UNIVERSITÀ DEGLI STUDI DELL'AQUILA

DSFC Dipartimento di Scienze Fisiche e Chimiche

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Rethinking the generation of privileged scaffolds in medicinal chemistry using continuous flow, mechanochemistry and paper-based platforms

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Electrochemical generation of NHC-boryl radicals for C–C bond formation

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Indole- and squaramide-based templates can be rightfully defined as privileged scaffolds. Despite indole primacy within the family, indolenines and their reduced counterparts (i.e. indolines) represent recurrent substructures in medicinally relevant compounds.[1] Fisher indolisation and its interrupted variation still represent the preeminent method for synthesizing the indole and indolenine cores. However, the privileged 3,3'-disubstitued indoline scaffold is associated with significant synthetic challenges, e.g. the tendency to undergo acid-catalyzed 1,2-migration towards the more thermodynamically stable indole counterparts. Moreover, Fischer indolisation itself is an energy-demanding process generating considerable waste. In our quest towards the development of a reliable methodology avoiding or at least minimizing the issues associated to the synthesis of (spiro)indolenines, we recently reported a telescoped sustainable synthesis of 3,3-disubstituted indolenines using flow chemistry.[2] This newly developed protocol displays the potential to turn into an effective coupling point for additional flow reactions for multistep syntheses. Accordingly, a telescoped approach coupling interrupted Fischer reaction and subsequent Joulliè-Ugi-type modification was established, using small amounts of solvent and requiring limited reaction times.[3] We have also extended this flow protocol to the generation of new captopril-inspired indoline-based metallo-β-lactamase (MBL) inhibitors, in high yields and optical purities, and requiring minimal manual handling and solvent consumption.[4] Flow-based approaches are also amenable for convenient organocatalytic applications. We then applied asymmetric catalysis in flow to our (spiro)indolenine substrates to develop a fast, sustainable and highly enantioselective Strecker synthesis of cyclic □-amino-nitriles.[5] Interestingly, we implemented the first mechanochemical protocol for generating indoline-based templates in short times and high yield using a mixture of solid oxalic acid and dimethylurea. The methodology displays broad scope and the potential to turn it into a practical coupling point for additional modification leading to compounds of pharmaceutical interest.[6]

A steady increase in the application of squaramides has been observed lately in various fields, such as organocatalysis, materials chemistry, and the development of novel drug candidates. We have recently disclosed a sustainable methodology for the synthesis of squaramide-based compounds, *via* an innovative eco-friendly protocol leveraging on the benefits of filter paper as a suitable reaction platform for water-based solvent systems.[7] Our newly conceived protocol guarantees high reaction yields and excellent green metrics, validating the suitability of a simple material like filter paper to not only streamline the overall process but also enhance the efficiency of the reaction.

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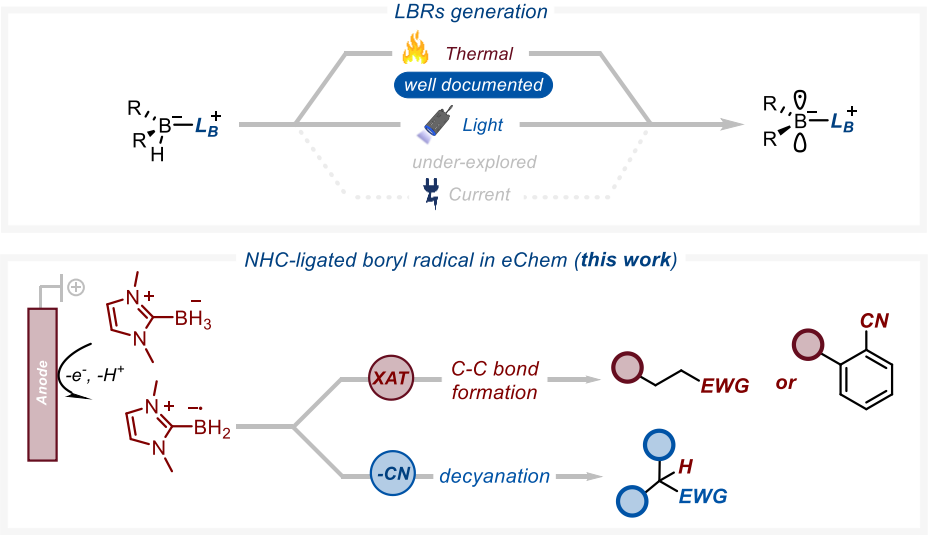
Boron-centered radicals have attracted significant attention in synthetic chemistry due to the broad range of radical transformations they can unlock. However, their pronounced electron deficiency and inherent instability have historically limited their wider application.[1] On the other side, coordination of boron to a Lewis base affords ligated boryl radicals (LBRs), which possess a seven-electron valence configuration that enhances their stability and unlocks valuable synthetic reactivity.[2,3] While photocatalysis has recently provided efficient access to these intermediates under mild conditions, their generation in an electrochemical context remains comparatively underexplored.[4,5] Although amine-ligated boranes exhibit prohibitively high oxidation potentials,[6] *N*-heterocyclic carbene (NHC)–ligated boranes display significantly lower redox potentials ($E_{p/2}$ ~ +0.8 V vs SCE), making their anodic activation feasible and compatible with functional group tolerance. In our latest investigation, we demonstrate that NHC-ligated boryl radicals can be efficiently generated through electrochemical oxidation of the corresponding boranes. The generality of this strategy is illustrated in several radical transformations, including decyanation of aliphatic nitriles, Giese-type additions via halogen atom transfer (XAT), and decyanative arylation processes. This work adds a new dimension to the rapidly evolving field of ligated boryl radicals by demonstrating their generation and application under eChem conditions.



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