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Dissertation Defense

When: May 12, 2023

Time: 11:00 AM

Location: CBL-16

New Methodologies for Sustainable Organic Synthesis in Water

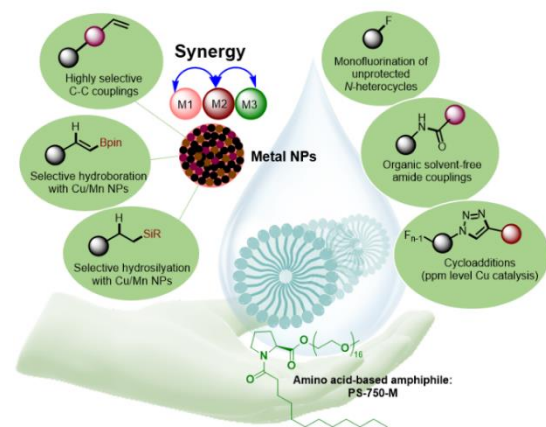
ABSTRACT:

Water is stable, benign, and green solvent. Micellar catalysis with designer surfactants significantly enhances its usage as a solvent in organic synthesis.^[1] The unique architecture of micelles enables water solubility of the catalyst and reactants, resulting in higher reaction rates. In this direction, our group has designed a proline-based benign amphiphile PS-750-M possessing an optimal balance between hydrophilic (mPEG) and hydrophobic (hydrocarbon) regions, guaranteeing the formation of aqueous nanomicelles maintaining controlled polarity in the micellar interior.^[1] The micelles of PS-750-M structurally mimic toxic dipolar-aprotic organic solvents, such as DMF, DMAc, and NMP. It has been recognized as a greener replacement for these toxic solvents in organic synthesis.^[1]

While showcasing the potential of PS-750-M, a greener strategy for ultrafast amide couplings in water is designed to empower aqueous chemistry in industrially-relevant reactions.^[2] The synergy between micelles of the coupling agent and PS-750-M enabled this transformation sustainably. The most common coupling agent used in amide couplings is 1-Ethyl-3-(3-(dimethylamino)propyl)-carbodiimide (EDC•HCl). The presence of lipophilic and hydrophilic regions in EDC•HCl allows its self-aggregation in an aqueous medium containing PS-750-M to form mixed micelles.^[3] These mixed micelles provide a very high local concentration of reactants and the coupling agent, resulting in ultrafast reaction rates without product epimerization. The methodology completely avoids toxic organic solvents, and the product spontaneously extrudes from the micelle, allowing its isolation by simple filtration.

The micelles of PS-750-M were also utilized to develop a highly-selective protocol for monofluorination of *N*-heterocycles in water. These nitrogen-rich monofluorinated scaffolds are essential in the number of bioactive molecules. The general procedure for highly-selective monofluorination of nitrogen-rich unprotected heterocycles is missing to date.^[4] To fill this gap, we have developed an unprecedented methodology for site-selective monofluorination of unprotected heterocycles in aqueous micelles of PS-750-M. The methodology is highly selective, green, easy to execute, and does not involve toxic metals or organic solvents. This greener methodology was employed to synthesize bioactive intermediates for BTK inhibitors, estrogen receptor modulators, and Merck's MK-8742 (hepatitis-C inhibitor). In addition, this methodology was extended to suppress the genotoxic impurity in Takeda's clinical molecule.

The last part of the talk will highlight the concerns about endangered and precious transition metal catalysis and their replacement with metal nanoparticles (NPs) derived from non-toxic, inexpensive 3*d*-transition metals using PS-750-M as a stabilizer.^[5] These NPs exhibit the synergy between two or more metals enabling powerful, sustainable, and selective catalysis. The bimetallic NPs of Cu and Mn, as well as trimetallic NPs of Cu, Mn, and Pd, enabled selective Suzuki-Miyaura cross-coupling, hydroboration, and hydrosilylation of alkenes, alkynes, and chalcones.



An overview of sustainable catalysis in

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