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Merging Nitrene and Carbene Reactivity: Flexible Access to High Fsp^3 Chemical Space

Abstract: Over 80% of marketed pharmaceuticals and many bioactive molecules contain at least one C–N bond; thus, methods to introduce nitrogen into hydrocarbon feedstocks in an efficient, selective manner are attractive. In particular, there has been renewed interest in diverse molecular scaffolds with high Fsp^3, as such compounds are underrepresented in current drug screening libraries. This lecture highlights our success in merging designer silver catalysts for tunable chemo-, site-, and enantioselective amination with carbene transfer to develop modular strategies for transforming simple alkenes and allenes into diverse *N*-heterocycles. Tandem nitrene/carbene transfer sequences furnish highly substituted, stereochemically complex azetidines, pyrrolidines, piperidines, amine-bearing carbocycles and other *N*-heterocycles in 1-2 steps. Computations to inform predictable tuning of substrate, carbene precursor, catalyst, and reaction conditions to divert key aziridinium ylide intermediates along different mechanistic pathways will be discussed. Application of methods to the synthesis of DNA-encoded libraries to speed the identification of amine chemical space with novel bioactivity may also be presented.