

A Cu-catalyzed click reaction forges ROS-triggered clippable linkages in aqueous media

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Click reactions that generate functional linkages are uncommon. Among the less than a handful of catalytic options, none delivers a cleavable connector directly. In this Lecture, an biorthogonal and operationally simple click reaction, copper(I)-catalyzed allene-ketone addition (CuAKA) will be presented. CuAKA, CuAAC (copper(I)-catalyzed azide–alkyne cycloaddition) and the recently disclosed CuPDF (copper(I)-catalyzed phenoxydiazaborinine formation) are mutually orthogonal owing to effective catalyst control and despite mechanistic homologies. Accordingly, these processes can be merged for efficient assembly of multifunctional entities. It will be discussed how CuAKA can be used to link a drug molecule in aqueous media to a ketone-containing derivative of unprotected penetratin, a cell penetrating peptide. The effectiveness of an allylmetal complex runs counter to the notion that C–C σ -bond formation and carbonyl addition chemistry are not suitable for click reaction development. Just as important, controllable cleavage of CuAKA-generated linkages, which can be triggered at 37 °C in dilute ($\sim 70 \mu\text{M}$) aqueous solution of H_2O_2 , the most abundant reactive oxygen species (ROS), will be presented.