Just a Drop: Unlocking NHC Reactivity in Water

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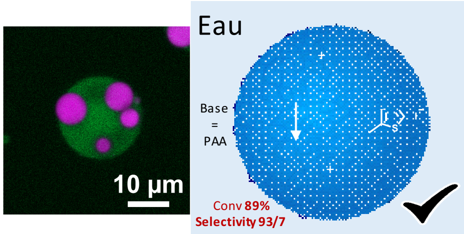
Bio-inspired *N*-heterocyclic carbenes (NHCs), designed as synthetic analogues of enzyme cofactors, have recently demonstrated their ability to catalyze C–C bond formation in aqueous media via the Stetter reaction.[1] However, harnessing NHC organocatalysis in water remains challenging due to catalyst stability issues[2] and the limited solubility of organic substrates. To overcome these limitations and broaden the scope of NHC-catalyzed reactions, we investigate their behavior at the water/organic phase interface, either in bulk aqueous medium or within coacervate droplets. Considered as protocell surrogates, synthetic coacervates are micrometer-sized droplets formed by liquid–liquid phase separation of oppositely charged polyions in water. These dynamic, membrane-free compartments spontaneously sequester biomolecules through selective partitioning, thereby creating microenvironments that support both enzymatic[3] and non-enzymatic reactions.[4] Their potentially reduced polarity compared to bulk water facilitates the accumulation of organic molecules, enhancing chemical transformations. In strong collaboration with physical chemists, we have developed novel bio-inspired, chemically active coacervate systems as tailored reaction media, significantly improving the efficiency and selectivity of NHC-catalyzed C–C bond-forming reactions in aqueous settings.[5] Given the low water solubility of organic reactants, these reactions involve phase-separated organic droplets suspended in the aqueous medium, suggesting activation at the organic/water interface. Such organic/aqueous phase separation highlights the potential of water not only as a solvent but also as a dynamic medium capable of concentrating organic reactants and facilitating interfacial chemical reactivity. Moreover, such systems enable key bio-relevant transformations such as oxidative esterification, underscoring the potential of interfaces for chemical reactivity in water.

Stetter reaction in presence of coacervates droplets PAA/PDDA



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Oxydative Esterification/amidation

Ongoing study

References

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