

Batch/continuous flow iron-catalyzed C-H functionalization for the synthesis of bioactive peroxides**Boopathy Gnanaprakasam**

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Iron is the most abundant metal on a planet earth after aluminum. The use of iron is a renaissance for the scientific community as the salts of iron are inexpensive, nontoxic, bench stable and easily available. The application of iron can be found in the synthesis of various intermediate in the pharmaceutical, cosmetics, fine chemicals, food, and agrochemicals industry. In recent years, iron-based catalysis via C-H functionalization has been significantly focused on C-C and C-N bond formation. Refining of the chemical processes into completely green approaches are major challenges in chemical industry. Chemical synthesis in continuous flow is considered as sustainable synthesis and it offer several advantages over traditional batch synthesis including ease of scale-up, highly selective, perform the reactions safely at extreme pressure and temperature, fast reactions, highly exothermic reactions, explosive reactions and reactions that involve energetic intermediates. In the last decades, many chemical reactions were successful in continuous flow processes towards the synthesis of fine chemicals, active pharmaceutical ingredients (APIs) and applied materials. Thus, development of iron catalyzed reactions under continuous flow in particular C-H functionalization is one of the challenges in chemical processes. Batch mediated C-H functionalization of 2-oxindole using Co and Cu has led to the respective peroxides under heating or in high catalyst loading, requires ligands. Furthermore, the use of the hazardous peroxides under batch reaction in large scale synthesis is unsafe. In collective report till today, missing part of the iron is oxidative C-O bond formation via C-H functionalization processes. Herein, we report the iron-catalyzed dehydrogenative cross-coupling of carbonyl compounds with aliphatic peroxide was developed under mild conditions. A library of linear alkylated and arylated peroxides are synthesized in good to excellent yield. This method is highly selective and general for a range of biologically important derivatives of 2-oxindole, barbituric acid and 4-hydroxy coumarin with a good functional group tolerance and without the cleavage of the peroxide bond. This peroxidation reaction is up-scalable to grams and also synthesizable in continuous flow with increased safety in short duration. Mechanistic investigation reveals Fe-(II) undergoes redox type process to generate the radical intermediates, which subsequently recombine selectively to form the stable peroxides. The potential of peroxides is evaluated by cell viability assay and found to exhibit the good anticancer and antimalarial activity.

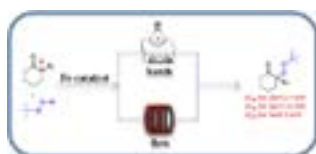


Figure: Highlights of the iron catalyzed C-H functionalization.

Recent Publications

1. Bauer I and Knölker H J (2015) Iron catalysis in organic synthesis. *Chem. Rev.* 115:3170-3387.
2. Cambié D, Bottecchia C, Straathof N J W, Hessel V and Noël T (2016) Applications of continuous-flow photochemistry in organic synthesis, material science, and water treatment. *Chem. Rev.*, 116:10276–10341.
3. Kong D L, Cheng L, Yue T, Wu H R, Feng W C, Wang D and Liu L (2016) Cobalt-catalyzed peroxidation of 2-oxindoles with hydroperoxides. *J. Org. Chem.* 81:5337-5344.
4. Klare H F T, Goldberg A F G, Duquette D C and Stoltz B M (2017) Oxidative fragmentations and skeletal rearrangements of oxindole derivatives. *Org. Lett.* 19:988-991.
5. Chaudhari M B, Moorthy S, Patil S, Bisht G S, Mohamed H, Basu S and Gnanaprakasam B (2018) Iron-catalyzed batch/continuous flow C-H functionalization module for the synthesis of anticancer peroxides. DOI: 10.1021/acs.joc.7b02854.

Biography

Dr. Gnanaprakasam Boopathy was born (1979) and raised in Chennai, India. He earned BS (1999) and MS (2001) in chemistry from the University of Madras. Lately, he obtained his Ph. D (2008) on the topic of "Synthetic methods towards terpenoids, steroids and macrocycles" from Bhavnagar University. Subsequently, he has completed a couple of Post-Doctoral program from Weizmann Institute of Science, Israel (September 2008-August 2011) under Professor David Milstein and AVH fellow from Gottingen University, Germany (September 2012- February 2014) under Professor Lutz. F Tietze. Prior to AVH post-doctoral fellowship, he joined as a scientist at ICES-ASTAR, Singapore (December 2012-July 2013). After Post-Doctoral program, he began his independent career as an Associate professor at SRM Research Institute (March 2014-June 2014). In late 2014, he moved to IISER-Pune in the department of chemistry where he currently holds the rank of Assistant Professor. The Gnanaprakasam group's research interests include development of metal catalyzed sustainable/green synthetic methods for the natural products, continuous flow synthetic methodology for bioactive molecules and Fluorinated organic scaffold. His recent research developed the use of highly hazardous materials under continuous flow open up the easy and safer handling of the peroxides in gram scale synthesis of bioactive peroxide derived from the 2-oxindole.

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