Abstract. The adoption and implementation of more sustainable practices in the development and manufacture of pharmaceuticals has gained significant momentum over the past decade. More recently, such considerations are increasingly being applied to medicinal chemistry strategies in the earlier drug discovery settings, where despite the smaller scale, synthesis methods and procedures utilized here are often carried through into development in total or in part. Waste reduction and greener choices for solvents and reagents used in common transformations are routinely targeted, though growing attention is also being paid to efficiency of processes through novel bond connection sequences and strategies. In particular, two strategies for more sustainable practices for synthesis in lead optimization settings are through the use of transition metal catalysis in a) telescoped sequences, where more than one key synthetic step is carried out in a single reaction vessel; and b) in the atom- and step-economical use of C-H functionalization methods. We describe a number of efficient methods for the utilization of telescoped sequences with MIDA boronates to enable molecular diversity, each involving cross-coupling reactions of heterocycles, and including regiospecific access to substitution patterns previously difficult to achieve. The ability to perform late-stage functionalization of carbon centers lacking pre-installed handles (halides, triflates, boronates, stannanes) in preparatively useful yields has the potential to profoundly accelerate the pace of medicinal chemistry. We describe our initial results at overcoming the significant and long-standing challenges of catalyst arrest and/or undesired directing effects of Lewis basic centers to enable selective allylic functionalization in good yields. Additionally, we highlight several examples of late-stage functionalization of complex natural products and related substrates to demonstrate the power of these methods to derivatize such molecules for applications ranging from the preparation of chemical probes for assessing biological function to efficiently accessing novel sites for further elaboration of structure-activity relationships.

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