

ORGANIC SEMINAR

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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