A3-07 Catalysis-Enabled Non-Obvious Transformations for Structural Modification

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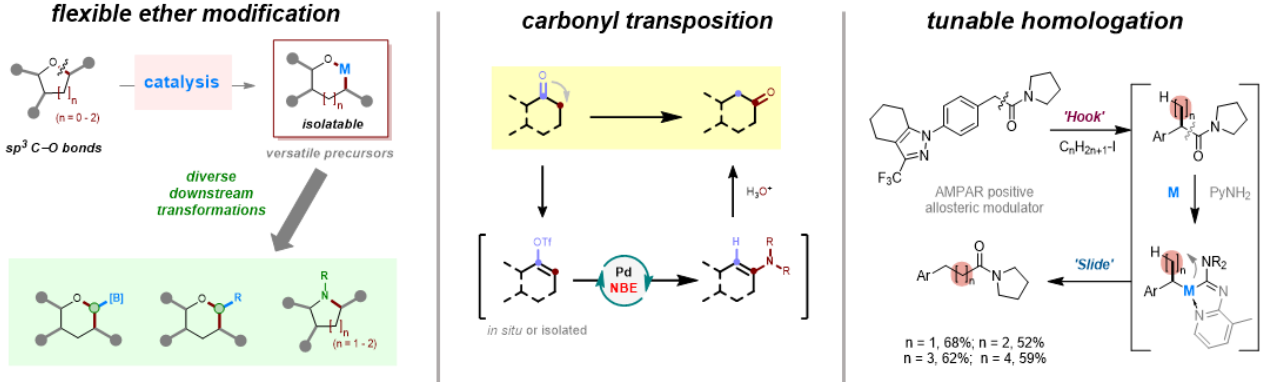
Structural modification or analogue synthesis, one of the cornerstones in drug discovery, is essential for lead optimization and development of analog drugs and follow-on drugs. Among various structural modification approaches, those that can directly manipulate or derivatize lead compounds are most attractive to medicinal chemists, as such “late-stage” modifications would allow divergent synthesis of a number of analogues from a common advanced intermediate. Currently, most late-stage modification methods are based on transforming existing more reactive functional groups or functionalizing C−H bonds. In contrast, transformations that are not intuitive or obvious have been rarely used for analog synthesis. This lecture focuses on three strategies that can realize non-obvious transformations for structural modification, which provide more direct access to valuable analogues that are either challenging or tedious to prepare. The first strategy is based on boron-insertion into ether C-O bonds via Ni/Zn tandem catalysis. The reaction goes through a cleavage-and-then-rebound mechanism. This



method enables one-carbon ring expansion and swapping oxygen to nitrogen in cyclic ethers. The second strategy is based on the carbonyl 1,2-transposition enabled by the palladium/norbornene cooperative catalysis. This approach first converts the ketone to the corresponding alkenyl triflate that can then undergo the palladium/norbornene-catalyzed regioselective α-amination/ipso hydrogenation enabled by a bifunctional H/N donor. The resulting “transposed enamine” intermediate can subsequently be hydrolyzed to give the 1,2-carbonyl-migrated product. This method allows rapid access to unusual bioactive analogues through late-stage functionalization. The third approach is centered on a hook-and-slide strategy for homologation of tertiary amides and carboxylic acids with tunable lengths of the inserted carbon chain. Alkylation at the α-position of the amide (hook) is followed by highly selective branched-to-linear isomerization (slide) to effect amide migration to the end of the newly introduced alkyl chain; thus, the choice of alkylation reagent sets the homologation length. The key step involves a carbon–carbon bond activation process by a carbene-coordinated rhodium complex with assistance from a removable directing group. The approach is demonstrated for introduction of chains as long as 16 carbons and is applicable to homologation of complex bioactive molecules.

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