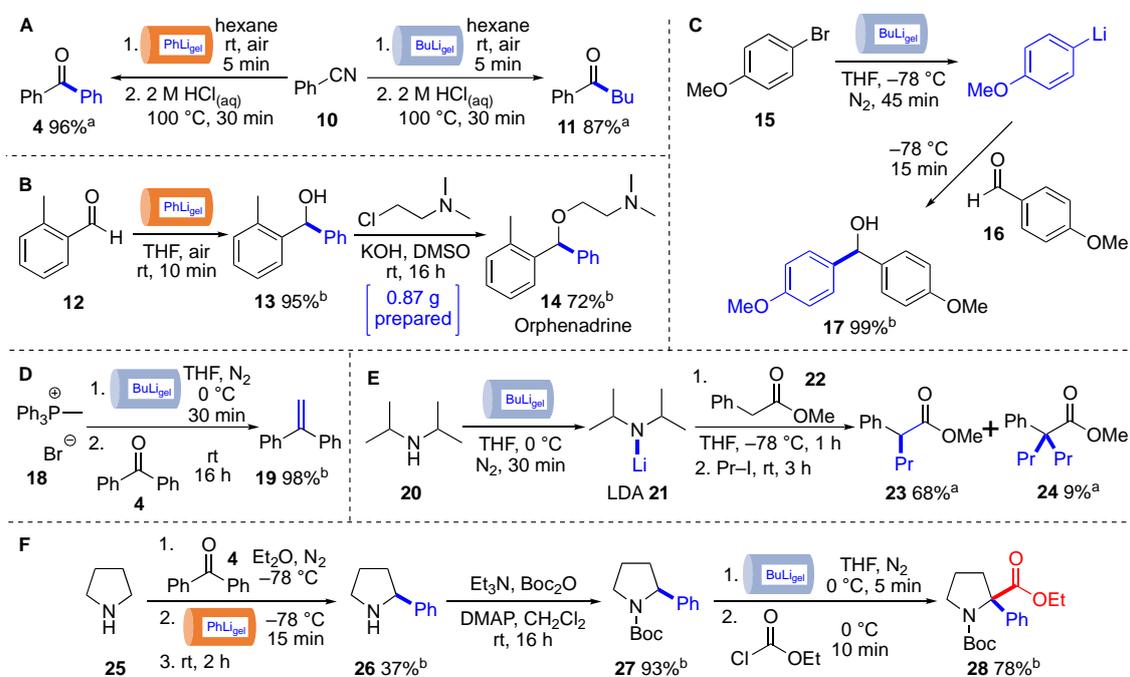


Figure 4. Synthetic applications of the PhLi_{gel} and BuLi_{gel} blocks. A Ketone synthesis. B Synthesis of 873 mg of Orphenadrine using 9.5 mmol of a PhLi_{gel} block. C Bromine-lithium exchange using a BuLi_{gel} block. D Wittig reaction. E Preparation of LDA and use in an enolate α -alkylation reaction. F α -C-H Bond difunctionalization of pyrrolidine using PhLi_{gel} and BuLi_{gel} blocks. ^a Conversions determined by ¹H NMR spectroscopy using DMF as an external standard. ^b % Yield after purification by chromatography.

The PhLi_{gel} and BuLi_{gel} blocks were then used in a wider array of synthetic applications, including more challenging reactions (Fig. 4). For example, reaction of each of the PhLi_{gel} and BuLi_{gel} blocks with benzonitrile **10** followed by hydrolysis⁴¹ resulted in the formation of ketones **4** and **11** in 96% and 87% NMR yields respectively (Fig. 4A). The preparation of a PhLi_{gel} block was scaled up (to 9.5 mmol of PhLi encapsulated, see ESI) and this PhLi_{gel} block was used in the synthesis of 0.87 g of the anticholinergic and antihistamine drug Orphenadrine **14**.⁴² Reaction of the PhLi_{gel} with 2-methylbenzaldehyde **12** was performed under ambient conditions in air to give alcohol **13** in 95% isolated yield and, after *N*-alkylation with 2-(*N,N*-dimethylamino)ethylchloride, Orphenadrine **14** was obtained in 68% yield over the two steps (Fig. 4B). To show that the organolithium gel blocks are also compatible with other types of reactions, a bromine-lithium exchange reaction⁴³ was performed with 4-bromoanisole **15** using a BuLi_{gel} block at -78 °C under an inert atmosphere followed by trapping the intermediate aryllithium with 4-methoxybenzaldehyde **16** to give alcohol **17** in 99% isolated yield (Fig. 4C). The BuLi_{gel} block was also successfully used to generate an ylid from phosphonium bromide **18** and deployed in a Wittig reaction with benzophenone **4**⁴⁴ to give alkene **19** in 98% isolated yield (Fig. 4D). The widely used strong base LDA **21** was readily prepared from diisopropylamine **20** and used in an enolate α -alkylation

reaction of ester **22**⁴⁵ to give **23** in 68% NMR yield (Fig. 3E). Finally, we successfully utilized both the PhLi_{gel} and BuLi_{gel} blocks in a three-step, double α -C-H functionalization of pyrrolidine under inert conditions (Fig. 4F). In the first step, using Seidel's approach⁴⁶ with the PhLi_{gel} block, deprotonation of the NH proton in pyrrolidine **25** by PhLi followed by hydride transfer to benzophenone **4** as a hydride acceptor and addition of PhLi to the *in situ*-generated imine provided 2-phenylpyrrolidine **26** in 37% isolated yield.⁴⁷ 2-Phenylpyrrolidine **26** was Boc-protected and then, following a method reported by O'Brien and Coldham,⁴⁸ benzylic lithiation using a BuLi_{gel} block at 0 °C and subsequent reaction with ethyl chloroformate gave α,α -disubstituted pyrrolidine **28** in 78% isolated yield.

In summary, we have shown that sensitive organolithium reagents such as PhLi and BuLi can be successfully incorporated within C₃₆H₇₄ organogel delivery vehicles. The gel network provides significant stability towards ambient conditions and, as a result, these organolithium gels have the potential to be used without the need for many of the special working protocols usually needed for this type of chemistry. Our gel-phase approach, using just a small amount of a readily available, low-cost gelator, C₃₆H₇₄, in an organic solvent, has several advantages, including solvent compatibility, simple manufacture and an even distribution of the reagent through the gel for effective subdivision and accurate reaction dosing. The use of gels as delivery vehicles for hazardous organometallic reagents has the potential to revolutionise this area of synthetic chemistry, making these widely-used reactions safer and more accessible, and enabling the more widespread use of these synthetic methods. We anticipate that gels could, for example, be commercially supplied as individual doses wrapped in foil, or alternatively in syringe tubes which enable the extrusion of the required amount of gel for the reaction to be carried out. We also perceive benefits in the use of this simple gel additive technology for the long-term storage and/or shipping of bulk samples of organolithium reagents in industry. It is anticipated that this simple gel-mediated approach to reagent stabilisation could also be applied to other moisture- and air-sensitive reagents and work in this direction is currently in progress.

Supplementary Information is available in the online version of the paper. It includes full details of gel fabrication and characterisation, all details of organic reaction methods and supporting characterisation data.

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Author Contributions PS helped devise, perform and interpret the experiments and wrote the first draft of the manuscript. DKS and POB raised funding, managed the project, helped devise experiments and developed the manuscript for publication. DKS initiated the concept.

Competing Interests The authors (PS, POB and DKS) have filed a patent, under the auspices of University of York, to provide commercial protection for this technology.

References

- 1 *The Chemistry of Organolithium Compounds*. Eds. Rappoport, J. & Marek, I. (Wiley, 2004).
- 2 Clayden, J. *Organolithiums: Selectivity for Synthesis*. (Elsevier, 2002).
- 3 *Organolithiums in Enantioselective Synthesis*. Ed. Hodgson, D. M. (Springer, Berlin, Heidelberg, 2003).
- 4 Wu, G. & Huang, M. Organolithium Reagents in Pharmaceutical Asymmetric Processes. *Chem. Rev.* **106**, 2596-2616, doi:10.1021/cr040694k (2006).

- 5 Halasa, A. F. & Hsu, W. L. Synthesis of high vinyl elastomers via mixed organolithium and sodium alkoxide in the presence of polar modifier. *Polymer* **43**, 7111-7118, doi: 10.1016/S0032-3861(02)00451-2 (2002).
- 6 Denmark, S. E., Nakajima, N. & Nicaise, O. J.-C. Asymmetric Addition of Organolithium Reagents to Imines. *J. Am. Chem. Soc.* **116**, 8797-8798, doi:10.1021/ja00098a044 (1994)
- 7 Firth, J. D., O'Brien, P. & Ferris, L. Synthesis of Enantiopure Piperazines via Asymmetric Lithiation–Trapping of N-Boc Piperazines: Unexpected Role of the Electrophile and Distal N-Substituent. *J. Am. Chem. Soc.* **138**, 651-659, doi:10.1021/jacs.5b11288 (2016).
- 8 Bootwicha, T., Feilner, J. M., Myers, E. L. & Aggrwal, V. K. Iterative assembly line synthesis of polypropionates with full stereocontrol. *Nature Chem.* **9**, 896-902, doi:10.1038/nchem.2757 (2017).
- 9 Schwindeman, J. A., Woltermann, C. J. & Letchford, R. J. Safe handling of organolithium compounds in the laboratory. *Chem. Health Saf.* **9**, 6-11, doi:10.1016/S1074-9098(02)00295-2 (2002).
- 10 Rathman, T. L. & Schwindeman, J. A. Preparation, Properties, and Safe Handling of Commercial Organolithiums: Alkylolithiums, Lithium *sec*-Organoamides, and Lithium Alkoxides. *Org. Proc. Res. Dev.* **18**, 1192-1210, doi:10.1021/op500161b (2014).
- 11 Godfrey, A. G., Michael, S. G., Sittampalam, G. S. & Zahoranszky-Kohalmi, A Perspective on Innovating the Chemistry Lab Bench. *Frontiers in Robotics and AI* **7**, 24, doi: 10.3389/frobt.2020.00024 (2020).
- 12 Sather, A. C., Lee, H. G., Colombe, J. R., Zhang, A. & Buchwald, S. L. Dosage delivery of sensitive reagents enables glove-box-free synthesis. *Nature* **524**, 208, doi:10.1038/nature14654 (2015).
- 13 Taber, D. F. & Frankowski, K. J. Grubbs' Catalyst in Paraffin: An Air-Stable Preparation for Alkene Metathesis. *J. Org. Chem.* **68**, 6047-6048, doi:10.1021/jo030005p (2003).
- 14 Dander, J. E., Weires, N. A. & Garg, N. K. Benchtop Delivery of Ni(cod)₂ using Paraffin Capsules. *Org. Lett.* **18**, 3934-3936, doi:10.1021/acs.orglett.6b01758 (2016).
- 15 Shen, C., Spannenberg, A., Auer, M. & Wu, X.-F. Utilizing an Encapsulated Solution of Reagents to Achieve the Four-Component Synthesis of (Benzo)Thiophene Derivatives. *Adv. Synth. Catal.* **359**, 941-946, doi:10.1002/adsc.201601343 (2017).
- 16 Mehta, M. M., Boit, T. B., Dander, J. E. & Garg, N. K Ni-Catalyzed Suzuki-Miyaura Cross-Coupling of Aliphatic Amides on the Benchtop, *Org. Lett.* **22**, 1-5, doi:10.1021/acs.orglett.9b03434 (2020).
- 17 Taber, D. F. & Nelson, C. G. Potassium Hydride in Paraffin: A Useful Base for Organic Synthesis, *J. Org. Chem.* **71**, 8973-8974, doi:10.1021/jo061420v (2006).
- 18 Cai, J., Huang, S., He, R., Chen, L., Chen, D., Jiang, S., Li, B & Li, Y. Access to functionalized thienopyridines via a reagent-capsule-assisted coupling, thiolation and cyclization cascade sequence. *Org. Biomol. Chem.* **15**, 333-337, doi:10.1039/c6ob02351g (2017).
- 19 Schwenger, A.; Frey, W.; Richert, C. Reagents with a crystalline coat. *Angew. Chem. Int. Ed.* **55**, 13706–13709 doi:10.1002/anie.201605507 (2016).
- 20 Li, T.; Xu, L., Xing, Y. & Xu, B. High-Throughput Synthetic Chemistry Enabled by Organic Solvent Disintegrating Tablet, *Chem. Asian J.* **12**, 190-193 doi:10.1002/asia.201601487 (2017).
- 21 Borlinghaus, N., Kaschel, J., Klee, J., Haller, V., Schetterl, J., Heitz, S., Lindner, T., Dietrich, J. D., Braje, W. M. & Jolit, A. Reagent and Catalyst Capsules: A Chemical Delivery System for Reaction Screening and Parallel Synthesis, *J. Org. Chem.* **86**, 1357-1370, doi:10.1021/acs.joc.0c025 (2021).
- 22 García-Álvarez, J., Hevia, E. & Capriati, V. The Future of Polar Organometallic Chemistry Written in Bio-Based Solvents and Water. *Chem. Eur. J.* **24**, 14854-14863, doi: 10.1002/chem.201802873 (2018).
- 23 Vidal, C., García-Álvarez, J., Hernán-Gómez, A., Kennedy, A. R. & Hevia, E. Introducing Deep Eutectic Solvents to Polar Organometallic Chemistry: Chemoselective Addition of Organolithium and Grignard Reagents to Ketones in Air. *Angew. Chem. Int. Ed.* **53**, 5969-5973, doi: 10.1002/anie.201400889 (2014).

- 24 Vidal, C., García-Álvarez, J., Hernán-Gómez, A., Kennedy, A. R. & Hevia, E. Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions. *Angew. Chem. Int. Ed.* **55**, 16145-16148, doi: 10.1002/anie.201609929 (2016).
- 25 Sanchez-Condado, A., Carriedo, G. A., Soto, A. P., Rodríguez-Alvarez, M. J., Garcia-Alvarez, J. & Hevia, E. Organolithium-Initiated Polymerization of Olefins in Deep Eutectic Solvents under Aerobic Conditions, *ChemSusChem* **12**, 3134-3143 doi: 10.1002/cssc.201900533 (2019).
- 26 Dilauro, G., Quivelli, A. F., Vitale, P., Capriati, V., Perna, F. M. *Angew. Chem. Int. Ed.* **58**, 1799-1802 doi: 10.1002/anie.201812537 (2019).
- 27 Weiss, R. G. The Past, Present, and Future of Molecular Gels. What Is the Status of the Field, and Where Is It Going? *J. Am. Chem. Soc.* **136**, 7519-7530, doi:10.1021/ja503363v (2014).
- 28 Hirst, A. R., Escuder, B., Miravet, J. F. & Smith, D. K. High-Tech Applications of Self-Assembling Supramolecular Nanostructured Gel-Phase Materials: From Regenerative Medicine to Electronic Devices. *Angew. Chem. Int. Ed.* **47**, 8002-8018, doi: 10.1002/anie.200800022 (2008).
- 29 Draper, E. R. & Adams, D. J. Low-Molecular-Weight Gels: The State of the Art. *Chem* **3**, 390-410, doi:10.1016/j.chempr.2017.07.012 (2017).
- 30 Weiss, R. G. *Molecular Gels: Structure and Dynamics*. (Royal Society of Chemistry, 2018).
- 31 Escuder, B., Rodríguez-Llansola, F. & Miravet, J. F. Supramolecular gels as active media for organic reactions and catalysis. *New J. Chem.* **34**, 1044-1054, doi:10.1039/B9NJ00764D (2010).
- 32 Fang, W., Zhang, Y., Wu, J., Liu, C., Zhu, H. & Tu, T. Recent Advances in Supramolecular Gels and Catalysis. *Chem. Asian J.* **13**, 712-729, doi:10.1002/asia.201800017 (2018).
- 33 Slavík, P., Kurka, D. W. & Smith, D. K. Palladium-scavenging self-assembled hybrid hydrogels – reusable highly-active green catalysts for Suzuki–Miyaura cross-coupling reactions. *Chem. Sci.* **9**, 8673-8681, doi:10.1039/C8SC04561E (2018).
- 34 Piras, C. C., Slavik, P., Smith, D. K. Self-Assembling Supramolecular Hybrid Hydrogel Beads, *Angew. Chem. Int. Ed.* **59**, 853-859, doi:10.1002/anie.201911404 (2020).
- 35 Amabilino, D. B., Smith, D. K. & Steed, J. W. Supramolecular materials. *Chem. Soc. Rev.* **46**, 2404-2420, doi:10.1039/C7CS00163K (2017).
- 36 Abdallah, D. J., Sirchio, S. A. & Weiss, R. G. Hexatriacontane Organogels. The First Determination of the Conformation and Molecular Packing of a Low-Molecular-Mass Organogelator in Its Gelled State. *Langmuir* **16**, 7558-7561, doi:10.1021/la000730k (2000).
- 37 Abdallah, D. J. & Weiss, R. G. n-Alkanes Gel n-Alkanes (and Many Other Organic Liquids). *Langmuir* **16**, 352-355, doi:10.1021/la990795r (2000).
- 38 Tavana, H., Amirfazli, A. & Neumann, A. W. Fabrication of Superhydrophobic Surfaces of n-Hexatriacontane. *Langmuir* **22**, 5556-5559, doi:10.1021/la0607757 (2006).
- 39 Bhushan, B. & Jung, Y. C. Natural and biomimetic artificial surfaces for superhydrophobicity, self-cleaning, low adhesion, and drag reduction. *Prog. Mater. Sci.* **56**, 1-108, doi: 10.1016/j.pmatsci.2010.04.003 (2011).
- 40 Singh, P., Venkatesan, R., Fogler, H. S. & Nagarajan, N. Formation and aging of incipient thin film wax-oil gels. *AIChE J.* **46**, 1059-1074, doi:10.1002/aic.690460517 (2000).
- 41 Rodríguez-Álvarez, M. J., Garcia-Álvarez, J., Uzelac, M., Fairley, M., O'Hara, C. T. & Hevia, E. Introducing Glycerol as a Sustainable Solvent to Organolithium Chemistry: Ultrafast Chemoselective Addition of Aryllithium Reagents to Nitriles under Air and at Ambient Temperature. *Chem. Eur. J.* **24**, 1720-1725, doi:10.1002/chem.201705577 (2018).
- 42 Bersani, G. *et al.* 5-HT₂ antagonist ritanserin in neuroleptic-induced parkinsonism: A double-blind comparison with orphenadrine and placebo. *Clinical Neuropharmacology* **13**, 500-506, doi:10.1097/00002826-199012000-00003 (1990).
- 43 Turan, I. S., Cakmak, F. P. & Sozmen, F. Highly selective fluoride sensing via chromogenic aggregation of a silyloxy-functionalized tetraphenylethylene (TPE) derivative. *Tetrahedron Lett.* **55**, 456-459, doi:10.1016/j.tetlet.2013.11.059 (2014).
- 44 Zhang, G., Bai, R.-X., Li, C.-H., Feng, C.-G. & Lin, G.-Q. Halogenation of 1,1-diarylethylenes by N-halosuccinimides. *Tetrahedron* **75**, 1658-1662, doi:10.1016/j.tet.2018.11.018 (2019).

- 45 Asada, M., Obitsu, T., Nagase, T., Tanaka, M., Yamaura, Y., Takizawa, H., Yoshikawa, K., Sato, K., Narita, M., Ohuchida, S., Nakai, H. & Toda, M. 3-(2-Aminocarbonylphenyl)propanoic acid analogs as potent and selective EP3 receptor antagonists. Part 1: Discovery and exploration of the carboxamide side chain. *Bioorg. Med. Chem.* **18**, 80-90, doi:10.1016/j.bmc.2009.11.023 (2010).
- 46 Chen, W., Ma, L., Paul, A. & Seidel, D. Direct α -C-H bond functionalization of unprotected cyclic amines. *Nat. Chem.* **10**, 165, doi:10.1038/nchem.2871 (2017).
- 47 In our hands, using commercial PhLi solution, 2-phenylpyrrolidine **26** was obtained in 50% isolated yield.
- 48 Sheikh, N. S., Leonori, D., Barker, G., Firth, J. D., Campos, K. R., Meijer, A. J. H. M., O'Brien, P. & Coldham, I. An Experimental and in Situ IR Spectroscopic Study of the Lithiation-Substitution of *N*-Boc-2-phenylpyrrolidine and -piperidine: Controlling the Formation of Quaternary Stereocenters. *J. Am. Chem. Soc.* **134**, 5300-5308, doi:10.1021/ja211398b (2012).