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Practical Lithiation Chemistry

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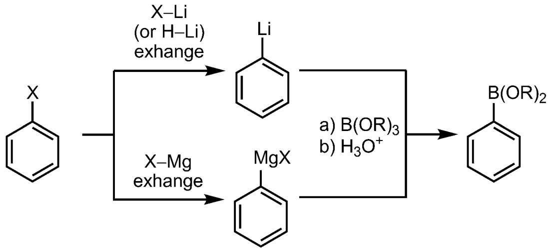
Overcoming the Limitations of Lithiation Chemistry for Organoboron Compounds with Continuous Processing

Aman A. Desai*

boron · industrial chemistry · flow chemistry · lithiation · synthetic methods

The Suzuki–Miyaura coupling reaction is arguably the most widely used C–C bond-forming reaction in industrial organic synthesis.[1–3] The synthesis of the organoboron coupling partners in these reactions has deservedly attracted significant attention from the academic community, and recent literature has seen the advent of several interesting and novel synthetic methods.[4,5] The implementation of these methods in the industry has however been rare, if not nonexistent, primarily because of the expensive and exotic nature of the catalysts, ligands, and boron sources involved. The cheapest and most prevalent methods for the industrial manufacture of organoboron compounds remain the batch mode reactions of an organolithium[4,6] or organomagnesium[4,7] intermediate with a trialkyl borate at low temperature with a subsequent aqueous acid work-up (Scheme 1).



Scheme 1. Prevalent manufacturing methods for organoboron compounds, illustrated for a phenyl boronic ester.

The organomagnesium route proceeds by halogen–magnesium exchange at low temperatures (typically -10 to 0 °C) and is usually utilized for the manufacture of low-value/high-volume boronic acids and esters. The organolithiation route can be utilized for similar halogen–lithium exchange processes, but more importantly, it can also facilitate hydrogen–lithium exchanges by directed metalation, thus leading to a broader range of boronic acids and esters. The caveat with the organolithiation route is the need for cryogenic temperatures (typically -78 to -40 °C) to tame the high reactivity (and instability) of the organolithium intermediates. This route is thus usually reserved for high-value/low-volume organoboron products.

A majority of the processes in the fine-chemicals and specialty-chemicals industry are run in batch mode. Scaling up cryogenic organolithiation chemistry in such settings has traditionally proven to be a significant challenge, and this is chiefly due to the need to handle large quantities of the hazardous lithium reagents (like *n*BuLi) and the excessive costs associated with cryogenic technology at scale. These challenges, along with the fact that these reactions occur almost instantaneously, make cryogenic organolithiation chemistry an ideal candidate for continuous processing, albeit with its own unique challenges. A significant area of concern is the possibility of precipitation of the intermediate lithium or boron salts, which can lead to irreversible clogging of the flow reactors. Other concerns associated with continuous cryogenic processing include solvent freezing, water ingress, and accurate temperature control. This Highlight will draw attention to three recent pioneering reports from the academia and showcase continuous processing for the preparation of organoboron compounds by lithiation chemistry.[8–10]

Ley and co-workers have reported the fabrication of a new mesoscale cryogenic flow reactor (dubbed the polar bear) and its use for the preparation of a variety of (hetero)aromatic boronic esters by lithium–halogen exchange chemistry in a segmented fashion (Scheme 2).[11] Attempts to translate the segmented-flow conditions into a continuous process led to clogging of the reactor coil as a result of the precipitation of, presumably, the intermediate boronate complex. They solved this problem by lowering the concentration of the product stream (0.2 to 0.16 M) and increasing its polar solvent content (1:1 to 4:1 THF/hexanes). Under the optimized reaction conditions, continuous processing at -60 °C for 5 hours enabled scale-up to 13 g of product after an acidic work-up with a 99 % yield and approximately 95 % purity, without any purification. Also worthy of note is the use of *n*BuLi directly from commercially available reagent bottles through piston pump heads. Finally, no frosting of the flow reactor was observed even after being kept at -60 °C for 12 days.

A microfluidic system, consisting of a series of perfluoroalkoxy-tubing flow reactors (0.04″ inner diameter), was utilized by Buchwald and co-workers for their recently reported three-step continuous synthesis of a range of biaryls

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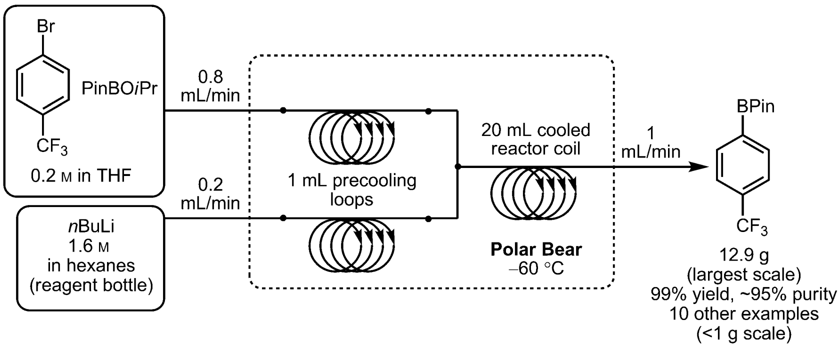
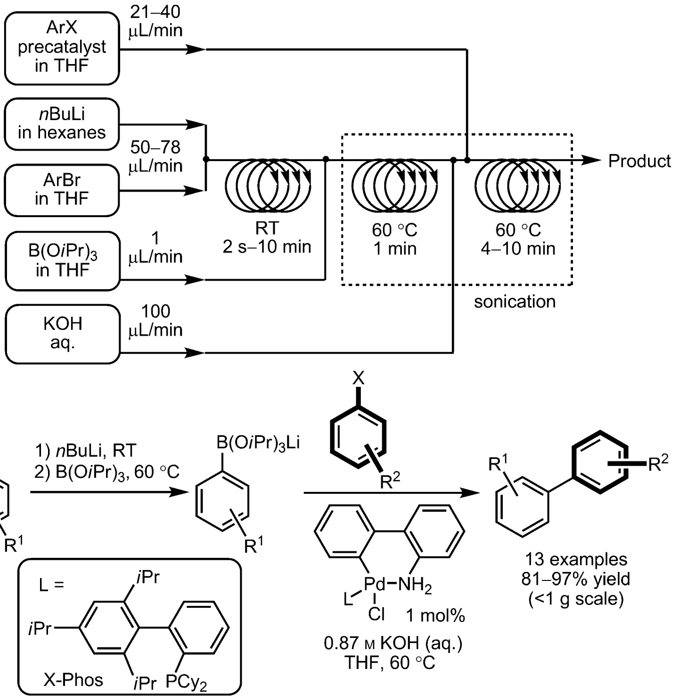
[*] Dr. A. A. Desai
Process Science, Core R & D, The Dow Chemical Company
Midland, MI 48674 (USA)
E-mail: aadesai@dow.com



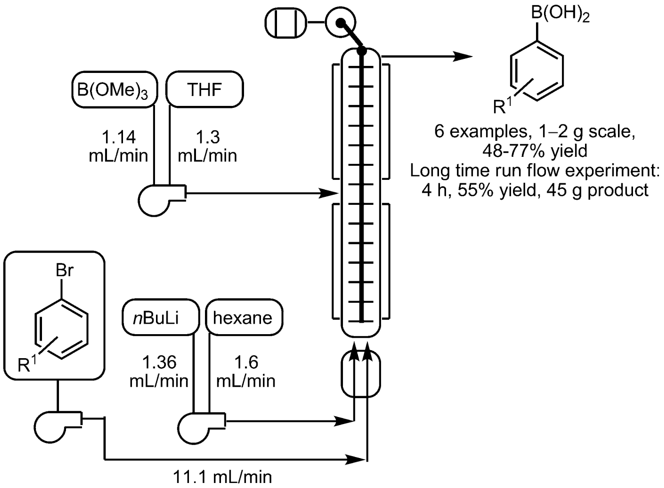
Scheme 2. Ley's continuous organolithiation/borylation process. pin = pinacolyl.



Scheme 3. Buchwald's continuous organolithiation/borylation/Suzuki–Miyaura cross-coupling process.

(Scheme 3).[12] The chemistry involved halogen–lithium exchange, subsequent borylation, and finally Suzuki–Miyaura cross-coupling. The problem of reactor clogging because of the precipitation of solids was circumvented by the use of acoustic irradiation with a sonication bath, which also ensured good mixing for the three-phase Suzuki–Miyaura cross-coupling reaction. Worthy of note in their protocol is that the lithiation was conducted at room temperature using commercially available *n*BuLi solutions. This three-step flow process was also extended to the reactions of heteroarenes (by hydrogen–lithium exchange) with aryl halides.

A multijet oscillating disc (MJOD) millireactor system has been designed, constructed, and employed by Bjørsvik and Sleveland for their cryogenic organolithiation protocol to generate a series of phenylboronic acids by bromine–lithium exchange (Scheme 4).[13] Throughput-improvement studies led to conditions which on extrapolation translated to a production capacity of 2 kg per day based on the yield of the isolated product. The net volumes in the reactor were at



Scheme 4. Bjørsvik's continuous organolithiation/borylation process ($T = -65$ °C, total residence time = 9.12 min).

the multi-milliliter scale rather than the microliter scale, that is, conditions more suitable for industrial implementation.

Transition metal catalyzed borylations[5] are ideal routes for the manufacture of organoboron products from the perspective of process ease and process safety. However, these methods are still in their infancy and their cost competitiveness remains a formidable question for industrial implementation. The lithiation/borylation route provides ready access to a range of organoboron products; this chemistry is well established in the literature and in industry, and is cost-competitive. Shifting these processes from batch to continuous mode can significantly alleviate the concerns associated with such chemistry at the manufacturing scale. The reports highlighted herein from the research groups of Ley, Buchwald, and Bjørsvik constitute proof of concept for such continuous lithiation/borylation processes, and certainly merit further investigation for appropriate industrial implementation.

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