Direct Alkyl Swap of Unprotected Amines: A Platform for Late-Stage Functionalization

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Aliphatic amines are among the most prevalent functional groups, present in countless natural products, agricultural compounds and pharmaceuticals.[1] Regardless of the ubiquity of alkylamines, the use of established synthetic methods to access and modify such motifs can often result in poor yields – a consequence of modest selectivity, harsh reaction conditions and/or functional group incompatibility.[2] There is substantial and continued interest in the development of new synthetic approaches for late-stage functionalization of complex amines, allowing for precise and rapid tuning of biological properties of small molecules.

To this end, we have developed a general acid-mediated transformation for the hydroaminoalkyklation of unactivated alkenes and alkynes using cheap and bench-stable reactants.[3,4] Our approach, which obviates the use of metal catalysts and external reducing agents, commences by the *in situ* formation of an iminium ion, followed by nucleophilic addition to generate a carbocation intermediate (Figure 1). The crucial step of this transformation is the subsequent internal redox event by 1,5-hydride transfer from the α-position of the amine. Thus, a new – albeit less electrophilic – iminium ion is formed, which furnishes desired secondary amine upon hydrolysis. The newly developed method distinguishes itself from the other state-of-the-art by a broad functional group tolerance, the absence of required directing/protecting groups and its applicability in a late-stage context.

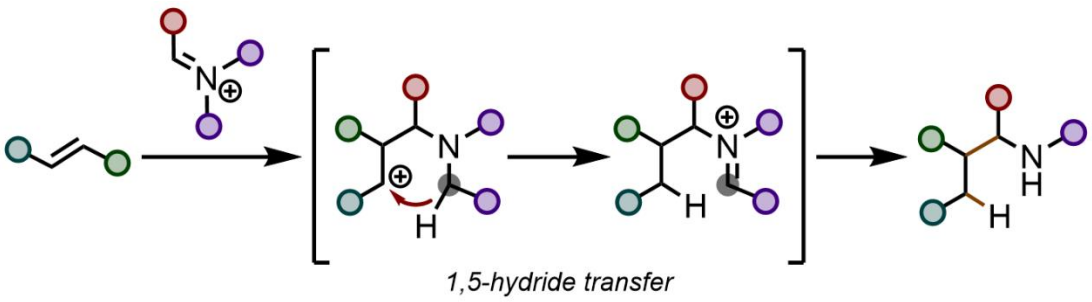

Figure 1. General acid-mediated hydroaminoalkylation of unactivated alkenes and alkynes.

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