Remote Aliphatic C-H Oxidation of Nitrogen-Containing Molecules

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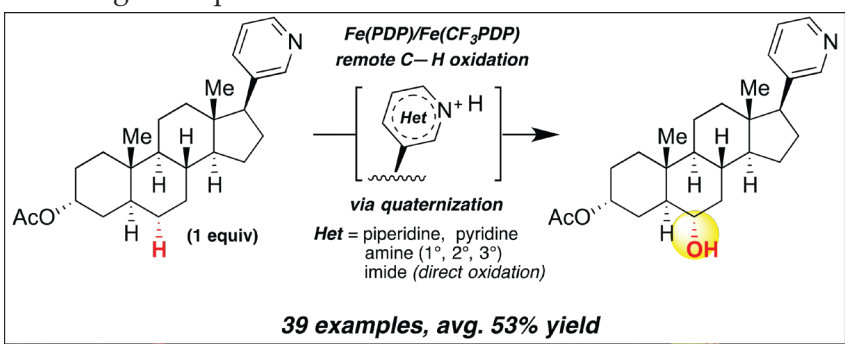
Nitrogen is ubiquitous among natural products and pharmaceuticals. Because of its strong Lewis basicity, C—H activation of nitrogen-containing molecules catalyzed by ligated transition metals has been limited in functionalizing sites proximal (i.e., α-, β-, γ-) to nitrogen. We developed an acid protecting strategy, using Brønsted acid HBF4 or Lewis acid BF3 to irreversibly protonate or complex with nitrogen. The complexation prevents metal binding and renders the nitrogen a strong electron-withdrawing group, thus inductively deactivates sites close to nitrogen. In a diverse set of substrates containing amine, pyridine, and various other functionalities, oxidation mediated by Fe(PDP) and Fe(CF3PDP) produced remotely oxidized alcohol or ketone products in preparative yields and good site-selectivity. Imides require no protection and directly promote remote oxidation. Furthermore, this method is capable of functionalizing complex nitrogen-containing molecules at late stage in synthetically useful yields, where the remote site-selectivity can be predicted using a computational model.



Removing Enzymatic Susceptibility of Imidazotetrazine Prodrugs for the Treatment of Glioblastoma

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Glioblastoma (GBM) is the most prevalent and infiltrative primary brain tumor and leads to a median patient survival of less than 15 months. The current standard of care includes temozolomide (TMZ), a prodrug that hydrolyzes at physiological pH and methylates at the O6-position of guanine nucleotides. O6-guanine methylation, however, is diligently repaired by suicide enzyme O6-methylguanine methyltransferase (MGMT), conferring tumoral resistance that is observed in ~55% of the GBM patient population. Our strategy is to develop an imidazotetrazine analog of TMZ that installs a DNA adduct irremovable by MGMT, thus subverting the main mechanism of resistance to TMZ and potentially providing a therapeutic option for all GBM patients irrespective of MGMT expression status.