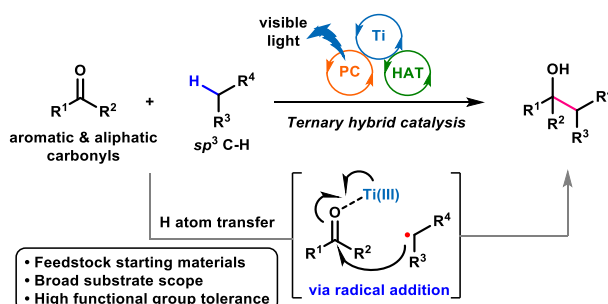


Titanium-Catalyzed Intermolecular Radical Addition to Ketones via sp^3 C-H Bond Activation

(¹The University of Tokyo, ²Kyoto University) ○Xue Peng¹, Yuki Hirao¹, Shunsuke Yabu², Hirofumi Sato², Masahiro Higashi², Harunobu Mitsunuma¹, Motomu Kanai¹

Keywords: Photoredox catalysis, HAT catalyst, Titanium complex catalyst, Late-stage functionalization, Radical addition

Tertiary alcohols exist widely in natural products, pharmaceuticals, pesticides, and ligands. Traditional synthesis of tertiary alcohols utilizes nucleophilic addition of organometallic reagents to ketones developed in the previous century. However, they exhibit low functional group tolerance, require stoichiometric quantities of organometallic reagents, and generate stoichiometric quantities of metal salt side products. Therefore, the interest in developing novel, safer and more sustainable reactions is growing within the scientific community, especially for the late-stage functionalization. In comparison of nucleophilic addition, direct radical addition of ketones can be an ideal approach due to the high functional group compatibility of radical species. However, radical addition to carbonyl groups is a thermodynamically uphill process.¹ Therefore, successful radical addition is only possible if the alkoxy radical can be intercepted via a subsequent fast event.² In particular, there are no reported radical addition of ketones with simple transient radicals derived from hydrocarbon feedstocks or natural products via C-H bond activation. Here we report a ternary hybrid catalysis composed of an acridinium photoredox catalyst, a thiophosphoric imide (TPI) catalyst, and a titanium complex catalyst. This catalytic system realized direct sp^3 C-H addition of organic molecules such as toluene, benzyl alcohol, alkenes, aldehydes, and THF to various ketones and aldehydes. The key for this transformation is the intrinsically unfavorable radical addition step promoted by single-electron reduction of the intermediate alkoxy radical by catalytically generated titanium(III) species which is supported by mechanistic studies. Due to the mildness and high functional group compatibility, the reaction is applicable to late-stage functionalization of biologically active compounds.³



1) P. Gray, A. Williams, *Chem. Rev.* **1959**, 59, 239. 2) a) P. Devin, L. Fensterbank, M. Malacria, *Tetrahedron Lett.* **1999**, 40, 5511. b) M. Saladrigas, C. Bosch, G. V. Saborit, J. Bonjoch, B. Bradshaw, *Angew. Chem., Int. Ed.* **2018**, 57, 182. c) B. Wu, R. Zhu, *ACS Catal.* **2020**, 10, 510. 3) **X. Peng**, Y. Hirao, S. Yabu, H. Sato, M. Higashi, H. Mitsunuma, M. Kanai, manuscript in preparation.