Chinese Chemical Letters 37 (2026) 112132

Contents lists available at ScienceDirect

Chinese Chemical Letters

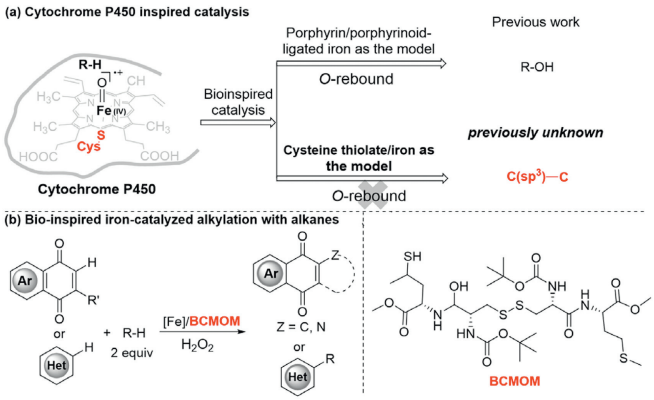
journal homepage: www.elsevier.com/locate/cclet

Editorial

# Non-canonical bio-inspired iron catalysis for aliphatic C–H functionalization

Cytochromes P450 (P450s or CYPs) constitute a largesuperfamily of heme-thiolate monooxygenases that are ubiquitous in nature. These remarkable enzymes serve as highly versatile biocatalysts capable of mediating selective oxidations across an exceptionally broad range of organic substrates. In 1979, the pioneering work of Groves and colleagues established the first biomimetic model of P450 enzymes, featuring a synthetic Fe(TPP)Cl catalyst. This landmark system was structurally inspired by the Fe(III)-protoporphyrin IX core that characterizes native P450 enzymes [1]. This seminal work inspired global research efforts and established the foundation of metalloporphyrin chemistry as a biomimetic oxidation catalytical system. Essentially, P450-inspired chemical catalysis aims to construct analogous with active-sites, particularly using porphyrin and porphyrinoid metal complexes, to emulate enzymatic oxidation reactions. However, the classical biomimetic heme iron catalysis involving high-valent iron-oxo species displays inadequate activity toward $C_{sp^3}$–H functionalization and is commonly limited to oxygenation reactions due to ultra-fast oxygen rebound (typical rate constant between $10^{10}$ $s^{-1}$ and $10^{12}$ $s^{-1}$) process [2]. The development of synthetic catalysts that emulate P450-like C($sp^3$)-H functionalization activity while circumventing competing oxygenation pathways remains a formidable challenge in catalysis, especially in intermolecular carbon–carbon bond formation reactions.

Han and co-workers have subverted the long-held perceptions in P450 biomimetic catalysis, and introduced a transformative P450-mimetic approach utilizing the characteristic axial cysteine-thiolate coordination (Scheme 1a) [3]. On the basis of this new concept, the Han group developed cysteine-inspired thiolate ligands to achieve P450-like catalysis, identifying Boc-Cys-Met-OMe (BCMOM) as the optimal ligand. This system promotes the iron-oxo species' hydrogen-atom abstraction capability from alkanes while suppressing its oxo-transfer reactivity when using $H_2O_2$ as the oxidant in $CH_3CN/H_2O$ mixture (Scheme 1b) [4]. The bioinspired iron/BCMOM catalyst enabled undirected methylene C–H functionalization with 1,4-quinones and azines, allowing direct formation of medicinally relevant C–C bonds while suppressing oxygen rebound. Notably, the reactions proceeded efficiently with only 2 equiv. of diverse alkane substrates, exhibiting site selectivities distinct from conventional approaches. Moreover, these selectivities could be rationally predicted by considering steric constraints, electronic perturbations, and

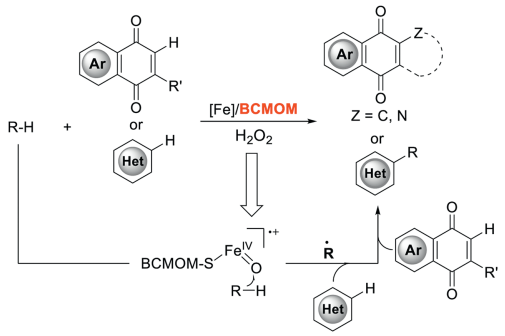



**Scheme 1.** Bio-inspired iron catalyzed aliphatic C–H functionalization.

stereoelectronic effects—even in structurally complex molecular frameworks.

Central to the success of the reactions is the use of the bioinspired BCMOM ligand. The thiolate BCMOM ligand plays a dual role in stabilizing the iron center and modulating its redox potential, thereby promoting the generation of high-valent iron-oxo intermediates. High-resolution mass spectrometry identified the formation of a key $[(acac)_2(BCMOM)_2^{\bullet+}Fe^{IV}(O)]$ species, confirming the catalytic active state. This highly electrophilic oxidant even selectively activates unactivated secondary C–H bonds without requiring directing or activating groups. Competitive kinetic isotope effect (KIE) studies using cyclohexane/$[D_{12}]$-cyclohexane mixtures revealed a moderate KIE of 2.05, significantly lower than the that observed for conventional heme iron catalysts (KIE > 3). This contrast highlights the superior efficiency of BCMOM/Fe system in cleaving inert C–H bonds, corroborating prior mechanistic studies on thiolate ligation in cytochrome P450 enzymes [5]. The hydrogen atom transfer (HAT) step generates alkyl radical intermediates, as evidenced by their efficient trapping with the radical scavenger $BrCCl_3$. This observation confirms radical escape dominates over oxygen rebound, enabling subsequent functionalization as illustrated in Scheme 2. The observed preference for secondary C–H bonds likely arises from two key factors: (1) their greater steric accessibility compared to more hindered tertiary C–H bonds, and

https://doi.org/10.1016/j.cclet.2025.112132
1001-8417/© 2025 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.




**Scheme 2.** Proposed mechanism.

(2) their higher electron density relative to primary C–H bonds. In cyclic systems, additional stereoelectronic effects may further enhance the site selectivity of secondary C–H bond functionalization.

In summary, Han and coworkers have pioneered an unconventional bioinspired iron/BCMOM catalytic system that achieves undirected functionalization of strong methylene C–H bonds using 1,4-quinones and azines. This remarkable system mimics P450-like hydrogen atom abstraction from alkanes while strategically suppressing the oxygen rebound pathway. The development of this small-molecule catalyst represents a significant breakthrough, as it enables methylene C–H functionalization with three key advantages: (1) exceptional substrate scope, (2) predictable selectivity patterns, and (3) synthetically useful yields. Such capabilities could fundamentally transform modern synthetic methodology by providing a practical solution to longstanding aliphatic C–H functionalization challenges.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Xiao-Hua Chen:** Writing – original draft. **Yifan Fan:** Writing – review & editing. **Zitong Wu:** Writing – review & editing. **Tao Tu:** Writing – review & editing.

Xiao-Hua Chen
*College of Life Sciences, Hengyang Normal University, Hengyang 421008, China*

Yifan Fan, Zitong Wu*
*State Key Laboratory of High-efficiency Utilization of Coal and Green Chemical Engineering, College of Chemistry and Chemical Engineering, Ningxia University, Yinchuan 750021, China*

Tao Tu*
*State Key Laboratory of High-efficiency Utilization of Coal and Green Chemical Engineering, College of Chemistry and Chemical Engineering, Ningxia University, Yinchuan 750021, China*
*Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Department of Chemistry, Fudan University, Shanghai 200438, China*
*Zhejiang Key Laboratory of Extreme Environment Functional Materials, Yiwu Research Institute of Fudan University, Yiwu 322000, China*

*Corresponding authors.
*E-mail addresses:* zitongwu1@nxu.edu.cn (Z. Wu), taotu@fudan.edu.cn (T. Tu).

Received 18 September 2025
Revised 13 November 2025
Accepted 17 November 2025
Available online 19 November 2025

## References

[1] J.T. Groves, T.E. Nemo, R.S. Myers, J. Am. Chem. Soc. 101 (1979) 1032–1033.
[2] M. Newcomb, M.H. Le Tadic, D.A. Putt, P.F. Hollenberg, J. Am. Chem. Soc. 117 (1995) 3312–3313.
[3] L. Cheng, H. Wang, H. Cai, et al., Science 374 (2021) 77–81.
[4] L. Zhou H. Cai, D. Xie, et al., Nat. Commun. 16 (2025) 4673.
[5] T.H. Yosca, A.P. Ledray, J. Ngo, M.T. Green, J. Biol. Inorg. Chem. 22 (2017) 209–220.