

A Minisci Approach to C–H Borylation of Azines

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Borylated (hetero-)aromatics are fundamental building blocks in modern synthetic chemistry. They are used as coupling partners in Suzuki–Miyaura cross-coupling reactions, which account for ~30% of C–C bond formations in drug manufacture,¹ as well as many other processes, such as oxidation, Chan–Lam amination and fluorination.²

In general, C–B bonds in borylated (hetero-)aromatic compounds are constructed using the corresponding (hetero-) aryl halides via metalation–borylation or by transition-metal-catalysed borylations, among which the Miyaura borylation³ is the archetypical example (Figure 1). Both approaches require pre-functionalisation of the aromatic core in a separate synthetic step, which sometimes can be problematic.

“Transforming an aromatic C–H bond into a C–B bond has so far been the ‘playground’ for transition-metal-catalysed C–H activation, mostly with Ir or Rh catalysts.⁴ This approach has had a profound impact in synthetic chemistry and it is frequently adopted both in academia and industry,” said Professor Daniele Leonori from the University of Manchester (UK).

“However, the generality and power of this approach are somewhat limited when azines are used as starting materials,” explained Professor Leonori, who added: “This is because C–H activation responds mostly to steric factors (unless of course directing groups are present) and always leads to borylation far from the azine N-atom. Furthermore, borylated azines, where the boron is next to the N-atom, are unstable under the C–H activation conditions.⁵”

According to Professor Leonori, an additional challenge is that, while α -N borylated azines (e.g. C2-borylated pyridines) can be made by other approaches (e.g. azine halogenation followed by Miyaura borylation), they are difficult to handle due to a very fast protodeboronation reaction. This synthetic challenge has been recognised in the literature and it is frequently referred to as the ‘2-pyridyl problem’.⁶

Professor Leonori said: “I learned about the difficulties in making and handling 2-borylated pyridines and other azines while I was working with Prof. Varinder Aggarwal in Bristol (UK). Indeed, one of the projects I contributed to was aimed at the development of novel transition-metal-free cross-couplings between C2-lithiated pyridines and alkyl boronic esters.⁷ This is also when I met Dr. Josep Lloveria, the industrial co-author in our *Nature* paper, who was the main researcher working on the topic and subsequently moved to Janssen.”

Professor Leonori recalls that when he started his independent career at Manchester (UK), he focused on radical chemistry where one of the most important and applied reactivities is the addition of alkyl radicals to azines, which is now referred to as the ‘Minisci reaction’.⁸ “This process is a great way of forming C–C bonds at α -N positions on N-heteroaromatics and, crucially, it targets C–H bonds sometimes difficult to reach with C–H activation,” explained Professor Leonori. He continued: “Furthermore, while our initial work was leading us towards the field of H-atom transfer (HAT),⁹ I became very familiar with the great work of Professor Brian Roberts (University College London, UK), who – between the 1960s and the 1980s – reported many fundamental studies on the formation of boryl radicals from simple amine-boranes.¹⁰ While these reactive intermediates have found limited application in synthesis, we were very interested by the underlying conclusions of Roberts’ studies demonstrating how boryl radicals are very nucleophilic species, more than a standard carbon radical. This immediately led us to recognize that if we were able to engage them in Minisci-style reactivity, then we would have developed a novel approach to access borylated azines with C–H selectivity orthogonal to the one observed in transition-metal catalysis (Scheme 1). We were also very interested by an additional aspect related to aromatic C–B bond formation under radical settings: while the addition of aryl

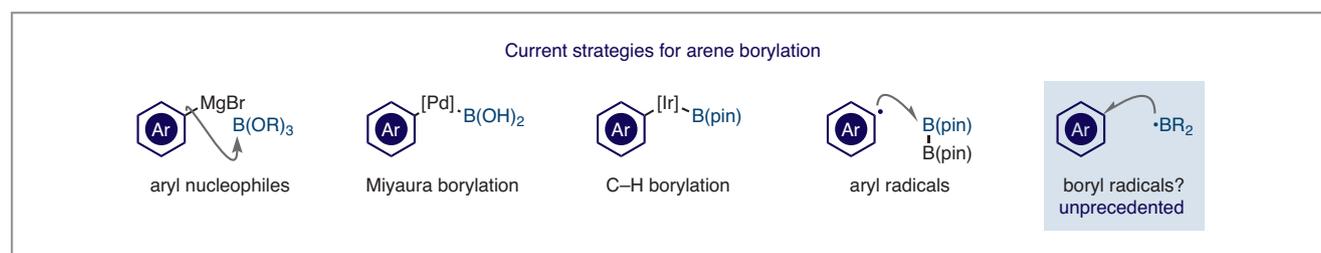
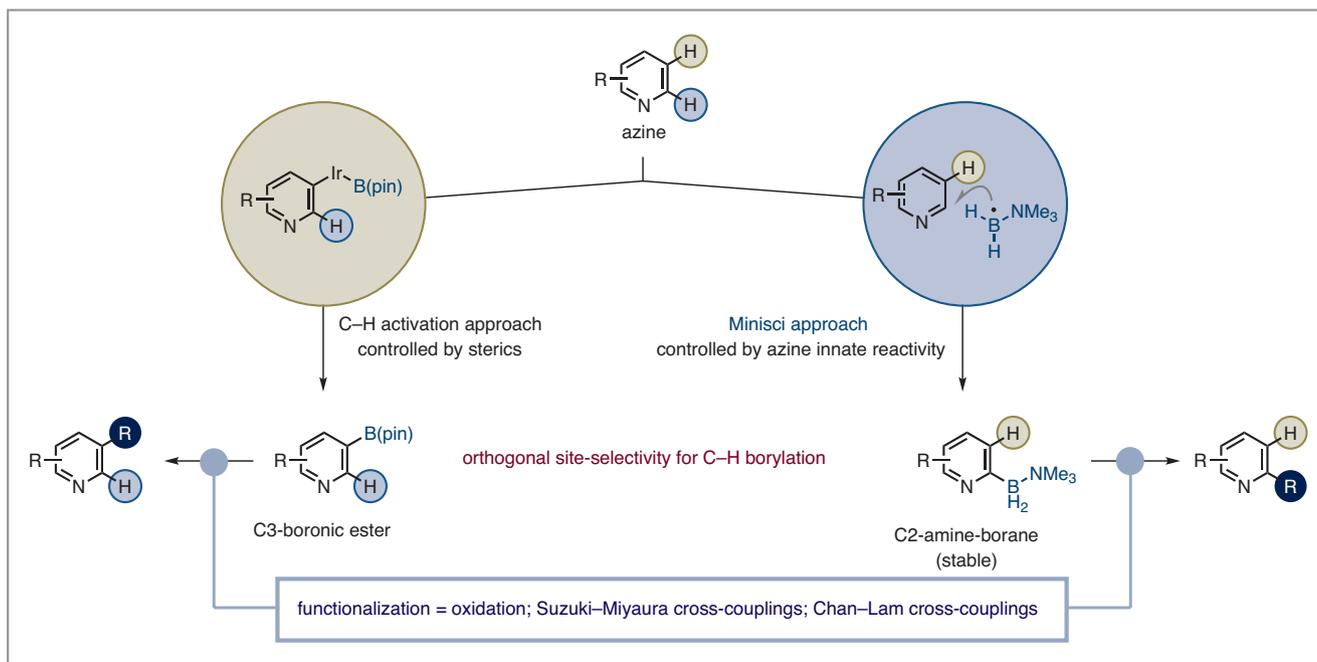


Figure 1 Approaches towards aromatic borylation



Scheme 1 An overview of the Minisci-style azine borylation using boryl radicals and its orthogonality with respect to C-H activation-based approaches

radicals to boron acceptors is well established, the other way around – the addition of boryl radicals to aromatics – is still very rare.”

Professor Leonori acknowledged that he was very fortunate to discuss this novel approach for azine borylation with Dr. Ji Hye Kim, while she was a Marie Curie Fellow in his group. “Dr. Kim immediately decided to tackle this challenge and very quickly showed me that it was feasible and that the reaction products were remarkably stable crystalline solids (even suitable for X-ray analysis),” explained Professor Leonori. He continued: “These initial results made us believe this method could have the potential to address the two key problems discussed above: (1) it could provide a mechanistically distinct tactic for azine C–H borylation targeting currently elusive positions, while (2) giving stable materials for further application in cross-coupling technology. We also became very excited about this reactivity upon examining the computational results obtained by Prof. Nadeem S. Sheikh, demonstrating how Minisci borylation is actually more facile than standard Minisci alkylation.”

To make sure that the group would address industrially relevant challenges, Professor Leonori reached out to Dr. Josep Llaveria at Janssen, informing him about the group’s initial results and discussing the possibility of starting a collaboration on this topic. “This initial discussion led to a very fruitful

collaboration; Dr. Llaveria was very involved in every aspect of the project and was also able to share with us many azine building blocks important to medicinal chemistry programs,” remarked Professor Leonori. He continued: “This allowed us to benchmark our Minisci-style borylation across a broad range of systems for which limited (if any) applications in C–H borylation existed.”

Upon evaluation of the synthetic versatility of the process, the group realised it was crucial to test the ability of these novel borylated materials in subsequent transformations. “This was a very exciting avenue for my group as the reactivity of azine–amine–boranes had never been evaluated before; in fact, these compounds had never even been made,” said Professor Leonori. He remarked: “This part of the project proved a challenging task, but the combined efforts of Dr. Kim, together with final-year PhD student Timothée Constantin and postdoctoral researcher Dr. Marco Simonetti, who has a lot of experience with palladium catalysis, demonstrated how classical reactivity associated with aryl organoborons, like oxidation to phenol, Suzuki–Miyaura cross-coupling with aryl halides and Chan–Lam amination with amine and alcohol partners, could all be achieved. These proof-of-concept results provide support to the idea that these novel borylated materials might be considered viable coupling partners for future applications.”

“The results described in our *Nature* paper have effectively opened a novel research line for my research group and we are now actively pushing the boundaries of boryl radical reactivity in different settings, as well as exploring the profile of the amine-borane products under transition-metal catalysis,” said Professor Leonori, who concluded: “As a final comment, I would like to express all my gratitude to my co-workers for their passionate and hard work on this project, during such a challenging time.”

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About the authors



Dr. J. H. Kim

Ji Hye Kim was born in Jinhae, South Korea and obtained her BSc and MSc degrees at Kyung Hee University (S. Korea). After short internship stays in the group of Prof. Sodeoka at RIKEN (Japan) and in the group of Prof. List at the Max-Planck-Institut für Kohlenforschung (Germany), which were sponsored by the National Research Foundation of Korea, she continued with her PhD studies under the supervision of Prof. List. Afterwards, Ji Hye conducted her postdoctoral research with Prof. Hyster at Princeton University (USA) and Prof. Leonori at the University of Manchester (UK).



T. Constantin

Timothée Constantin received his BSc (2016) and MSc (2018) in chemistry from Ecole Nationale Supérieure de Chimie de Montpellier (France). He then moved to the University of Manchester (UK) to pursue a PhD under the supervision of Prof. Daniele Leonori. His research focuses on the activation of carbon–halogen bonds and carbon–boron bond assembly.



Dr. M. Simonetti

Marco Simonetti received his MSc in 2010 from University of Insubria (Italy) under the supervision of Prof. Andrea Penoni. In 2011, he joined the group of Prof. Antonio Papagni at the University of Milano-Bicocca (Italy). Later, he joined Prof. Igor Larrosa's group at Queen Mary University of London (UK) where he obtained his PhD in 2015. He continued working with Prof. Larrosa at the University of Manchester (UK) on the development of Ru-catalyzed C–H functionalization reactions, until January 2018. In March 2018, he joined Prof. Daniele Leonori's group at the University of Manchester (UK) where is currently developing photocatalytic transformations.

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Dr. J. Lloveria

Josep Lloveria earned his PhD in 2011 from the Universitat Rovira i Virgili (Tarragona, Spain) under the supervision of Prof. Sergio Castellón. His work was focused on the synthesis of sphingoid bases by transition-metal-catalysed reactions. During his PhD, he enjoyed a short-term stay at Boston College (USA) under the supervision of Prof. A. H. Hoveyda, working on Z-selective cross-metathesis. After completing his PhD, Josep joined the

Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) as a postdoctoral research associate to work on the synthesis of natural products under the supervision of Prof. A. Fürstner. He then moved to the University of Bristol (UK) in 2014 for a second postdoctoral stay, working in Prof. V. K. Aggarwal's group, to investigate new strategies towards stereospecific coupling of heterocycles with boronic esters. Josep started his industrial career at UCB (Slough, UK) in 2015 as a medicinal chemist before moving to Janssen (Toledo, Spain) in 2019.



Prof. N. S. Sheikh

Nadeem S. Sheikh was born in Lahore (Pakistan) and obtained his BSc and MSc from Government College University and Punjab University, respectively (both in Pakistan). He continued his doctoral studies with Prof. Richard Brown at Southampton, UK (2008) and then moved to Sheffield, UK (2008–2011) as a postdoctoral research assistant in the group of Prof. Iain Coldham. He has received several awards, including a gold medal and academic roll of honour during his BSc, merit and talent awards during his MSc and the ORSAS award for his PhD studies.

In 2011, he joined King Faisal University, Saudi Arabia where he is currently serving as Associate Professor of Organic Chemistry. His research interests include computational catalysis for target-oriented organic synthesis and mechanistic investigations for synthetically significant organic transformations.



Prof. D. Leonori

Daniele Leonori obtained his PhD at the University of Sheffield (UK) under the supervision of Professor Iain Coldham (2010). After postdoctoral studies with Prof. Magnus Rueping (RWTH Aachen University, Germany) and with Prof. Peter H. Seeberger (Max Planck Institute, Germany) he joined the group of Prof. Varinder K. Aggarwal FRS as Research Officer (University of Bristol, UK). In 2014 he commenced his independent career

at the University of Manchester (UK), where he is now Professor of Organic Chemistry. The group's main research interests are in the area of catalysis and synthetic chemistry, with a focus on the assembly of N-containing molecule.