

## Organogel Delivery Vehicles for the Stabilization of Organolithium Reagents

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Organometallic reagents such as organolithiums and organomagnesiums are valuable tools in modern synthesis. However, their high reactivity makes them challenging to handle. It is usual to perform reactions using them under strictly inert conditions and at low temperatures. This has limited the take-up of such methods by non-specialist researchers. Even for well-trained researchers, there are hazards associated with the use of these reagents that would be good to mitigate. Furthermore, the long-term storage of these reagents is an issue, as samples can decompose over time. These factors are problematic in the research laboratory setting but also in industry, where organolithium reagents see use in polymer synthesis and pharmaceutical manufacture.

In their recent *Nature Chemistry* paper, Drs. Petr Slavik (currently at Santiago Lab, Czech Republic) and Benjamin Trowse (currently at Apex Molecular, UK) and Professors Peter O'Brien and David K. Smith (University of York, UK) report a way of stabilizing organolithiums in the gel phase. They make use of a simple low-molecular-weight gelator (LMWG) that assembles via non-covalent interactions into a nanostructured solid-like network within commercial organolithium reagent solutions, providing them with significantly enhanced stability, and improved handleability. This work combines Professor Smith's expertise in supramolecular gels and Professor O'Brien's experience in working with organolithiums to create a unique outcome – highly stabilized organolithium gels.

Professor Smith picked up the story: "For many years in York, I had worked alongside Peter in the Organic Chemistry section and always been impressed by the skills of his research team in handling hazardous organolithiums. Some years ago, Professor Eva Hevia (now at University of Bern, Switzerland) visited the Department. She talked about her work using deep eutectic solvents to stabilize organolithiums,<sup>1</sup> and it captured my interest. My lab had been working on some self-assembling gels made in deep eutectics, and my first thought was that we might be able to apply our technology to organolithiums. I remember chatting to Peter after the seminar, buzzing with excitement, and we stored the idea away for testing."

"In 2017, a brilliant postdoctoral researcher, Dr. Petr Slavik, joined my group. He had a strong synthetic focus, something relatively unusual in my 'molecular materials' lab, and this opened up some new possibilities for us. After completing his

main project developing palladium-loaded supramolecular gels to act as recyclable catalysts for the Suzuki–Miyaura reaction, we decided it might be fun to play with some of the ideas about stabilizing organolithium reagents and see where they might lead. We talked with Peter, who was excited to bring his expertise in organolithium chemistry to the table."

Professor O'Brien explained: "I'd known Dave for many years – as new academics in York, we had worked in adjacent offices, and supported one another through many of the stresses and strains of academic life. It was exciting to join this project. In all honesty, I was somewhat skeptical about whether the organolithiums could be stabilized in gels!"

Indeed, as Dr. Slavik remembers, this initially turned out to be the case. "I tried very hard to use the group's deep eutectic gels to stabilize organolithium reagents, but nothing really worked. We just couldn't create homogeneous systems or produce effective gels. By this stage, there was some 'Proof of Principle' university funding to explore the idea further, and honestly, we were a little worried we might not be able to deliver proof of anything. Fortunately, Dave had an idea to get round the problems we were facing."

Taking up the story, Professor Smith recalls: "I remember thinking it'd be great if we could gelate the organolithium straight out of the bottle that it was supplied in, without having to co-mix it with anything. I started to think about what might form gels in PhLi/dibutyl ether or *n*-BuLi/hexane. Most of the best supramolecular organogels, that operate in such apolar solvents, use hydrogen bonds to assemble their low-molecular-weight building blocks – of course, such molecules would be susceptible to deprotonation by highly basic organolithiums. However, somewhere at the back of mind was the knowledge that long-chain alkanes could form gels in non-polar solvents. Indeed, this type of gel-like aggregate can cause problematic blockages in oil pipelines. Long-chain alkanes are essentially functionally inert, and they are therefore ideal potential gelators for highly reactive organometallics. We therefore decided to test hexatriacontane (C<sub>36</sub>H<sub>74</sub>), which had previously been explored as a gelator for organic solvents by Professor Richard Weiss and co-workers.<sup>2</sup>"

Dr. Slavik added: "It really worked straight away. We essentially just mixed ca. 3% wt/vol hexatriacontane with the organolithium solution and made gels. Of course, to make the

gel, we had to treat the organolithium solution with all the usual precautions. We therefore developed a method in which we could perform the required manipulations under inert conditions, with gentle heating and cooling giving rise to the gel."

"Pretty quickly, we started testing the gels made in sample vials, and found they could perform standard nucleophilic addition reactions into ketones or imines, simply by placing the reagents and solvent on top of the gel and vigorously stirring. Excess gelator could be removed from the reactions via a simple plug filtration methodology once the reaction was complete. The results came in very fast. I designed some protocols to test the gels, which involved things like leaving the vial open to air before using the gel. Remarkably, we found that the gels could be left open to air at room temperature for significant amounts of time without adversely affecting reaction yield."

Reflecting further, Professor Smith added: "Around this time, we came across a landmark paper that had previously been published in *Nature* by Professor Stephen Buchwald and co-workers.<sup>3</sup> They had created drilled-out paraffin capsules in a glove box, filled them with reactive catalyst in solution form, and then sealed them. They used these paraffin capsules to carry out reactions outside of the glove box. We realized the conceptual similarity in what we were trying to achieve, and wondered whether we could turn our gels into something more like a capsule that could be physically handled outside of its sample vial."

"To achieve this, Petr increased the loading of hexatriacontane. It is well known that increasing gelator loading enhances mechanical properties, and on increasing to ca. 15% wt/vol, it became possible to make the gels in a mould, and remove them by cutting the mould away to leave a self-standing gel. Petr chose to use a plastic syringe as the mould, as it was ideal for handling the solution of organolithium required prior to gel assembly."

Dr Slavik explained further: "Once we had the gel cylinders, we found they could be left in a petri dish in air, and still retained activity in our test reactions. We decided to probe how far we could push them, leaving them for increasing periods of time under ambient conditions. The optimal handling conditions were to expose them to air and handle them like any other reagent, but for prolonged storage, we kept them in a sealed vial. In one crazy moment, we decided to try dropping a gel cylinder into water to see if it survived. Remarkably, we found that even after water exposure, we still got the test addition reaction to work, albeit with a lower yield, presumably because of deactivation of some organolithium at the gel cylinder surface. We increased the loading of gelator

to stabilize the cylinders further, and they survived better in water."

Professor O'Brien added: "Our colleague Dr Will Unsworth suggested that we should take a photograph of a someone holding the gel cylinder in their hand – it is a striking image (Figure 1) and Petr's gloved hand has become rather famous since the paper was published!"



**Figure 1** A hand-held PhLi gel cylinder ready for a reaction!

Professor Smith noted: "We realized that an advantage of our gel-based system was that it was homogeneous, and the organolithium was equally distributed throughout it. Furthermore, unlike a filled capsule, the system was amenable to subdivision simply by cutting the gel into portions. Petr therefore divided a gel cylinder into three with a razor blade and demonstrated that each part could be used to perform a separate reaction. At this point, I realized we could have something really useful – potentially, large volumes of organolithiums could be easily turned into gels by chemical companies, and then subdivided into portions ready for packaging and shipping – a simple and cost-effective workflow that would provide end-users with gel-stabilised reagents with longer shelf-lives, better safety profiles and much easier use."

With his synthetic experience, Professor O'Brien pushed the team towards expanding the range and scope of reactions being tested: "We decided to try some more challenging reactions. We added the organolithiums into nitriles, performed bromine–lithium exchange, carried out a Wittig reaction, and used the gel to prepare LDA. We then performed an  $\alpha$ -C–H difunctionalisation of pyrrolidine, using two different organolithiums in sequence. Given our long-standing interest in the lithiation-trapping of nitrogen heterocycles, this was a parti-

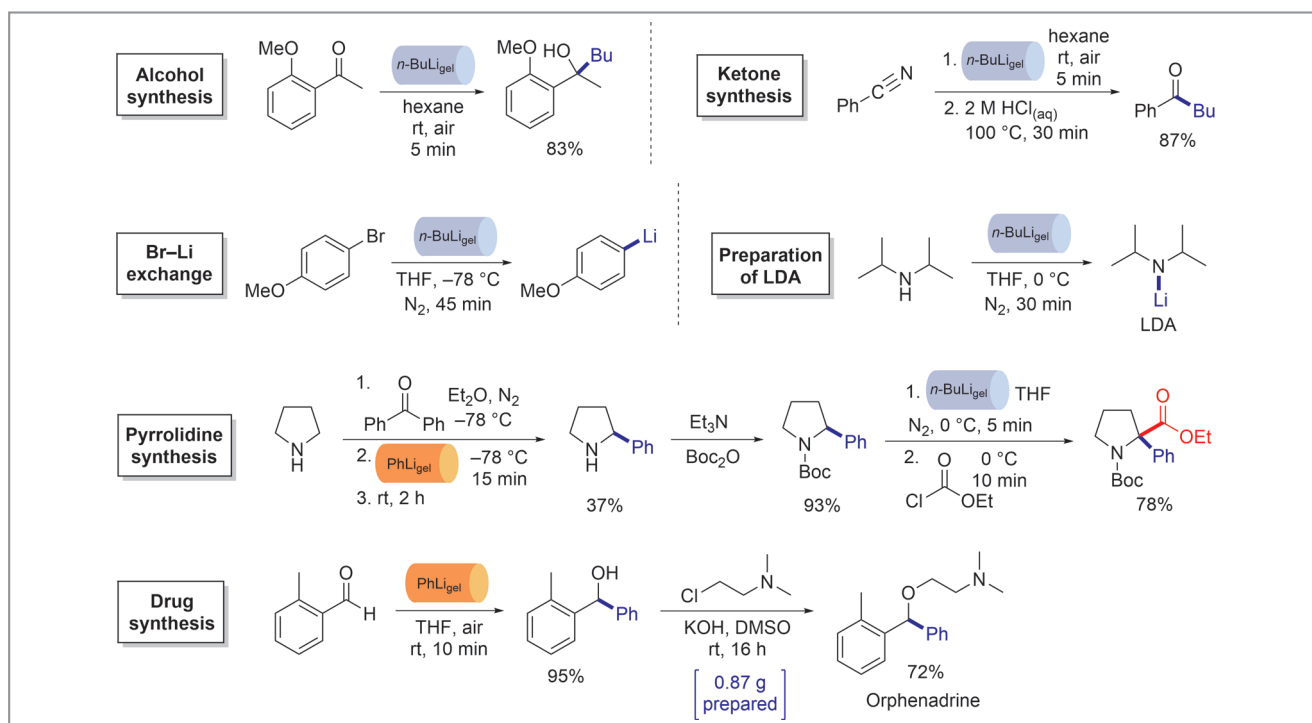
cularly satisfying application. Finally, we demonstrated that the methodology could be scaled up to the gram-scale, and performed a synthesis of the anticholinergic and antihistamine drug Orphenadrine. Pleasingly, the gel blocks were trivial to use across these different synthetic approaches, without the need for inert atmosphere conditions, and performed just as well as the classical use of organolithiums, which would have required much more careful handling.” A selection of these synthetic applications is captured in Scheme 1.

“With one eye on expanding the technology to other reactive organometallics, we also tested the gel encapsulation of some organomagnesium reagents and demonstrated that this worked very well. At this point, I was impressed with the potential of this gel encapsulation technology and the project team got together to discuss the next steps.”

According to the authors of this study, there are a range of technologies being developed to make it easier to work with sensitive reagents, including alternative solvents, waxes, crystalline coatings, solid tableting technologies, polymer capsules, and dissolvable bag-style delivery vehicles. However, gels, and in particular supramolecular gels, had not really been explored in this regard. Realizing they were onto something new, the researchers decided to file a patent, to protect the invention.<sup>4</sup>

Professor Smith remembers: “Once our patent was in the public domain in 2021, we moved to disseminate the work further, publishing a preprint focused on the organolithium gels in *ChemRxiv*.<sup>5</sup> Once the preprint was available online, we then submitted a version to *Nature Chemistry*. At around the same time, we employed Benjamin Trowse using EPSRC Impact Accelerator Funding, with the view of moving the project towards some commercial outcomes. We were working with potential industrial partners, and it was important for us to answer some questions they had about the technology, and further expand the scope of what it could achieve.”

Professor O'Brien explained: “Fortunately, having Ben in place meant we were well-positioned to carry out some additional experiments suggested by the reviewers of our *Nature Chemistry* paper. In particular, they were keen for us to perform many more titrations of the organolithium reagents in gels – something Ben had actually been exploring as part of a study into long-term stability for organolithium shipping and storage. They also wanted us to explore the limits of the technology with more reactive organolithiums. The paper had been based on PhLi and *n*-BuLi. Ben therefore completed some work on *s*-BuLi and demonstrated that in vials, *s*-BuLi could be effectively stabilized by the gel.”



**Scheme 1** Selected synthetic applications of PhLi and *n*-BuLi gel cylinders

Dr. Trowse explained: “We found that if we left a normal solution of *s*-BuLi to stand in air for 10 minutes at room temperature, it degraded to just 24%. However, within the protective organogel, 73% of the *s*-BuLi remained intact. The gels could not be left in air for very extended periods of time, but it was clear that for short time periods, very significant stabilization was provided by the gel, facilitating easier handling. Furthermore, the fact that the gel slows reactivity in ambient conditions, will increase the safety profile.”

Professor O'Brien added: “We considered also testing *t*-BuLi in the same way, but we had some reservations about heating the very pyrophoric *t*-BuLi reagent in the gelation processing steps. We are therefore continuing to explore the stabilization of *t*-BuLi in collaboration with a partner who specializes in handling highly hazardous chemicals.”

“The reviewers were keen for us to extend the scope of the organolithium synthetic chemistry. In particular, they highlighted the importance of ortho-lithiation methodology. The reviewers also made the interesting suggestion of co-incorporating a ligand into the gel alongside the organometallic. Ben therefore incorporated TMEDA into one of the gels alongside *n*-BuLi. The ligand significantly enhances the organometallic reactivity, and it was therefore necessary to add additional gelator to stabilize the gels in vials (25% wt/vol). The gel was then used for organolithiation of methoxybenzene, demonstrating that this important type of reaction was feasible using our gel-based approach.”

Thinking back to the reviewers' comments, Professor Smith added, “Most of the reviewers were excited by the work, and wanted us to demonstrate broader scope than organolithiums – ideally the broadest scope possible. Fortunately, Petr had already laid the groundwork with his earlier organomagnesium studies, so Ben finished this work off and we added it to the paper. We do have work ongoing with other organometallics too, but that is something for the future.”

Reflecting on the project as a whole, Professor Smith concluded: “With the paper now published, we believe there are a number of ways in which this gel-based stabilization method might find applications. In research labs, the supply of gel-stabilised organolithiums could open up their use to a much wider range of researchers, as well as potentially providing these reagents with longer shelf-life, easier handling, and better safety profiles for all researchers. In industrial processes at production scale, the gels may offer significant potential in terms of the on-site storage of organolithium reagents. The ease by which the gel can be gently melted, and then transferred as a solution, may also allow transfer of these gel-loaded reagents through pre-existing, inert-atmosphere, liquid-handling systems. Finally, global industry requires the

shipping (and storage) of relatively large volumes of organolithiums. Shipping gel-stabilised organolithiums may have advantages in terms of removing the need to transport at low temperature, as well as mitigating the risk of liquid leakage and lowering the flammability hazard. In summary, the capacity of these simple low-cost gelator additives to stabilize reactive organometallics has the potential to transform the way in which chemists can engage with these types of reagents.”

*Matthew Farnok*

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## About the authors



Prof. D. Smith

**David Smith** is Professor of Chemistry at the University of York (UK), where he has pioneered the understanding and application of self-assembled supramolecular soft materials. He was educated at the University of Oxford, UK (BA 1993, DPhil 1996) and carried out postdoctoral research at ETH Zurich, Switzerland (1997–1998), before being appointed Lecturer in York in 1999, and promoted to a Professorship in 2006. He received the RSC Bob Hay Award (2010), the RSC Corday Morgan Prize (2012) and the RSC Tilden Prize (2022). A renowned educator, Dave received a Higher Education Academy National Teaching Fellowship (2014), was named ‘Most Inspiring Academic’ (2019) by York University Students Union, and received the SCI ‘Science for Society’ Award (2022). Dave works extensively towards equality, diversity and inclusion. He was shortlisted for the Gay Times Barbara Burford Award (2017) for work representing LGBTQ+ scientists, and *Chem. Eng. News* named him as one of their ‘Trailblazer LGBTQ+ Chemists’ (2022). He is well-known for his work aiming to make the prevailing culture in STEM more inclusive.



Prof. P. O'Brien

**Peter O'Brien** studied for a degree and PhD at the University of Cambridge (UK), carrying out a PhD under the supervision of Stuart Warren. After the award of his PhD in 1995, he moved to the University of York (UK) as a Royal Commission for the Exhibition of 1851 Research Fellow. In March 1996, he was appointed as a lecturer at York and was promoted to Professor in 2007. His research interests include asymmetric synthesis, organolithium methodology, the synthesis of saturated heterocycles,  $sp^3$ – $sp^2$  Suzuki–Miyaura cross-coupling and medicinal chemistry – and his efforts in these areas have been recognized by the award of the Royal Society of Chemistry Organic Stereochemistry Award in 2013 and the AstraZeneca, GlaxoSmith-

Kline, Pfizer & Syngenta prize for Process Chemistry Research in 2017. In 2019, he was awarded a Royal Society Industry Fellowship to work in collaboration with AstraZeneca on fragment-based drug discovery in 3-dimensions. Peter is also a passionate teacher and was awarded a Vice-Chancellor's Teaching Award in 2015 and the University's Teacher of the Year in the York University Student Union Excellence Awards in 2019.



Dr. P. Slavik

**Petr Slavik** was born and raised in Třebíč, Czech Republic. He obtained his PhD in organic chemistry from the University of Chemistry and Technology (UCT), Prague, Czech Republic, in 2017. After that, he joined Professor David K. Smith's group as a postdoctoral fellow supported by the Experientia Foundation. In York (UK), he studied supramolecular hydrogels and their use for catalysis and the stabilisation of highly reactive compounds. He currently works as a Head of Chemistry at the company Santiago Lab (Czech Republic), which focuses on custom synthesis and contract research in organic, bioorganic and medicinal chemistry.



Dr. B. Trowse

**Benjamin Trowse** obtained his MChem from Heriot-Watt University (UK) in 2018 working under the guidance of Dr. Graeme Barker on lithiation-trapping methodologies of unprotected benzyl tetrazoles. He then moved to the University of York (UK) where he completed his PhD under the supervision of Dr. Thomas Farmer, Prof. Peter O'Brien and Dr. James Sherwood on the use of green solvents in palladium cross-coupling and lithiation-trapping reactions. Following this, he joined Profs. David Smith and Peter O'Brien as a postdoctoral researcher working on the use of gels for the encapsulation of organometallic reagents. He is currently a researcher at Apex Molecular in Alderley Park (UK).