C(sp^3)—H Methylation for Late-Stage Functionalization

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Often referred to as the "magic methyl" effect, the introduction of methyl groups in bioactive molecules, particularly at sites α to heteroatoms, has the potential to significantly increase their potency. A method to directly install methyl groups in these molecules could expedite the drug discovery process and reduce time and cost for discovery. However, known methods that allow this transformation are extremely limited in scope and functional group tolerance that they are only applicable in the simplest heterocycles. The electron neutrality of methyl group further creates significant challenge in product isolation at late stages. Because of these limitations, medicinal chemists often resort to laborious de novo synthesis to access these methylated analogs or avoid such exploration altogether. This talk will discuss the discovery of a methylation strategy that addresses all these challenges. Using a small-molecule base-metal catalyst, the target molecules methylated in one sequence in synthetically useful yields in 15 oxa-aza-, and carbocycles. Late-stage functionalization was demonstrated in 18 small-molecule drugs or drug derivatives and natural products, including a linear amine and a carbocycle in a steroid.