Azetidines with All-Carbon Quaternary Centers: Merging Relay Catalysis with Strain Release Functionalization

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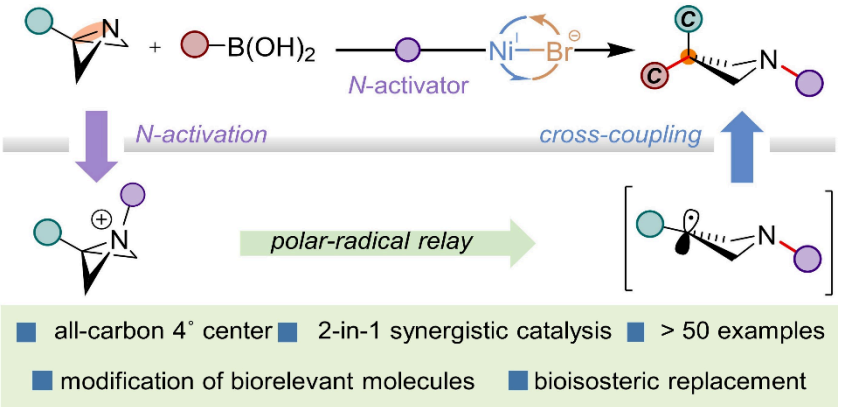
Given the importance and the beneficial characteristics of decorated azetidines in medicinal chemistry, efficient strategies for their synthesis are highly sought after. My group reports a facile synthesis of the elusive all-carbon quaternary center-bearing azetidines.[1] By adopting a well-designed polar-radical relay strategy, we harness the release of ring strain from bench-stable benzoylated 1-azabicyclo[1.1.0]butane (ABB) for nickel-catalyzed Suzuki Csp^3–Csp^2 cross-coupling. This involves the ring-opening of ABB facilitated by synergistic bromide and nickel catalysts derived from a sole nickel source ($NiBr_2$), leading to ABB's conversion into a redox-active species that subsequently engages in cross-coupling through a radical pathway. Late-stage functionalization of natural products, biologically relevant molecules, and pharmaceuticals have been successfully achieved, as well as the synthesis of melanocortin-1 receptor (MC-1R) agonist and vesicular acetylcholine transporter (VAChT) inhibitor analogs through bioisosteric replacements of piperidine with azetidine moieties, highlighting the potential of the method in drug optimization studies.



Reference

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