# Enantioconvergent cyclopropyl radical C–C coupling

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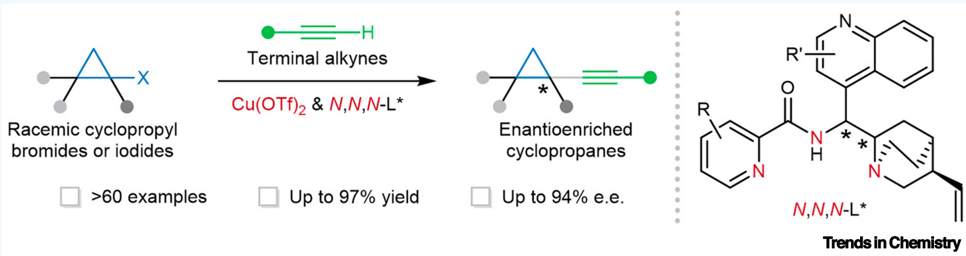
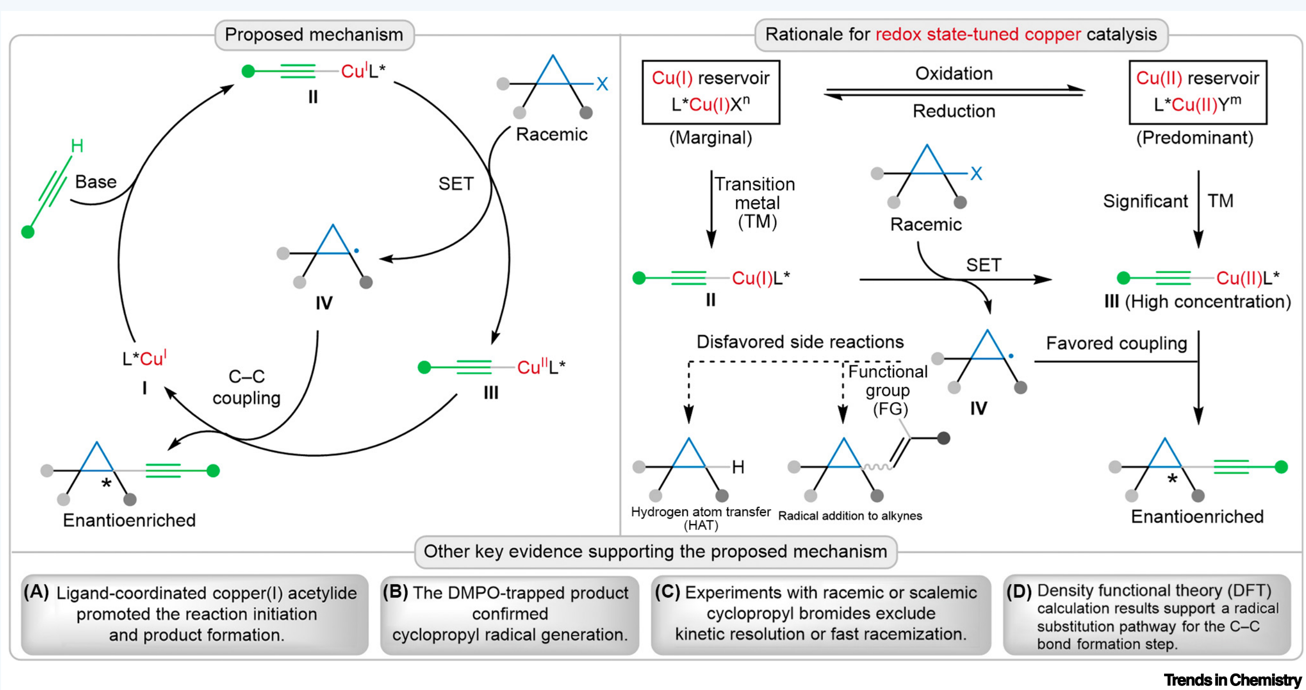



## ORIGIN

Despite successful methods for constructing synthetically useful and pharmaceutically valuable chiral cyclopropanes, catalytic enantioconvergent transformations remain underdeveloped due to challenges arising from side reactions involving highly reactive cyclopropyl radicals. Recently, our group developed a redox state-tuned Cu(II)/*N*,*N*,*N*-ligand-catalyzed enantioconvergent radical C–C coupling of readily available cyclopropyl halides with terminal alkynes, yielding enantioenriched cyclopropanes with high chemoselectivity and stereoselectivity.

## REACTION MECHANISM

Based on mechanistic experiments and previous reports, a possible reaction mechanism was proposed. Initially, the L*Cu(I) intermediate **I** undergoes transmetalation to form the L*Cu(I)–acetylide intermediate **II**. This intermediate then reduces cyclopropyl halides via single-electron transfer (SET), generating the L*Cu(II)–acetylide intermediate **III** and a cyclopropyl radical **IV**. The enantioselective C–C bond formation occurs via the coupling of intermediate **III** and radical **IV**, producing the enantioenriched cyclopropane products. Regarding redox state tuning, the Cu(I) and Cu(II) species dynamically interconvert through redox processes during the reaction. Under conditions where Cu(I) species are present in low concentrations and Cu(II) species dominate, a high proportion of Cu(II) intermediate **III** is generated through direct transmetalation. Simultaneously, a small amount of Cu(I) species reduces cyclopropyl halides, producing a low concentration of the highly reactive cyclopropyl radical **IV**. This radical efficiently reacts with the abundant Cu(II) species **III**, promoting the desired C–C cross-coupling. As a result, side reactions involving the cyclopropyl radical **IV** are significantly suppressed, demonstrating a clear chemoselectivity shift that depends on the concentration of Cu(II) species.

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https://doi.org/10.1016/j.trechm.2024.10.008

### IMPORTANCE

A robust strategy for the enantioconvergent radical carbon–carbon cross-coupling of abundant racemic cyclopropyl halides with terminal alkynes has been successfully established. Critical to its success is the redox-state tuning of copper catalysts, which provides a new method for assembling a diverse range of synthetically challenging enantioenriched cyclopropanes. We anticipate that this strategy will be further applied to enantioconvergent cross-coupling reactions of highly reactive alkyl radicals with assorted nucleophiles.

### Acknowledgments

Financial support from the National Natural Science Foundation of China (Nos. 22025103, 92256301, 22331006 to X.-Y.L.; 22271133 to Q.-S.G.; 22201127 to L.L.), the National Key R&D Program of China (Nos. 2021YFF0701604 and 2021YFF0701704 to X.-Y.L.), the Guangdong Innovative Program (No. 2019BT02Y335 to X.-Y.L.), the Guangdong Major Project of Basic and Applied Basic Research (No. 2023B0303000020 to X.-Y.L.), the New Cornerstone Science Foundation through the XPLORER PRIZE (to X.-Y.L.), the Shenzhen Science and Technology Program (Nos. KQTD20210811090112004 to X.-Y.L. and Q.-S.G.; JCYJ20220818100600001 to X.-Y.L.), the Shenzhen Key Laboratory of Cross-Coupling Reactions (No. ZDSYS20220328104200001 to X.-Y.L.), the High-Level of Special Funds (No. G03050K003 to X.-Y.L.), and the High-Level Key Discipline Construction Project (No. G030210001 to X.-Y.L. and Q.-S.G.) is gratefully acknowledged.

### Declaration of interests

The authors declare no competing interests.

### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to correct the English grammar of the initial draft. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## Literature

1. Gao, Z. *et al.* (2024) Copper-catalysed synthesis of chiral alkynyl cyclopropanes using enantioconvergent radical cross-coupling of cyclopropyl halides with terminal alkynes. *Nat. Synth.*, Published online September 26, 2024. https://doi.org/10.1038/s44160-024-00654-x
2. Fu, G.C. (2017) Transition-metal catalysis of nucleophilic substitution reactions: a radical alternative to $S_N1$ and $S_N2$ processes. *ACS Cent. Sci.* 3, 692–700
3. Dong, X.-Y. *et al.* (2022) Ligand development for copper-catalyzed enantioconvergent radical cross-coupling of racemic alkyl halides. *J. Am. Chem. Soc.* 144, 17319–17329
4. Mondal, S. *et al.* (2022) Enantioselective radical reactions using chiral catalysts. *Chem. Rev.* 122, 5842–5976
5. Talele, T.T. (2016) The "cyclopropyl fragment" is a versatile player that frequently appears in preclinical/clinical drug molecules. *J. Med. Chem.* 59, 8712–8756
6. Dian, L. *et al.* (2018) Asymmetric preparation of polysubstituted cyclopropanes based on direct functionalization of achiral three-membered carbocycles. *Chem. Rev.* 118, 8415–8434
7. Bhat, V. *et al.* (2017) Advances in stereoconvergent catalysis from 2005 to 2015: transition-metal-mediated stereoablative reactions, dynamic kinetic resolutions, and dynamic kinetic asymmetric transformations. *Chem. Rev.* 117, 4528–4561
8. Cohen, T. *et al.* (1977) A simple preparation of phenols from diazonium ions via the generation and oxidation of aryl radicals by copper salts. *J. Org. Chem.* 42, 2053–2058
9. Teator, A.J. *et al.* (2016) Switchable polymerization catalysts. *Chem. Rev.* 116, 1969–1992
10. Chen, S.-J. *et al.* (2023) Copper-catalyzed benzylic C–H cross-coupling enabled by redox buffers: expanding synthetic access to three-dimensional chemical space. *Acc. Chem. Res.* 56, 3604–3615



https://doi.org/10.1016/j.trechm.2024.10.008