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Research Seminar

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Nanocatalysis in Water for C–C and C–N Cross-Couplings: Sustainable, Affordable, and Scalable

Abstract

According to Pfizer's solvent selection guide, water is by far the green reaction medium.[1] However, in organic synthesis, it is predominantly used for reaction work-ups rather as an alternative solvent.[2] Nonetheless, it has many exciting features to offer better and cleaner chemistry for chemical synthesis. The very forward-thinking statement by Sheldon[3] more than a decade ago, "the best solvent is no solvent, but if a solvent is needed, then water has a lot to recommend it," has experimentally been proven correct for many areas of chemistry.[4,5] For example, micellar catalysis, a significant enabler of chemistry in water, has been applied to many diverse classes of organic chemistry reactions, often with improved reactivity and/or selectivity compared to their organic solvent enabled counterparts.[6,7] Although some pharmaceutical industries have adopted the micellar nanocatalysis, its wide adoption is still limited. The reason behind its limited adoption is the lack of fundamental understanding of how and why it works better than the traditional chemistry. Therefore, this research talk focuses on the fundamental understanding of micellar nanocatalysis and their new applications.

Our laboratory has developed a proline-derived amphiphile PS-750-M that enables various value-added transformations under aqueous conditions for the aforementioned fundamental understandings and applications. The presence of a tertiary amide group within this amphiphile imparts enhanced polarity to the micellar inner core, allowing the accommodation of polar reactive intermediates. Likewise, this structural feature also permits stabilizing metal nanoparticles (NPs) and facilitates various NP-mediated cross-couplings. The first part of the talk involves synthesis, characterization, and catalytic exploration of PS-750-M stabilized Pd(II) and Pd(0) NPs.[8] Notably, this technology also circumvents the use of any toxic organic solvents and costly σ-donor ligands for NPs synthesis and their catalytic reactions. These NPs were thoroughly characterized using various state-of-the-art techniques, such as, 13C NMR, IR, XPS, HRMS, and HRTEM. The NPs were employed on base-free oxidative Heck couplings at rt, cross-couplings of water-sensitive acid chlorides in water, and Suzuki-Miyaura couplings of aryl halides. These approaches are scalable, and the applications are demonstrated on multi-gram scale reactions, including the synthesis of valued intermediate of boscalid.

In the second part, PS-750-M enabled α-arylation of arylacetonitriles will be discussed.[9] Traditionally, due to water-sensitive carbanion reaction intermediation, this transformation never be performed under aqueous conditions and always requires anhydrous toxic organic solvents. Here, PS-750-M-derived nanomicelles provide sufficient shielding effect to stabilize these intermediates and enable the desired reaction between nitriles and aryl halides. The reaction is catalyzed by phosphine (XPhos) bound in-situ generated ultrasmall Pd(0) NPs. The reaction mechanism was probed using 31P NMR studies confirming all the elementary steps, including the carbanion binding to the NP surface. The catalytic activity was demonstrated on over 30 substrates. This catalytic technology's scalability was showcased on a 50 g scale example leading to the formation of diphenoxylate intermediate.

In the end, to harness the synergy between two metals (Pd and Cu) in NP, the development of a novel heterogeneous bimetallic nanocatalyst for micellar Buchwald-Hartwig aminations will be discussed.[10] This Pd-Cu system stabilized by the phosphine ligand (cBRIDP) was immobilized on the carbon surface. The resulting catalyst was thoroughly characterized by state-of-the-art techniques. The catalytic activity of these NPs was demonstrated over a broad range of substrates, emphasizing the arylations of primary and secondary amine—highly useful educts to the pharmaceutical industry. The recyclability of these NPs was assessed using Scott's method.[11] Besides, a domino approach for constructing the C–N bond will be discussed. It was achieved in a highly selective fashion using quasi-homogeneous Pd-Cu bimetallic nanocatalyst, leading to tandem selective reduction of nitroarenes followed by coupling with aryl halides without any dehalogenation. The dehalogenation pathway was suppressed by Cu-Pd interaction in the NP.

References

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