

Iron-Catalyzed Arene C–H Hydroxylation

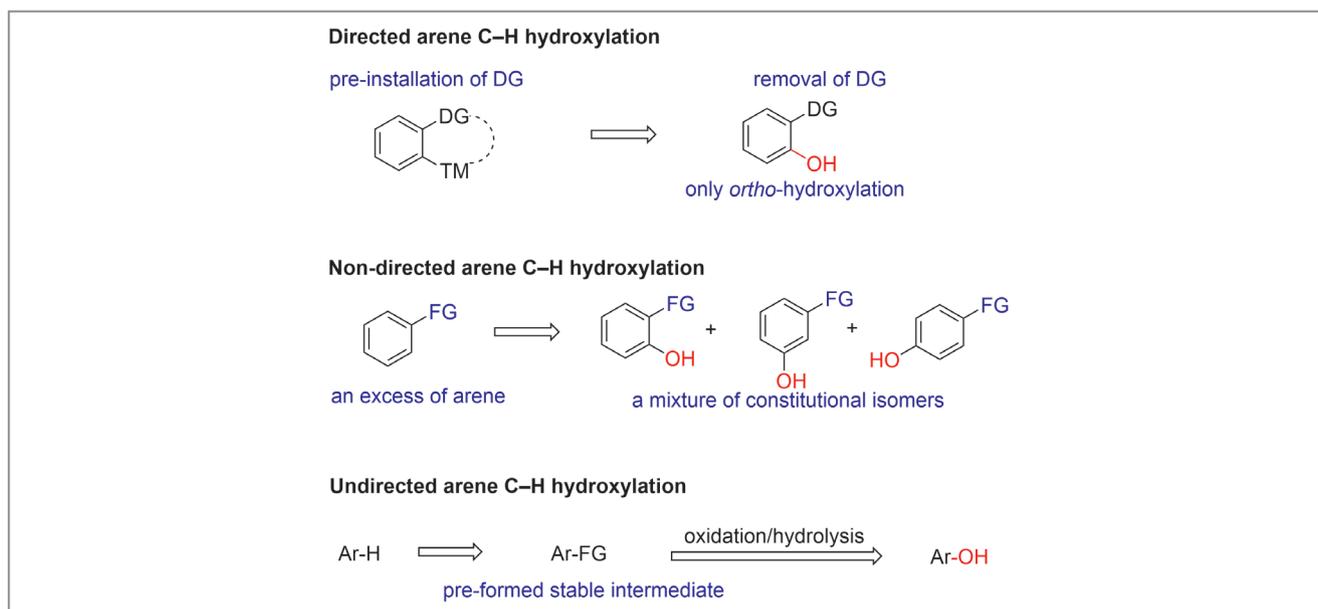
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Phenols are among the most important precursors for the manufacture of pharmaceuticals, dyes, and functional polymers. The group of Professor Wei Han at Nanjing Normal University (P. R. of China) has been investigating novel, more efficient and greener methods to produce functionalized phenols from readily available starting materials. Professor Han said: “Benzene C–H hydroxylation is generally regarded as the most straightforward and direct of all approaches to phenol. However, direct and selective conversion of benzene into phenol with molecular oxygen as oxidant is referred to as one of the ‘ten challenges for catalysis’ because the C–H bond dissociation energy (BDE) of benzene is high (ca. 470 kJ/mol), thus phenol is far more reactive toward oxidation than benzene itself, producing over-oxygenated by-products. Moreover, substituted benzenes usually lead to an inseparable mixture of constitutional isomers and – among them – alkylarenes preferentially undergo oxidation of the sp^3 C–H bonds in the aromatic side-chains (which have lower BDE, ca. 375 kJ/mol) rather than oxidizing the sp^2 C–H bonds in the aromatic ring.”

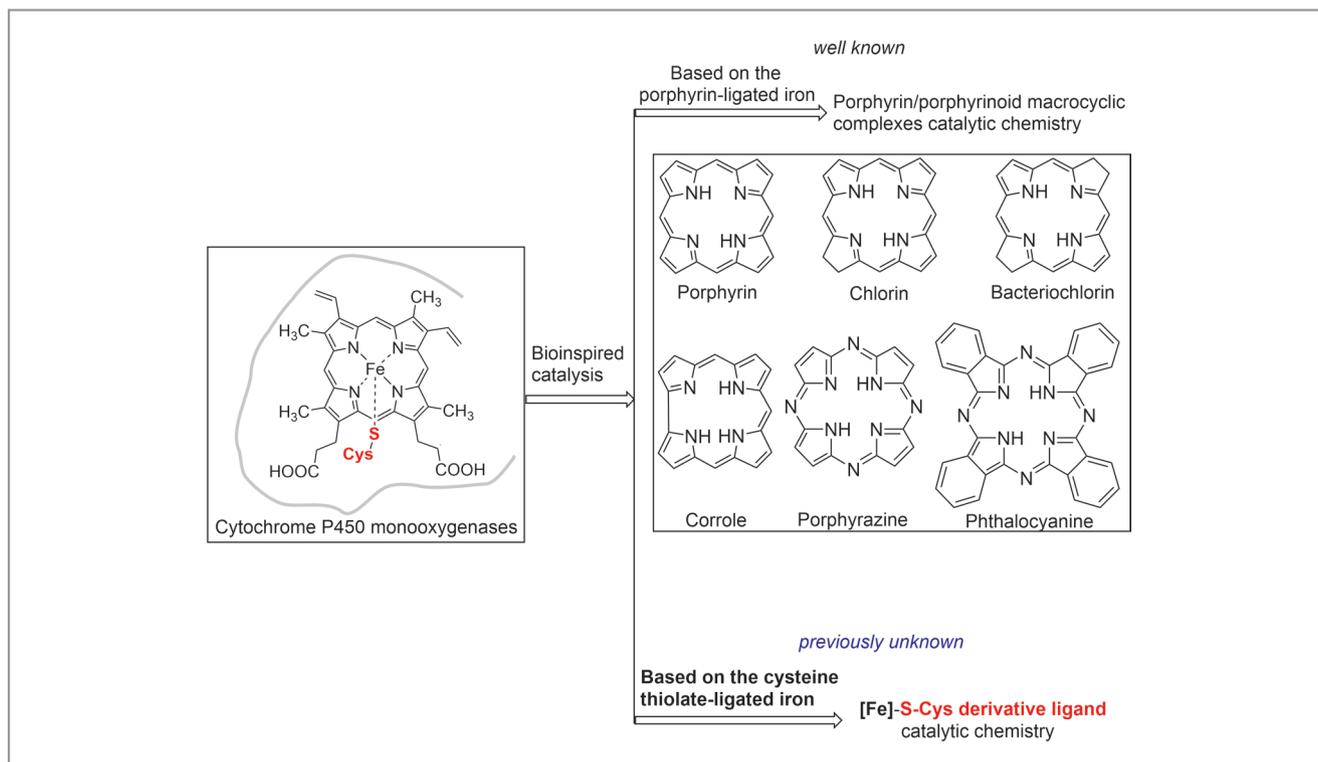
Although transition-metal-catalyzed chelation-assisted C–H hydroxylation of arenes has been reported previously, leading to an improvement of both selectivity and reactivity

of this kind of approach to phenols, the strategy often requires pre-installed directing groups, which makes only *ortho*-hydroxylation attainable. “Non-directed arene C–H hydroxylation can reach sites that are currently inaccessible by a directed approach; however, besides the issues mentioned above, an excess of arene is frequently required to ensure sufficient reactivity,” explained Professor Han. He continued: “To obviate the need for directing groups and excess arene, an alternative strategy to access phenols would be the use of a pre-formed stable intermediate via aromatic C–H borylation, silylation, thianthrenation, or oxygenation, followed by additional steps to give the phenols (Scheme 1).”

Professor Han noted that cytochrome P450 enzymes are capable of hydroxylation of strong aryl C–H bonds in the absence of directing groups with high selectivity, and have an active site that consists of an iron porphyrin cofactor. “Cytochrome P450-bioinspired enzymatic catalysis relies on the design and synthesis of porphyrin and porphyrinoid ligands (Scheme 2). However, these bioinspired methods for non-directed arene C–H hydroxylation are often severely hampered by low activities, poor selectivities, narrow scope of arenes, and/or high substrate loadings,” remarked Professor Han, who



Scheme 1 State-of-the-art arene C–H hydroxylation



Scheme 2 Strategies for bioinspired cytochrome P450 catalysis

added: “In cytochrome P450 enzymes, the proximal ligand is the thiolate moiety of a residual cysteine, which coordinates to the haem iron center, which in turn is believed to control the oxidative activity of the enzymes and to facilitate C–H oxidation.¹ Unfortunately, the use of this property to design ligands for catalysis has been so far overlooked, probably due to the affinity of the sulfur atom for transition metals, which leads to a strong coordination and eventually to catalyst poisoning.”

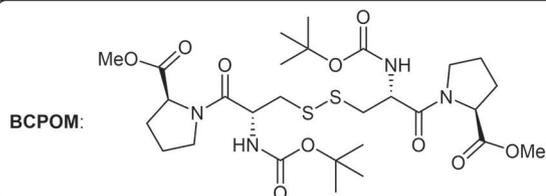
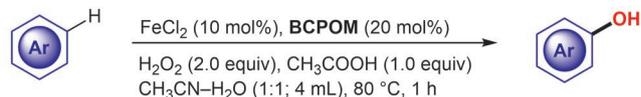
Professor Han continued: “Inspired by the proximal thiolate moiety of a residual cysteine ligand in cytochrome P450 enzymes, we designed an unprecedented iron-catalysed non-directed arene C–H hydroxylation enabled by L-cysteine-derived ligands, which features excellent selectivities (Scheme 3). This transformation is defined by its broad substrate scope, excellent selectivity, good yields, and cost-efficient and environmentally friendly properties. Furthermore, it showcases compatibility with oxidation-sensitive functional groups such as alcohols, polyphenols, aldehydes, and even boronic acids. Notably, this method is well suited for the synthesis of polyphenols through multiple C–H hydroxylations of arenes, and the late-stage functionalization of natural products and drug molecules.” Professor Han concluded: “We anticipate that this novel method will find wide-ranging synthetic applications,

including drug metabolite synthesis, and will also enable the achievement of important insights into biological pathways.”

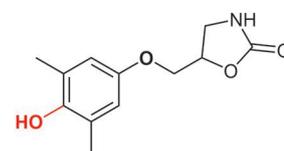
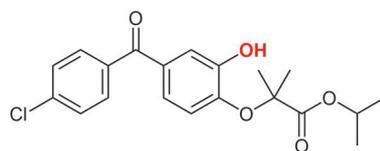
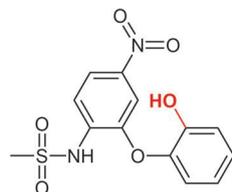
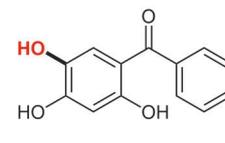
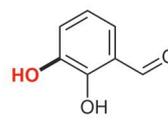
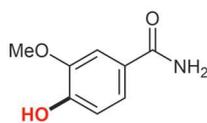
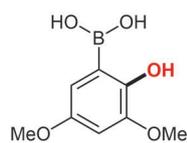
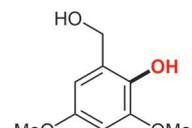
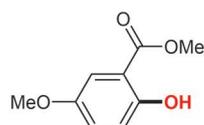
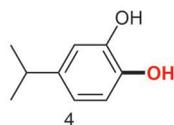
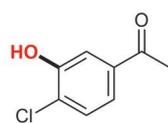
Mattias Hansson

REFERENCES

- (1) P. R. O. Montellano *Cytochrome P450: Structure, Mechanism, and Biochemistry*; Springer: Boston, 2005.



- Biologically inspired iron catalysis
- Highly selective oxidation of substituted arenes with diverse functional groups
- One-step hydroxylation of arenes without directing/protecting groups
- Compatibility with oxidation-sensitive functional groups [B(OH)₂, OH(ArOH), BnOH], CHO, CONH₂]
- General (electron-deficient, electron-rich, and electron-neutral aryl ring)
- Water as the only by-product
- Well suited for late-stage transformations



Scheme 3 Selected substrate scope

About the authors



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Lu Cheng was born and raised in Shanxi, P. R. of China. She earned her Bachelor's degree at Jinzhong University (P. R. of China). She joined Professor Wei Han's lab, Nanjing Normal University (P. R. of China), in 2017, where she started transition-metal-catalyzed C–H functionalization. She earned her Master's degree in 2020.



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iron-catalyzed C–H bond functionalization, which was rated as excellent at the end of the project.



X. Gong

Xu Gong was born in Hunan, P. R. of China. She is a senior undergraduate of the School of Chemistry and Materials Science, Nanjing Normal University (P. R. of China). In 2019, she joined Prof. Wei Han's group at the same university and hosted a provincial college students' innovation and entrepreneurship training project on iron-catalyzed oxidation, which was rated as excellent research.



Prof. W. Han

Wei Han received his B.Sc. in chemistry from the Wuhan Institute of Chemical Technology (P. R. of China) in 2005, and obtained his M.Sc. in applied chemistry from the Dalian University of Technology (P. R. of China) in 2008. In 2011, he earned his Ph.D. in organic chemistry, working with Prof. Herbert Mayr at Ludwig-Maximilians-Universität München (Germany). Subsequently, he started his independent career at Nanjing Normal University (P. R. of China) and was promoted to full professor in 2018. From 2019 to 2020, he worked with Prof. M. Christina White at the University of Illinois Urbana-Champaign (USA) as a visiting scholar. His current research interests focus on the development of novel synthetic methodologies and bioinspired catalysis.