Methylating the aromatic core — Chemoselective mono- and dimethylation by SAM-dependent *C*-methyltransferases

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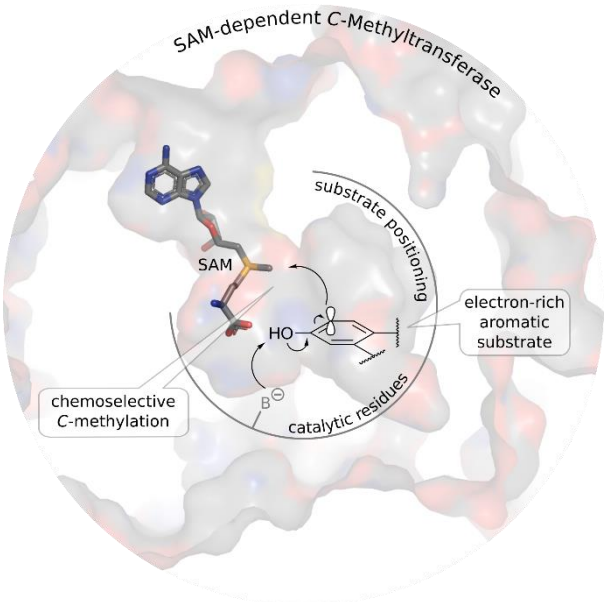
S-adenosyl-L-methionine (SAM)-dependent methyltransferases (MTs) can methylate various nucleophiles in an S_N2 reaction[1,2] and are involved in the methylation of a variety of natural products, such as DNA, proteins, or small molecules.[3,4] Compared to methylation on polarizable heteroatoms, *C*-methylation requires activation of the carbon atom of the substrates by an adjacent functional group to form a nucleophilic intermediate/ carbanion and allow nucleophilic attack on the methyl moiety of SAM. Exemplary substrates are enolizable ketones or phenolic compounds.[4]

Here, we focus on the *C*-methylation of aromatic compounds by comparing the streptomycete MTs NovO, NapB5, and SfmM2.[5–7] In addition to bioinformatic studies on the sequences and enzyme structures, we analyzed the (di-)methylated products by HPLC-MS and NMR experiments. The structural prerequisite of electron-rich phenolic substrates and their precise positioning to SAM as a methyl donor in the active site of the MTs enable the chemoselective mono- and dimethylation of the aromatic core.



Scheme 1: Enzymatic SAM-dependent *C*-methylation of aromatic compounds.

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