LATE-STAGE DIVERSIFICATION THROUGH MANGANESE-CATALYZED C−H ACTIVATION: ACCESS TO ACYCLIC, HYBRID, AND STAPLED PEPTIDES

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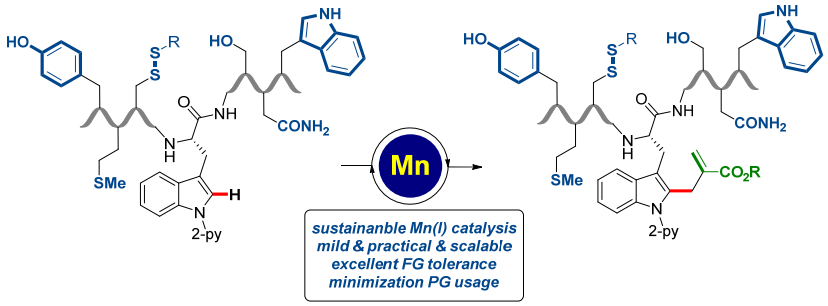
Non-natural peptides have emerged as increasingly potent scaffolds in medicinal chemistry and the pharmaceutical industry. As a consequence, the chemoselective assembly and modification of structurally complex peptides continues to be of utmost importance [1]. Significant recent momentum was gained through the development of palladium-catalyzed cross-couplings of peptides. A significantly more atom- and step-economic strategy relies on the direct activation of otherwise unreactive C–H bonds [2, 3], with recent transformative applications towards peptide modification [4]. As part of our program on sustainable C–H activation [4, 5], we reported on the first manganese-catalyzed C–H allylation of structurally complex peptides with easily accessible Morita–Baylis–Hillman adducts [6]. Notable features of our strategy include 1) an unprecedented manganese(I)-catalyzed peptide C–H alkylation, 2) the first metal-catalyzed peptide modification that installs synthetically useful α,β-unsaturated esters, and 3) a uniquely versatile manganese catalyst that proved applicable to C–H fusion with peptides, natural products, steroids, drug molecules, and nucleobases, among others.



[1] M. Jbara, S. K. Maity, A. Brik, *Angew. Chem. Int. Ed.* **2017**, *56*, 10644–10655.

[2] P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199–222.

[3] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.

[4] W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700–14717.

[5] L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281-295.

[6] N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 3476–3480.