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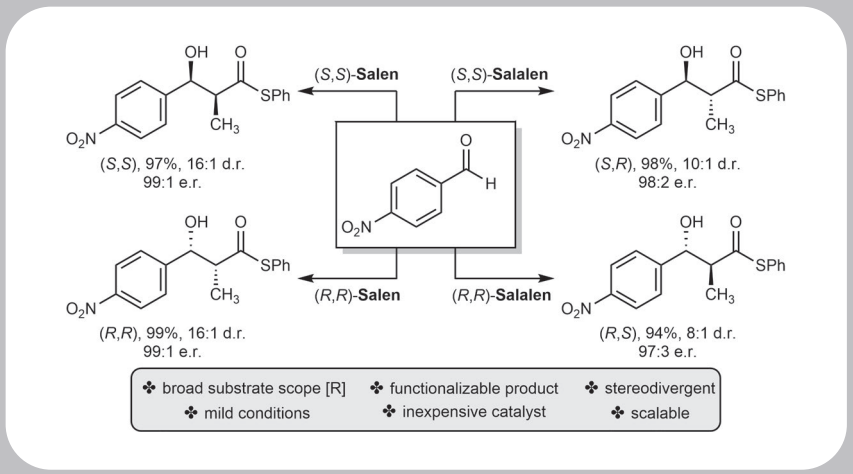
2023/07

# A Catalytic Enantioselective Stereodivergent Aldol Reaction

*Highlighted article by M. A. Rahman, T. Cellnik, B. B. Ahuja, L. Li, A. R. Healy*



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# Dear Readers,

As a beach enthusiast who does not particularly like crowds, I always spend my holidays off the peak season, which in the Mediterranean region means early in June and late in September. So here I am right now, enjoying crystal-clear turquoise waters, picturesque and mesmerizing beaches with white sand and rugged cliffs, combined with superb cuisine. Unfortunately, the weather has not been the best so far, but good enough to earn a bit of sunburn despite an extensive use of creams... In this breath-taking context of relaxation and natural beauty, I am even finding the time to write this brief editorial for a very hot July issue of SYNFORM! The kick-off article is a Young Career Focus on A. Masarwa (Israel), followed by a very original piece of research authored by P. O'Brien and D. K. Smith (UK) on the use of organogels as delivery vehicles for the stabilization of organolithium reagents. You will agree that the results are quite impressive and could lead to a change in the way organic chemists use to handle these highly reactive compounds in the lab. The third article focuses on a warhorse of organic chemistry – the stereoselective aldol reaction – that is still being studied with highly innovative outcomes, such as the one described in the work of A. R. Healy (UAE). Another classic of organic chemistry – which never seems to get old – is total synthesis of complex molecules, that is still the focus of exciting research, as demonstrated by N. K. Garg's (USA) work on lissodendoric acid A, recently published in *Science*, closes the issue.

Enjoy your reading!

## In this issue




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# Young Career Focus: Asst. Prof. Ahmad Masarwa (The Hebrew University of Jerusalem, Israel)

**Background and Purpose.** SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Asst. Prof. Ahmad Masarwa (The Hebrew University of Jerusalem, Israel).

## Biographical Sketch

*Asst. Prof. A. Masarwa*

**Ahmad Masarwa** was born and raised in Taibe, Israel, and later moved to Haifa to pursue his undergraduate studies in chemistry at the Technion-Israel Institute of Technology, which he completed in 2005. He then pursued his M.Sc. and Ph.D. studies with Prof. Ilan Marek at the Technion between 2006 and 2013, where his research focused on several areas, including kinetic resolution, sigmatropic rearrangements, carbometalation, and selective cleavage of small, strained materials to create all-carbon quaternary stereogenic centers. Ahmad's research work during his Ph.D. earned him several accolades, including the IUPAC-SOLVAY International Award for Young Chemists and the ICS-Israel Chemical Society Prize.

Following his Ph.D. studies, Ahmad joined the Department of Chemistry at the University of California, Berkeley (USA) in 2013 as a postdoctoral scholar under the supervision of Prof. Richmond Sarpong, where he worked on metal-catalyzed selective C–C/C–H bond activations of carvone-derived pinene scaffolds. This work aimed to create enantiopure natural product cores, including those found in phomactin A and suaveolindol, as well as anticancer compounds in the taxoid family. Ahmad completed his postdoctoral studies in October 2015.

In July 2016, Ahmad Masarwa started his tenure-track faculty position as an Assistant Professor (Senior Lecturer) at The Institute of Chemistry of the Hebrew University of Jerusalem (Israel), where he was appointed as The Azrieli Early Career fellow. Ahmad is a recipient of the 2023 Thieme Chemistry Journals Award. His research interests lie within the field of synthetic organic chemistry.

## INTERVIEW

**SYNFORM** *What is the focus of your current research activity?*

**Asst. Prof. A. Masarwa** My current research includes the development of new methodologies for the synthesis and applications of new classes of phosphonium salts and organoborons.[1–11] Accordingly, my group is actively engaged in pursuing innovative solutions to the stereoselective synthesis of architecturally complex molecules through the discovery of a new reactivity for novel chemical species, mainly phosphonium salts and polyborylated compounds. The identification and investigation of transformative mechanisms, and the development of new chemo- and stereoselective strategies in synthesis, is the principal driving force for my research. The program includes applying these new strategies for the synthesis of bioactive natural product cores. Selected specific examples are given below.

***(1) Polyborylated compounds:*** For the chemistry of polyborylated compounds, we have been aiming to discover new reactivity of these poly-metalated-like species.[1–3] For example, in our recent work, we developed breakthroughs in the design, reactivity, and transformation of the *gem*-bismetalated carbon-centered radical.[4–6] Our approach resulted in a gem-metalated carbon-centered radical species, which is considered a new concept. This resulting radical chemistry represents a new methodology that has the potential to be utilized for the multi-functionalization of natural products and even bioactive molecules.[5,6] Moreover, we reported a novel stereoselective desymmetrization of *gem*-diborylalkanes by 'trifluorination' which provides chiral *gem*-diborylalkanes bearing a trifluoroborate group.[7–10] Furthermore, we recently reported the stereoselective cycloaddition reactions of *gem*-diborylalkenes. In this study, we developed a method that addresses the long-standing challenge of regio- and stereoselective Diels–Alder cycloadditions with poly-alkenylboranes.[8]



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The products of these reactions enable the formal synthesis of polyborylated cycloadducts, particularly the 1,1,2-tri- and 1,1,3,4-tetraborylcyclic adduct, which would be difficult to accomplish with the existing strategies. In addition, the reaction offers the stereodivergent synthesis of norbornenes by using a diastereoselective trifluorination reaction. We demonstrated the use of the *gem*-diborylalkenes as ketene equivalents in [4+2] cycloadditions. Additionally, for the first time, we utilized *gem*-diborylnorbornene in the synthesis of *gem*-diboryl-based polymers through ROMP.[8] These polymers underwent successful postpolymerization modifications to access new polymers, which also demonstrates the potential diversity of the main chain replacement (Figure 1A).[8]

***(2) Functionalization of the C–P bond:*** Here, we developed a straightforward method to access a variety of benzhydrylamines, benzhydrylthioethers, and triarylmethanes from commercially available arenes and aldehydes through direct sequential C–H/C–P bond functionalization. In this study, we discovered unprecedented reactivity of the C–P bond.[11] The setup is simple and can be carried out in a (transition-) metal-free manner. This way, benzhydrylamine, benzhydrylthioether, and triarylmethane structural motifs, which are featured in many pharmaceuticals and agrochemicals, are readily accessed. These include the synthesis of two anticancer agents from simple materials in only two to three steps. Additionally, we developed a protocol for the late-stage functionalization of bioactive drugs using benzhydrylphosphonium salts. This protocol should greatly simplify access to pharmaceutically relevant compounds, and further advance their use in a variety of new applications (Figure 1B).[11]

**SYNFORM** *When did you get interested in synthesis?*

**Asst. Prof. A. Masarwa** I became interested in synthesis during my undergraduate studies, specifically in the organic chemistry lab course. I was fascinated by the process of creating new compounds from simple starting materials, and I was drawn to the challenge of designing efficient and effective synthetic routes. As I continued my studies and gained more experience in the lab, my interest in synthesis only grew. I found myself constantly asking questions and exploring new techniques and strategies for creating complex molecules.

This interest was further fueled when I worked as a research assistant in Prof. Ilan Marek's group. Under his guidance, I was exposed to cutting-edge synthetic methodologies and had the opportunity to work on complex synthesis projects. It was an incredibly formative experience that solidified my interest in the field of synthesis and inspired me to continue pursuing it as a career. Today, I continue to be driven by the excitement and intellectual challenge of synthesis, and I look forward to exploring this fascinating field in the years to come.

**SYNFORM** *If you had not become a chemist, what other profession do you think you would have entered?*

**Asst. Prof. A. Masarwa** A chef! Although synthetic chemistry and culinary arts may seem like vastly different fields, they share some important similarities. Both require working with raw materials to create a final product, which can be a complex and intricate process.

Another similarity between these professions is the importance of precision and attention to detail. Synthetic chemists must carefully measure and mix chemicals to create the desired reaction, while chefs must use precise measurements and cooking techniques to achieve the perfect flavor and texture in their dishes. Both professions require a high level of skill and expertise, as well as a willingness to experiment and innovate.

Creativity is also an important aspect of both synthetic chemistry and culinary arts. In synthetic chemistry, chemists must find new ways to synthesize molecules that may have never existed before, while in cooking, chefs must develop innovative and unique flavor combinations that set their dishes apart. Both professions allow for a great deal of experimentation and creativity, which can be highly rewarding for those with a passion for their work.

**SYNFORM** *What is the most exciting aspect of your job, the one you like the most?*

**Asst. Prof. A. Masarwa** For me, the most exciting aspect of my job is the opportunity to supervise and invest in my team, and to watch as they grow and develop into successful researchers in the field of organic chemistry. As a mentor and teacher, I find it deeply rewarding to share my knowledge and experience with others, and to learn from my students as they develop their own skills and expertise. It's incredibly fulfilling to see my team members succeed, and to know that I played a part in helping them to achieve their goals. Ultimately, by investing in my team and helping them to reach their full potential, I believe that I am contributing to the future of organic chemistry and helping to develop the researchers of the next generation.

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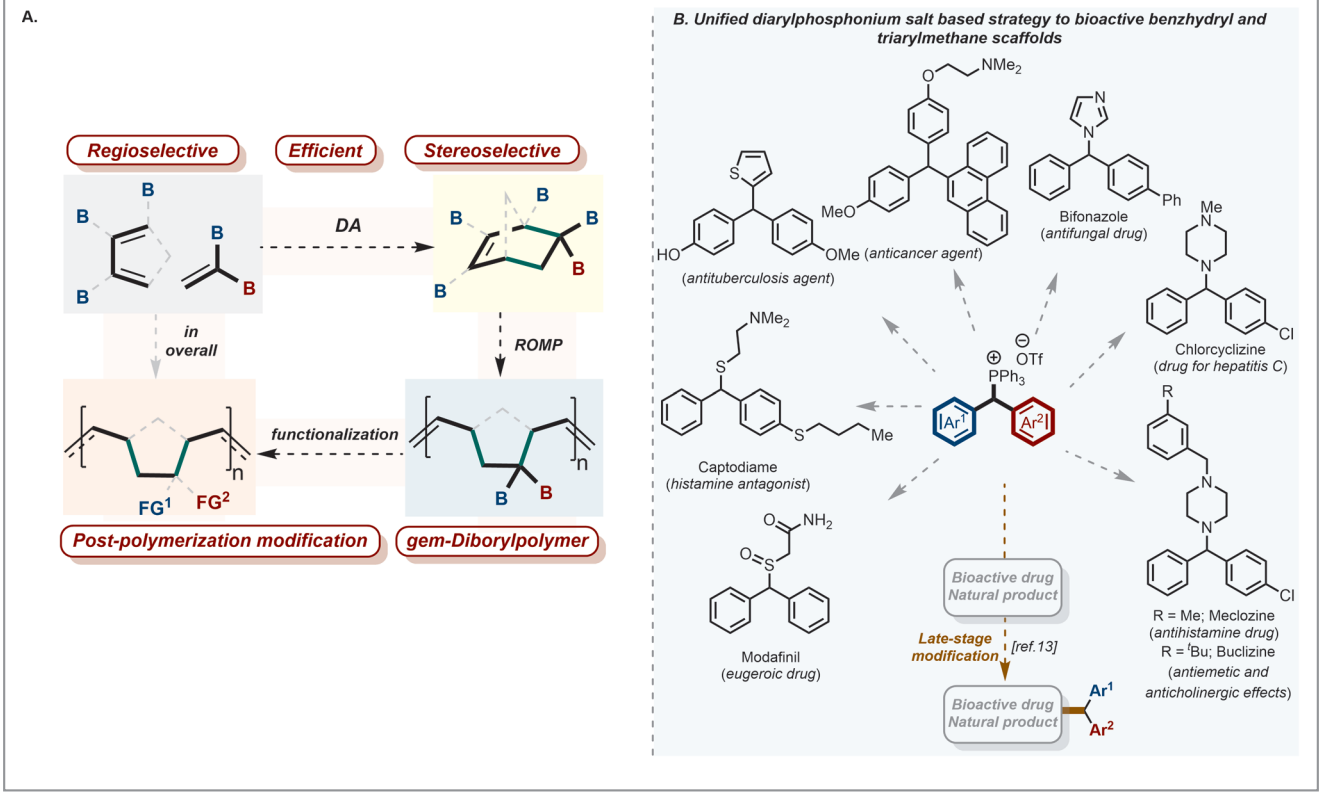
**SYNFORM** *Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?*

**Asst. Prof. A. Masarwa** Outside of the lab, I like to stay active and pursue a variety of hobbies and interests. One of my favorite ways to relax and unwind is by spending time with my cat, Simba. He's a great companion and always manages to put a smile on my face. I also enjoy watching movies, particularly comedies, as well as spending time on scientific trends and videos. Additionally, I find that going for walks is a great way to clear my mind and recharge my batteries, particularly after a long day in the lab. Overall, I believe that maintaining a healthy work–life balance is important for staying motivated and focused, and I try to pursue my hobbies and interests outside of work whenever possible.

## REFERENCES

(1) R. Nallagonda, K. Padala, A. Masarwa *Org. Biomol. Chem.* **2018**, *16*, 1050–1064.
(2) R. Nallagonda, N. Kumar, R. R. Reddy, I. Shioukhi, H. Sagi, A. Masarwa. A. *Synthesis and Reactivity of 1,1 and 1,2-Bisboronate Species, In Patai's Chemistry of Functional Groups*; John Wiley & Sons: Chichester, **2020**.
(3) K. N. Babu, F. Massarwe, R. Reddy, N. Eghbarieh, M. Jakob, A. Masarwa *Molecules*, **2020**, *25*, 959.
(4) N. Kumar, R. R. Reddy, N. Eghbarieh, A. Masarwa *Chem. Commun.* **2020**, *56*, 13–25.
(5) N. Kumar, N. Eghbarieh, T. Stein, A. I. Shames, A. Masarwa *Chem. Eur. J.* **2020**, *26*, 5360–5364.
(6) A. Nagaraju, T. Saiaede, N. Eghbarieh, A. Masarwa *Chem. Eur. J.* **2022**, *28*, e202202646.
(7) N. Kumar, R. R. Reddy, A. Masarwa *Chem. Eur. J.* **2019**, *25*, 8008–8012.
(8) N. Eghbarieh, N. Hanania, A. Zamir, M. Nassir, T. Stein, A. Masarwa *J. Am. Chem. Soc.* **2021**, *143*, 6211–6220.




**Scheme 1** (A) General scheme of the Diels–Alder reaction of polyboronated compounds with dienes, and the application of their cycloaddition product in the ROMP reaction to generate the *gem*-diborylpolymers. (B) A phosphonium salt based strategy for obtaining bioactive benzhydryl and triarylmethane scaffolds.

(9) N. Hanania, M. Nassir, N. Eghbarieh, A. Masarwa
*Chem. Eur. J.* **2022**, *28*, e202202748.
(10) N. Eghbarieh, A. Masarwa *Nat. Synth.* **2023**, *2*, 391–392.
(11) K. N. Babu, F. Massarwe, I. Shioukhi, A. Masarwa
*Angew. Chem. Int. Ed.* **2021**, *60*, 26199–26209.



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# 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,[1] 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 ($C_{36}H_{74}$), which had previously been explored as a gelator for organic solvents by Professor Richard Weiss and co-workers.[2]"

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

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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.[3] 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!"

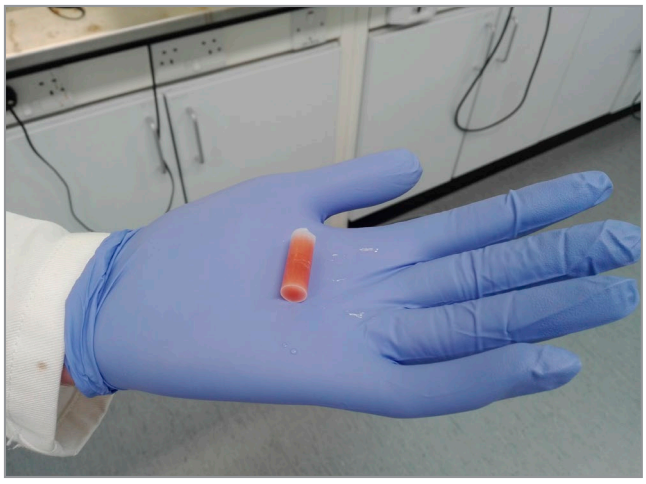


**Figure 1** A hand-held PhLi gel cylinder ready for a reaction!

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 α-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-

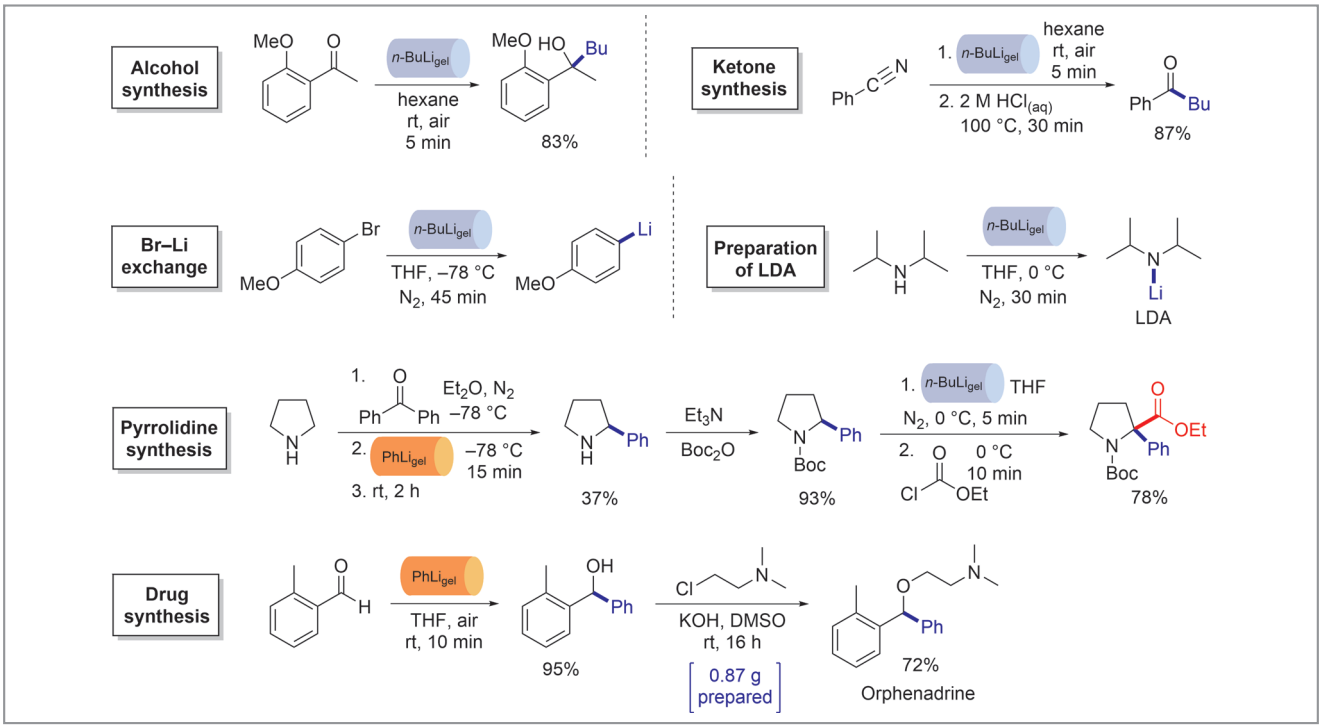
cularly satisfying application. Finally, we demonstrated that the methodology could be scaled up to the gram-scale, and performed a synthesis of the anticholinergic and antihistamine drug Orphenadrine. Pleasingly, the gel blocks were trivial to use across these different synthetic approaches, without 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.[4]

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*.[5] 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."

## REFERENCES

(1) C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy, E. Hevia *Angew. Chem. Int. Ed.* **2014**, *53*, 5969–5973.
(2) D. J. Abdallah, R. G. Weiss *Langmuir* **2000**, *16*, 352–355.
(3) A. C. Sather, H. G. Lee, J. R. Colombe, A. Zhang, S. L. Buchwald *Nature* **2015**, *524*, 208–211.
(4) D. K. Smith, P. O'Brien, P. Slavik Patent WO 2021/214453 A1.
(5) P. Slavik, P. O'Brien, D. Smith *ChemRxiv* **2022**, preprint; DOI: 10.26434/chemrxiv-2022-q2txr.

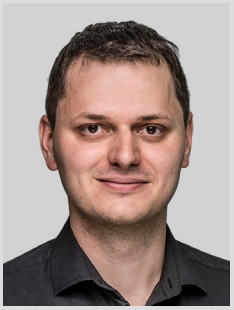
## About the authors

*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, GlaxoSmithKline, 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).

# A Catalytic Enantioselective Stereodivergent Aldol Reaction

*Sci. Adv.* **2023**, *9*, eadg8776

The aldol reaction – which is the C–C bond-forming reaction at the α-carbon of a carbonyl-derived enolate with an aldehyde or ketone functionality of another molecule, under basic or acidic conditions, to afford a β-hydroxy-carbonyl derivative – is an essential transformation in organic chemistry, and in particular in polyketide synthesis. After its independent discovery by the Russian chemist/composer Alexander Borodin (1869) and the Alsatian-French chemist Charles-Adolphe Wurtz (1872), the aldol reaction has become the subject of countless studies and developments, especially concerning its stereoselective aspects and applications to the synthesis of bioactive and natural compounds. The lab of Professor Alan Healy at New York University Abu Dhabi (NYUAD, UAE) is interested in developing an efficient and general approach for polyketide synthesis, with the ultimate goal of automating this approach. "Despite the storied history of the aldol reaction, we were surprised to find a dearth of general and readily usable catalytic aldol methods," remarked Professor Healy. He continued: "Several powerful methods exist, but these often require expensive or hard-to-access catalysts. Furthermore, different methods are often required depending on the aldehyde substrate or desired stereoisomer of the product."

Professor Healy's lab was specifically interested in developing a practical and synthetically useful stereodivergent aldol reaction, one in which all four possible stereoisomers of the aldol product could be obtained from the same reactants by just varying the catalyst. Professor Healy explained: "We were inspired by previous research demonstrating the utility of malonic acid half thioesters (MAHTs) in mild C–C bond-forming reactions. The very mild conditions that are required to activate the latent pronucleophilic MAHTs had been shown to be compatible with a wide range of reactive functional groups."

"We sought to develop a decarboxylative aldol that could be achieved using an inexpensive and easily accessible catalyst," said Professor Healy, who continued: "We decided to focus on the salen ligands, as these are readily synthesized in one step by condensation of an inexpensive chiral diamine (~$3/gram, Ambeed) and a salicaldehyde derivative. We found that a methoxy-substituted salen ligand in the presence of titanium(IV) isopropoxide was a highly selective catalyst for the *syn*-aldol reaction. After further ligand screening, we found that the partially reduced salalen ligand provided the *anti*-aldol as the major product. As both enantiomers of the chiral diamine are commercially available, we were able to access all four stereoisomers of the aldol product from the same reactants by just varying the catalyst."

An extensive substrate survey (35 examples in total) was conducted, including aromatic, heteroaromatic, aliphatic and unsaturated aldehydes, and it was found that the method was compatible with substrates that are not always compatible with traditional enolate-based aldol chemistry, including enolizable aldehydes, and aldehydes containing free hydroxyl, nitrile and ketone functional groups. Professor Healy pointed out: "Importantly, no side products were observed during this reaction, and as a result sluggish reactants can be pushed to completion by increasing the reaction time, concentration and/or catalyst loading."

An abiding goal of this work was for the lab to develop a method that was very practical and would be an enabling tool for research groups around the world with varying resources. "To demonstrate its utility, we carried out the reaction on 50 mmol scale, open to air, using just 2.5 mol% catalyst, and we were able to achieve full conversion after 24 hours," explained Professor Healy. The group found that in the majority of cases, simple filtration of the reaction mixture through celite and concentration gave the product in high purity. An additional benefit of using MAHTs as the pronucleophile was that the resulting aldol products contain a highly synthetically tractable thioester functionality. Professor Healy said: "We demonstrated that the thioester can be converted into a range of carboxylic acid derivatives under mild conditions without requiring any protecting group chemistry. Furthermore, thioesters can be converted directly into the aldehyde or ketone using Pd-mediated transformations."

"We are very excited about the future of this approach," said Professor Healy, who concluded: "Our goal is to develop a suite of mild, stereodivergent, carbon–carbon bond-forming reactions and apply these methods in the automated synthesis of chiral building blocks and polyketides."



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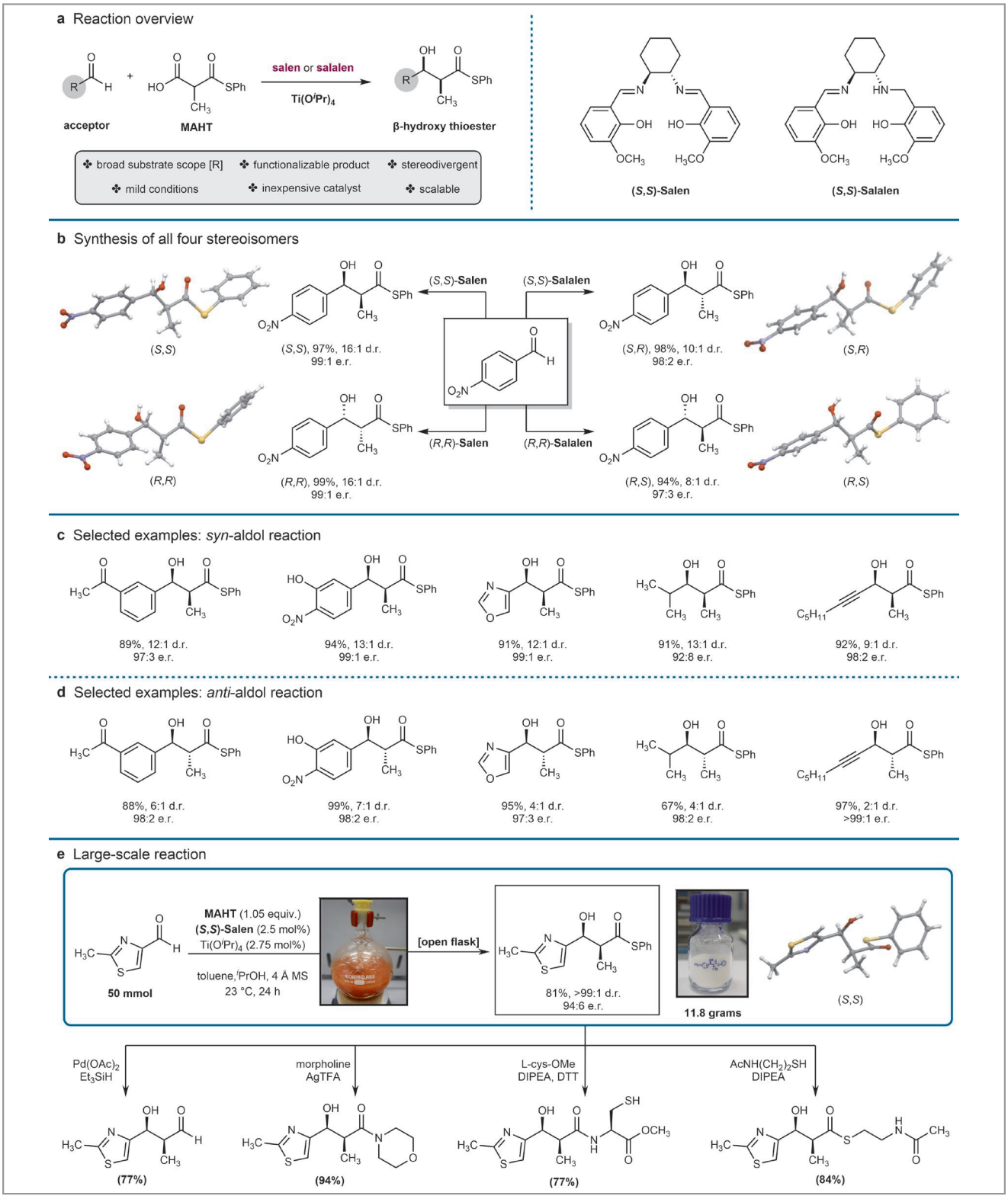


**Scheme 1** A catalytic stereodivergent aldol reaction. Selected examples illustrating the scope and application of the method.



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## About the authors

*Prof. A. Healy*

**Alan Healy** was born in Co. Clare, Ireland. He completed his undergraduate studies in medicinal chemistry at Trinity College Dublin (TCD, Ireland) followed by an MSc in biomedical science from the University of Edinburgh (UK). He obtained a PhD from St Andrews University (UK) in 2014 under the guidance of Nicholas J. Westwood, and was a Charles H. Revson Senior Fellow with Seth B. Herzon and Jason M. Crawford at Yale University (USA) from 2015–2018. He began his independent career at New York University Abu Dhabi (NYUAD, UAE) in 2019 where he is currently an Assistant Professor in the chemistry program. His research group focuses on the development of novel methods to accelerate the discovery and study of dark matter metabolites.

*Dr. T. Cellnik*

**Torsten Cellnik** was born in Remscheid, Germany. He obtained his BSc in 2013 followed by his MSc in 2015 from Bergische Universität Wuppertal, Germany. Afterwards he stayed at Bergische Universität Wuppertal and received his PhD under the supervision of Professor Stefan Kirsch (2019). In 2019 he joined the Healy group at New York University Abu Dhabi (NYUAD, UAE) as a research associate. Currently his work is focused on the development of synthetic methods and their integration into automation.

*Dr. M. A. Rahman*

**Md Ataur Rahman** was born in the state of Bihar, India. He obtained a BSc and MSc degree in chemistry from Jamia Millia Islamia, New Delhi, India (2008). He received a PhD in 2015 under the supervision of Dr. J. S. Yadav (FNA, Director of IICT) at the Indian Institute of Chemical Technology, Hyderabad, India through the Academy of Scientific and Innovative Research (AcSIR). He was as a postdoctoral research fellow with Professor Andrew G. Myers at Harvard University, USA from 2016–2019. Since 2019 he has been working as a research associate in the Healy research group at New York University Abu Dhabi (NYUAD, UAE).

*Dr. B. B. Ahuja*

**Brij Bhushan Ahuja** was born in Haryana, India. He received his PhD (2015) with Dr. A. Sudalai at National Chemical Laboratory, Pune, India. After graduation, he joined Professor Arkadi Vigalok's group at Tel Aviv University (Israel), where he worked on the development of new chemo- and electrochemical sensors for the detection of nitric oxide (NO), a cell signaling molecule. In 2019, he joined the Healy group at New York University Abu Dhabi (NYUAD, UAE). His research interests include the synthesis of bioactive natural products, the development of new methodologies, drug discovery, conjugated polymer synthesis, and supramolecular chemistry.

*Prof. L. Li*

**Liang Li** is a highly accomplished researcher in the field of materials science, with a PhD from Bayreuth University in Germany. He has held research positions at King Abdullah University of Science and Technology (KAUST, Saudi Arabia) and New York University Abu Dhabi (NYUAD, UAE). In 2021, he joined Sorbonne University Abu Dhabi (SUAD, UAE) as an Assistant Professor, where he continues to pursue his research interests in quantum technology, maximum entropy method, smart materials, and crystallography. Additionally, Dr. Liang Li maintains a Visiting Professor position at NYUAD, further contributing to the advancement of the field.

# Total Synthesis of Lissodendoric Acid A via Stereospecific Trapping of a Strained Cyclic Allene

*Science* **2023**, *379*, 261–265

Over the last decades, it has become apparent that a key priority in the realms of medicinal chemistry and drug discovery was the transition from predominantly aromatic 2D drug candidates (the so called 'flatlands') to more complex 3D structures, in order to access novel chemical spaces and – consequently – expanding the structural range of drug candidates. In this context, highly strained and reactive cyclic compounds are increasingly used for accessing complex non-aromatic cyclic structures in stereo- and regio-controlled manner.

Very much influenced by the pharmaceutical community and desires to 'escape the flatlands', the laboratory of Professor Neil Garg at UCLA (USA) became interested in non-aromatic strained heterocyclic compounds. "One such scaffold is the strained cyclic allene. This is an interesting scaffold because it had been understudied since its initial discovery in the 1960's relative to benzyne. The group saw a great opportunity in being able to make nitrogen-containing cyclic allenes," said Professor Garg, adding: "When I began my career at UCLA, the laboratory was interested in developing strained derivatives of important heterocycles. Early on in my career, we focused on aromatic heterocyclic arynes, like 'indolynes' and 'pyridynes'. This led to several total syntheses and helped establish the synthetic utility of these fleeting unconventional intermediates."

The laboratory ultimately found that they could make azacyclic allenes and employ them in cycloaddition reactions (reported in *Nat. Chem.* **2018**, *10*, 953–960). "Our initial study was very fundamental and provided insight into how substituents control regioselectivity, as cyclic allenes have two doubles that could potentially react," explained Professor Garg.

Along with their interest in methodology, the laboratory was simultaneously interested in evaluating azacyclic allenes in total synthesis. "Often, the pursuit of natural product total synthesis reveals gaps in the methodology and drives innovation," remarked Professor Garg, who continued: "Such is the case as we began to pursue the total synthesis of manzamine alkaloids. We briefly dabbled with a complex natural product called acantholactone, but then one day in 2017, a new manzamine called lissodendoric acid A was reported in the literature. This target made it clear that our azacyclic allene methodology was not perfect for synthetic applications."

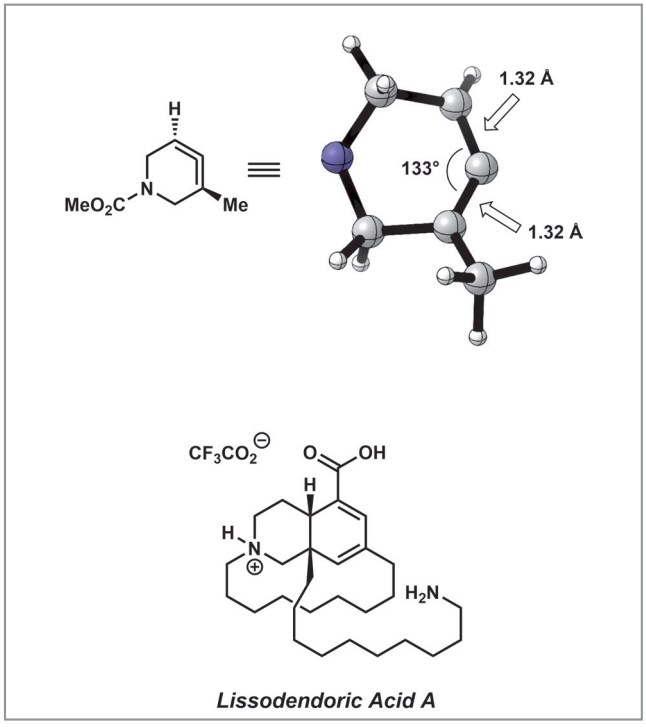



**Figure 1** The strained azacyclic allene, its geometry-optimized structure and the target lissodendoric acid A.

More specifically, the group realized that the regioselectivity needed for the total synthesis was opposite to what was developed in their methodology studies. Professor Garg explained: "Specifically, if one has an alkyl group directly on a cyclic allene double bond, typically cycloaddition (with furan and the like) occurred at the alkene distal to the alkyl substituent. Our total synthesis of lissodendoric acid A would require the opposite sense of selectivity."

After extensive experimentation, the group found that using pyrones as Diels–Alder partners allowed them to obtain the desired regioselectivity. "We then had a greater problem in having to control absolute stereochemistry," said Professor Garg. He went on: "What we found, as reported in our recent study, is that we could make a cyclic allene precursor in enantioenriched fashion. To do this, we took advantage of robust CBS-reduction chemistry and coupled it to a general

  • Published online: June 16, 2023 • DOI: 10.1055/s-0040-1720600

approach discovered by West and co-workers (*Org. Lett.* **2019**, *21*, 6231–6234). Then, in the key step, we found we could transfer stereochemistry from the cyclic allene precursor, to the cyclic allene, then onto the cycloadduct with a quaternary stereocenter. This allowed us to complete a very short total synthesis, thus establishing that strained cyclic allenes can be used to build very complex structures, including those with multiple stereocenters."

Professor Garg paid tribute to his co-authors, saying: "A tremendous amount of intellectual and experimental effort went into this study by the remarkable lissodendoric acid A team at UCLA: Francesca Ippoliti, Nathan Adamson, Laura Wonilowicz, Daniel Nasrallah, Evan Darzi, and Joyann Donaldson. Our first-generation total synthesis of the racemic natural product was lengthy. It is incredibly telling that the team had the drive and determination to develop the short and enantiospecific route that was ultimately published."

Professor Garg concluded: "The important take aways from this study include the importance of teamwork and collaboration, innovation, and curiosity. Of course, we hope our total synthesis provides a roadmap to derivatives of lissodendoric acid A, while also enabling the further use of strained cyclic allenes (and related intermediates) in the synthesis of complex structures."

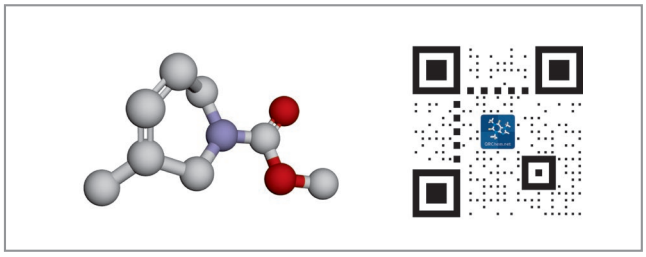
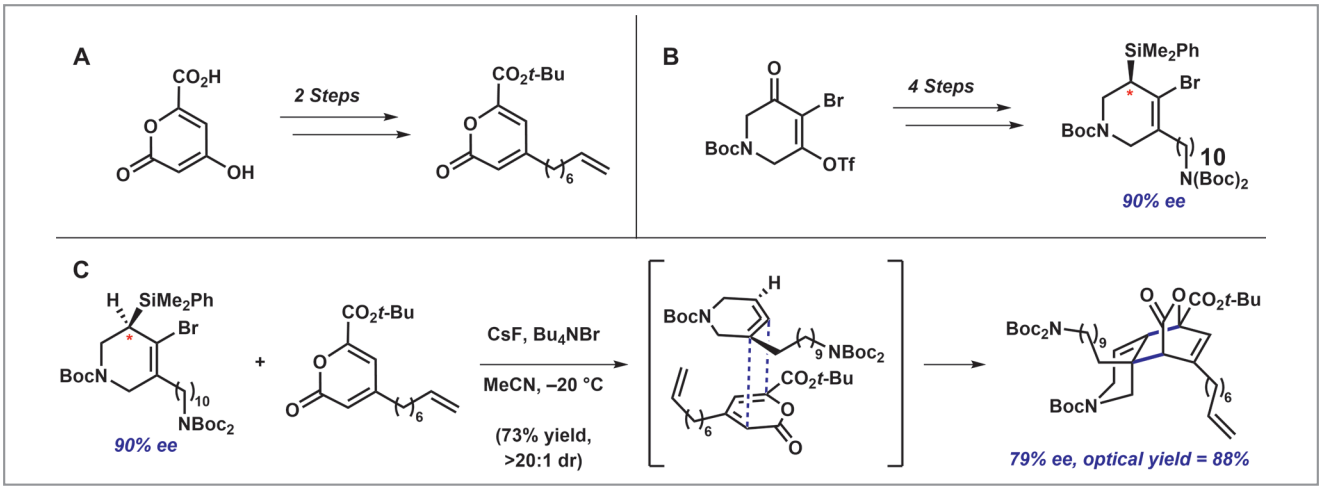
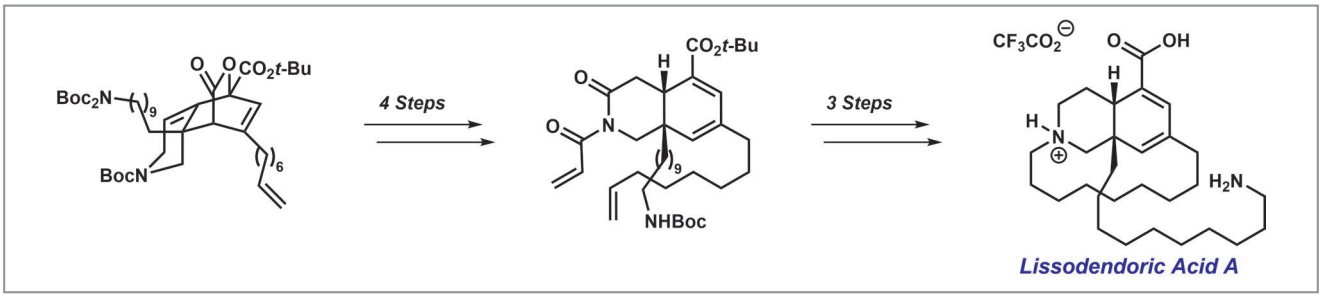


**Figure 2** QR Chem code for the strained azacyclic allene.

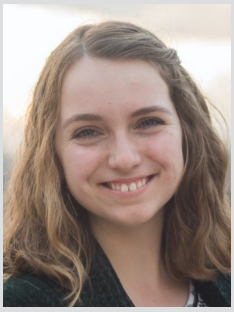



**Scheme 1** (A) Synthesis of the pyrone dienophile; (B) Enantioselective route to the silyltriflate cyclic azacyclic allene precursor; (C) Stereo and regio-controlled Diels-Alder cycloaddition of the strained cyclic allene with the pyrone dienophile.




**Scheme 2** Completion of the total synthesis of lissodendoric acid A.

## About the authors

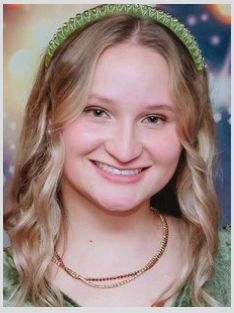


*Dr. F. Ippoliti*

**Francesca Ippoliti** was born and raised in St. Paul, MN (USA). In 2017, she received her B.S. in chemistry from the University of St. Thomas (USA), where she carried out research under the direction of Professor Lisa E. Prevette. In 2022, she received her Ph.D. in chemistry from the University of California, Los Angeles (USA), where her graduate research focused on total synthesis in the laboratory of Professor Neil K. Garg. She is currently a postdoctoral researcher at the University of Wisconsin–Madison (USA), where she is conducting research on photochemical reactions in the laboratory of Professor Tehshik P. Yoon.

*Dr. N. Adamson*

**Nathan Adamson** was born in Greenville, SC (USA) and obtained his B.S. in biochemistry from the College of Charleston (USA) in 2015. He subsequently received his Ph.D. from Duke University (USA) under the supervision of Prof. Steven Malcolmson in 2020. From 2020–2022, Nathan was a Ruth L. Kirschstein postdoctoral fellow in Prof. Neil Garg's group at UCLA (USA). He is currently a scientist in the Discovery Chemistry group at Genentech (USA).



*L. Wonilowicz*

**Laura Wonilowicz** was born and raised in Westminster, MD (USA). In 2019, she received her B.S. in biochemistry and a B.A. in chemistry from Virginia Tech (USA), where she carried out research under the direction of Professor Webster L. Santos. She began her graduate studies at the University of California, Los Angeles (USA), where she is currently a fourth-year graduate student in Professor Neil K. Garg's laboratory. Her studies primarily focus on total synthesis and synthetic methods using strained cyclic allenes.

*Prof. D. Nasrallah*

**Daniel Nasrallah** was born and raised in Winston-Salem, NC (USA). In 2014, he received his B.S. in chemistry with a concentration in research from the University of North Carolina, Greensboro (USA), where he carried out research under the direction of Professor Mitchell P. Croatt. In 2020, he received his Ph.D. in chemistry from the University of Michigan (USA), where he carried out research under the direction of Professor Corinna S. Schindler. Currently, he is the Donald J. Cram Assistant Adjunct Professor of Chemistry at the University of California, Los Angeles (USA), where he teaches organic chemistry laboratory courses and conducts research in Professor Neil K. Garg's laboratory.

*Dr. E. Darzi*

**Evan Darzi** received his B.S. in medicinal biochemistry from Arizona State University in Tempe, AZ (USA), where he performed undergraduate research under Professor Edward Skibo on the synthesis of extended amidines. He received his Ph.D. from the University of Oregon in Eugene, OR (USA), under the guidance of Professor Ramesh Jasti. There he developed syntheses of highly strained [n]cycloparaphenylenes and other 'nanohoops'. He completed his NIH postdoctoral fellowship in Professor Neil K. Garg's laboratory at the University of California, Los Angeles (USA). His postdoctoral studies are focused on the development of strained intermediates in synthetic methodology. Currently, he is the co-founder and CEO of ElecrtraTect, Inc. a spinout company from Professor Neil Garg's laboratory focused on the development of a marijuana breathalyzer.

*Dr. J. Donaldson*

**Joyann Donaldson** was born and raised in Southern California (USA). She received her B.S. in chemistry from Cal Poly Pomona (USA) in 2014. In 2014, she began her doctoral studies at the University of California, Los Angeles (USA) in Professor Neil K. Garg's laboratory where her research primarily focused on harnessing the reactivity of strained intermediates for the construction of heterocycles.

>>



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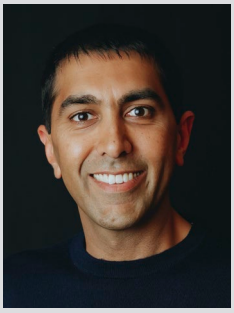
In 2019, she graduated and moved to San Diego, CA (USA) where she currently works as a medicinal chemist at Pfizer.



*Prof. N. Garg*

**Neil Garg** is the Distinguished Kenneth N. Trueblood Professor of Chemistry at the University of California, Los Angeles (USA). His laboratory develops new synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.



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