Title: Catalytic asymmetric oxidative coupling between C(sp^3)–H bonds and carboxylic acids

Authors: Xian-Ming Liu[1,#], Fu Li[1,#], Tongkun Wang[2], Ling Dai[1], Yin Yang[1], Neng-Quan Jiang[1], Li-Yuan Xue[1], Jing-Yuan Liu[1], Xiao-Song Xue[2,*], Li-Jun Xiao[1,*], and Qi-Lin Zhou[1,*]

Affiliation:

[1] State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Frontiers Science Center for New Organic Matter, Nankai University, Tianjin 300071, China

2 State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Corresponding author email: xuexs@sioc.ac.cn, ljxiao@nankai.edu.cn, qlzhou@nankai.edu.cn

[#]These two authors contributed equally

One Sentence Summary: A copper-catalyzed direct enantioselective oxidative coupling of allylic and propargyl C(sp^3)–H bonds with carboxylic acids is developed.

Abstract: Direct enantioselective functionalization of C(sp^3)–H bonds in organic molecules could fundamentally transform the synthesis of chiral molecules. In particular, the enantioselective oxidation of these bonds would dramatically change the production of chiral alcohols and esters, which are prevalent in natural products, pharmaceuticals, and fine chemicals. Remarkable advances have been made in the enantioselective construction of carbon-carbon and carbon-nitrogen bonds through C(sp^3)–H bond functionalization. However, the direct enantioselective formation of carbon-oxygen bonds from C(sp^3)–H bonds remains a considerable challenge. We herein report a highly enantioselective C(sp^3)–H bonds oxidative coupling with carboxylic acids using molecular copper catalyst activated by blue light. The method applies to allylic and propargyl C–H bonds and more importantly employs various carboxylic acids as oxygenating agents. By this method, we have successfully synthesized a range of chiral esters directly from readily available alkenes and alkynes, greatly simplifying the synthesis of chiral esters and related alcohols.

Introduction

Direct enantioselective functionalization of C(sp^3)–H bonds in organic molecules is one of the ultimate goals of organic synthesis due to its remarkable atom-economy and step-economy (*1–6*). Methods such as the enantioselective oxidation of the C(sp^3)–H bonds, which involve directly introducing oxygen functionalities into alkanes, hold significant potential for the discovery and development of new pharmaceuticals (*7–9*). Chiral oxygenated aliphatic structures are common in bioactive compounds such as natural products and pharmaceuticals (*10*, *11*). Recent progress has been made in enantioselective C–C and C–N bond formation from C(sp^3)–H bonds using transition-metal catalysts (*12–16*). However, the enantioselective formation of C–O bonds by C(sp^3)–H oxidation remains a formidable challenge (Fig. 1A) (*17–24*). This difficulty stems from oxygen's tendency as a harder base to coordinate strongly with hard acids according to the Hard and Soft Acids and Bases (HSAB) theory (*25–26*). Oxygen often exhibits poor coordination with late-transition metals, which are soft acids (*27–29*). This mismatch results in low reactivity and enantioselectivity in these oxidation reactions and frequently causes overoxidation to ketones. (*30*).

In nature, enzymes such as cytochrome P-450 (Fig. 1A) demonstrate remarkable efficiency in catalyzing stereoselective oxidations (*31*, *32*), utilizing an iron-porphyrin center to target C(sp^3)–H bonds (*33–40*). Inspired by the high oxidation state (Fe(IV)) iron-oxo complexes in heme-containing enzymes, we hypothesized that increasing the electropositivity at the metal center of catalysts may benefit the enantioselective oxidation of the C(sp^3)–H bonds (Fig. 1A) (*27–29*). Our strategy employs a bulky counter anion, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F^-), to enhance the electropositivity of the copper center of the catalyst (Fig. 1B). This electropositivity enhancement improves the coordination of carboxylic acids with copper, and facilitates their interactions with radicals generated by the C(sp^3)–H hydrogen atom abstraction. Crucially, the anion BAr_F^- stabilizes the copper^{III} intermediate, which undergoes reductive elimination to form the C–O bond.

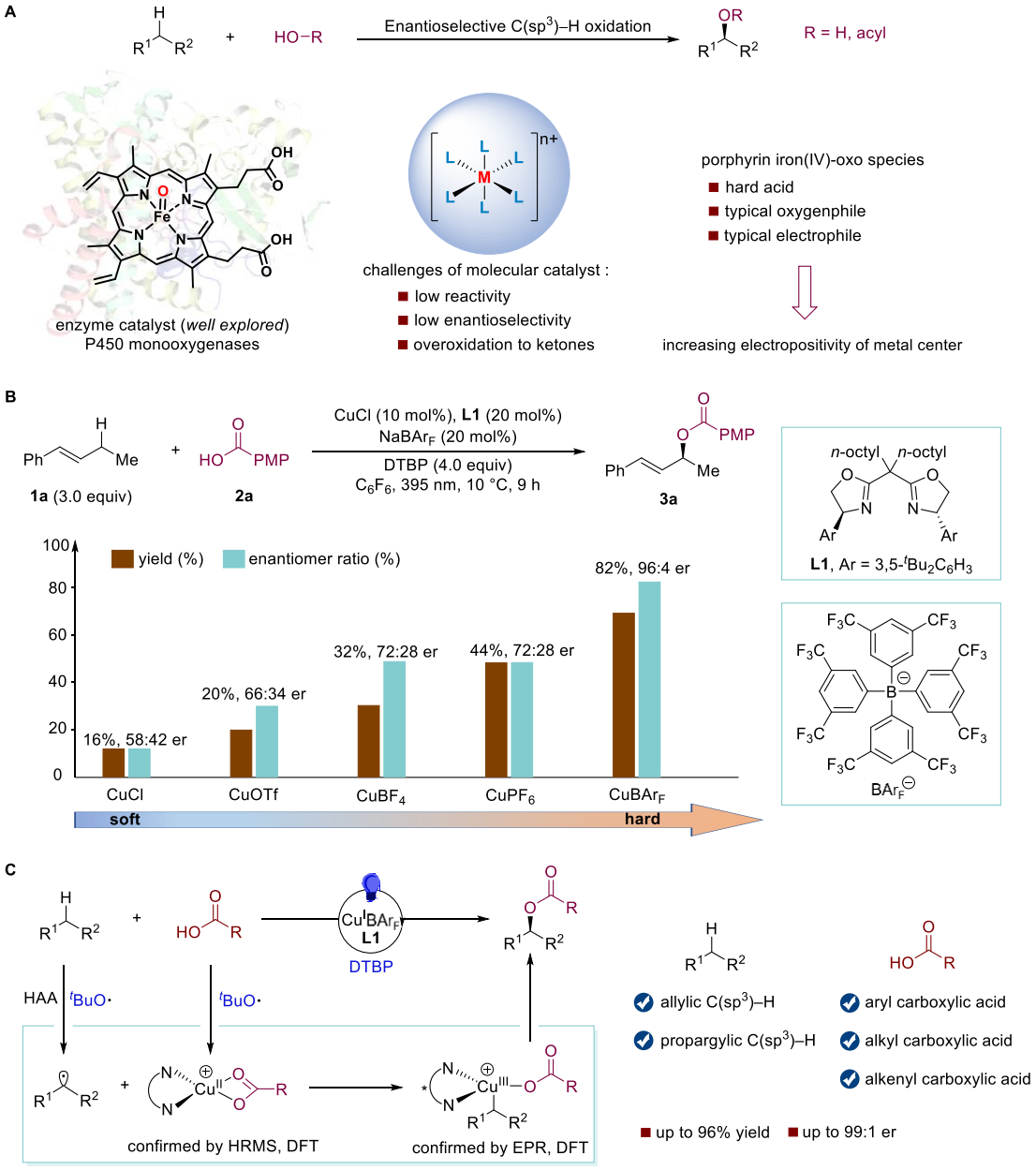

Fig. 1 | Overview of the strategies for enantioselective C(sp^3)–H oxidation. A, Challenges of enantioselective oxidation of C(sp^3)–H bonds. **B**, Effect of electropositivity at the copper center. **C**,

Design for enantioselective oxidative coupling of C(sp^3)–H with carboxylic acids using a molecular copper catalyst. PMP, *para*-$MeOC_6H_4$. DTBP, di-*tert*-butyl peroxide.

We are excited to present our newly developed method for the enantioselective oxidative coupling of C(sp^3)–H bonds with various carboxylic acids using a cationic copper catalyst under blue light irradiation (Fig. 1C). This innovative approach addresses major limitations that have constrained the Kharasch reaction—a traditional method for oxidizing alkenes into allyl esters—for over six decades (*41*, *42*). While recent progress has been made in improving the enantioselectivity of the Kharasch reaction of cyclic alkenes (*43–50*), challenges remain, in particular the poor performance of open-chain alkenes and the limitations imposed by the use of peroxy esters as oxygen nucleophiles. By utilizing open-chain alkenes and alkynes, our method greatly expands the reaction's scope. More significantly, our method employs carboxylic acids instead of peroxy esters as oxygen nucleophiles, thus endowing the C(sp^3)–H bond oxidation reaction practical. Furthermore, we have identified Cu^{III} intermediates in this reaction using electron paramagnetic resonance. Traditionally, only Cu^{I} and Cu^{II} states have been observed in catalytic cycles; the identification of high oxidation states such as Cu^{III} adds an essential dimension to our understanding of copper-catalyzed oxidation reactions.

Results and discussion

We initiated our study by exploring the oxidative coupling reaction of (*E*)-1-phenyl-1-butene (**1a**) with 4-methoxybenzoic acid (**2a**), detailed in the Supplementary Material. After an extensive screening process, such as various copper sources, ligands, oxidants, solvents, temperature settings, and light sources, we found that the chiral copper catalyst, with BAr_F^- as counter anion, promoted the enantioselective oxidation of the allylic C–H bond of **1a** under mild conditions (10 °C, illuminated by 395 nm LEDs). Under the optimal conditions, the reaction yielded the target product **3a** with high yield (82%) and excellent enantioselectivity (96:4 enantiomer ratio [er]) (see Table. S1). Control experiments confirmed the necessity of CuCl, ligand **L1**, $NaBAr_F$, di-*tert*-butyl peroxide (DTBP), and light for the success of the reaction. Among the tested oxidants, DTBP was superior, with others like Selectfluor and *N*-fluorobenzenesulfonimide (NFSI) yielding low yield and enantioselectivity, or failing to produce the target product at all. Bisoxazoline ligands with bulky substituents enhanced enantioselectivity, with the ligand **L1** containing 3,5-di-*tert*-butylphenyl groups, having the highest enantioselectivity (Table. S1–S4).

Substrate scope. Under optimal conditions, we first studied a range of (*E*)-1-arylbutenes **1** in the reaction with *p*-methoxybenzoic acid (**2a**) (Fig. 2). The substituent at the *para* position of the benzene ring of the alkene substrates has little impact on the enantioselectivity of the reaction (**3b**–**3k**, 91:9–98:2 er), but the strong electron-withdrawing group *p*-CF_3 (**3e**) leads to a decrease in yield (40%). Notably, in the presence of both benzylic and allylic C–H bonds, the oxidation occurred exclusively at the allylic C–H bond (**3h**). Substrates with *meta*- (**3l**–**3n**, **3q**) and *ortho*-substituents (**3o** and **3p**) on the benzene ring afforded higher enantioselectivities (94:6–99:1 er) due to steric effect. However, the 3-bromo- (**3n**, 45%) and 3,5-dichloro-substitution (**3q**, 38%) resulted in lower yields. The alkene substrate with a 2-naphthyl ring also worked well, yielding the desired product **3r** with 51% yield and 93:7 er. Furthermore, the reaction has good compatibility with the substrate alkyl chain and its functional groups, and the corresponding chiral allyl esters (**3s**–**3w**) were obtained with a yield of 51–70% and enantioselectivity of 92:8–98:2 er. The configuration of the

product **3k** was determined to be *S* by single crystal X-ray diffraction analysis.

Next, we investigated a range of carboxylic acids in the reaction with alkene **1a**. The allylic C–H oxidation reaction has a broad scope of carboxylic acids (Fig. 2). Aromatic acids, including those with diverse substituents on the aryl ring and heteroaromatic acids afforded the desired allyl esters (**3x**–**3ae**) with good yields (69–88%) and high enantioselectivities (91:9–96:4 er). Aliphatic acids with different alkyl chains, alkyl rings and ketone group can undergo the reaction, and showed high enantioselectivity (**3af**–**3am**, 94:6–96:4 er). Moreover, the unsaturated cinnamic acid can also react with alkene **1a**, yielding oxidative coupling product **3an** with excellent enantioselectivity (98:2 er). These results demonstrated that the reaction has a broad substrate scope.

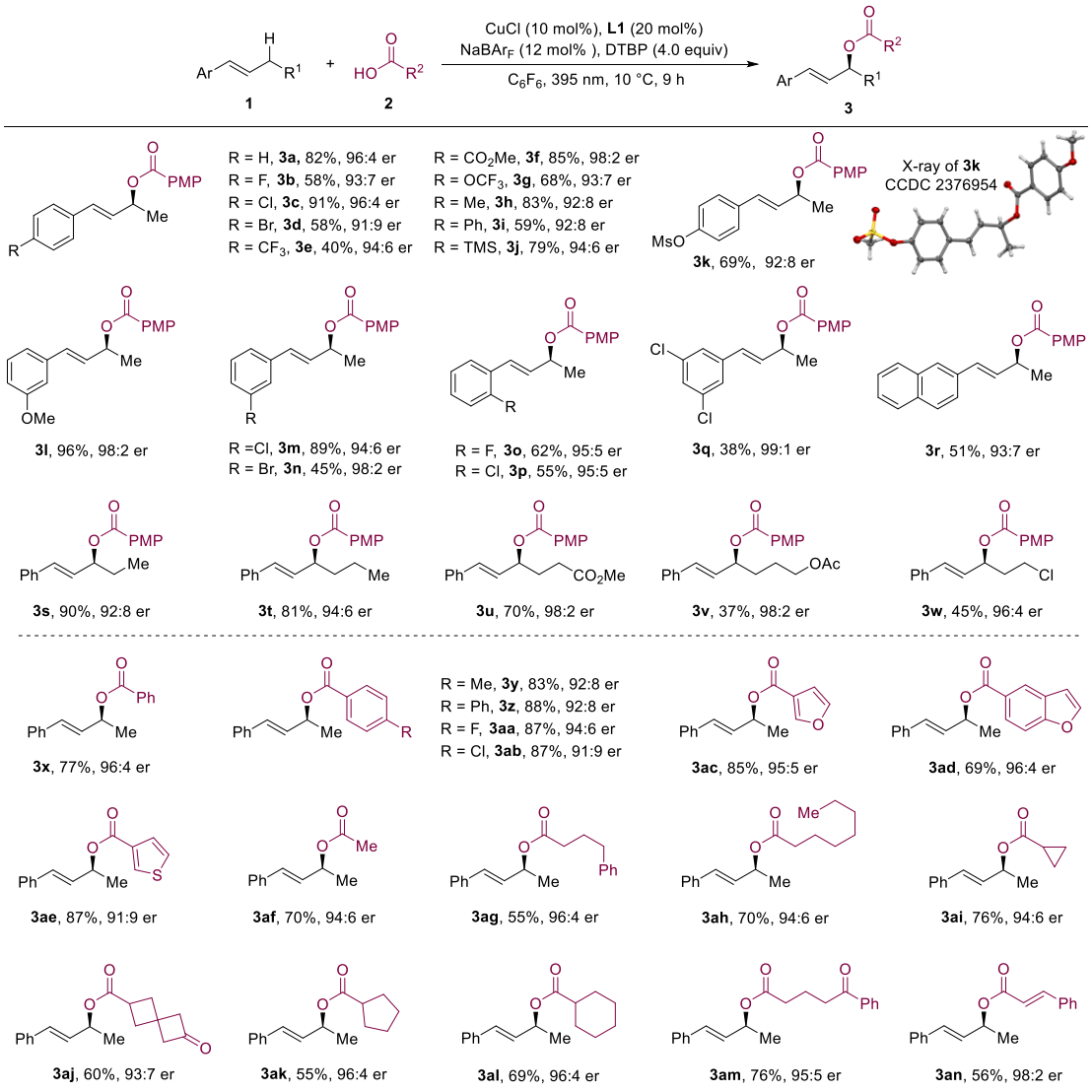

Fig. 2 | Enantioselective oxidative coupling of alkene C(sp^3)–H bonds with carboxyl acids. PMP, *para*-MeOC$_6$H$_4$.

Alkynes are also suitable substrates for the enantioselective oxidative coupling with carboxylic acids, producing propargyl esters (*51*–*52*). By switching the solvent from hexafluorobenzene to 1,2-dichlorobenzene, changing the light wavelength from 395 nm to 365 nm, and lowering the reaction temperature to 0 °C, we successfully realized the reaction of various alkynes with acid **2a** (Fig. 3). All tested aryl alkynes, including those with substituents at the aryl ring and heteroarylalkynes

showed reasonable yield and high enantioselectivities (**5s**–**5v**, 91:9–97:3 er). The effect of substrate alkyl chain and its ester group on the enantioselectivity of the reaction is negligible (**5s**–**5v**).

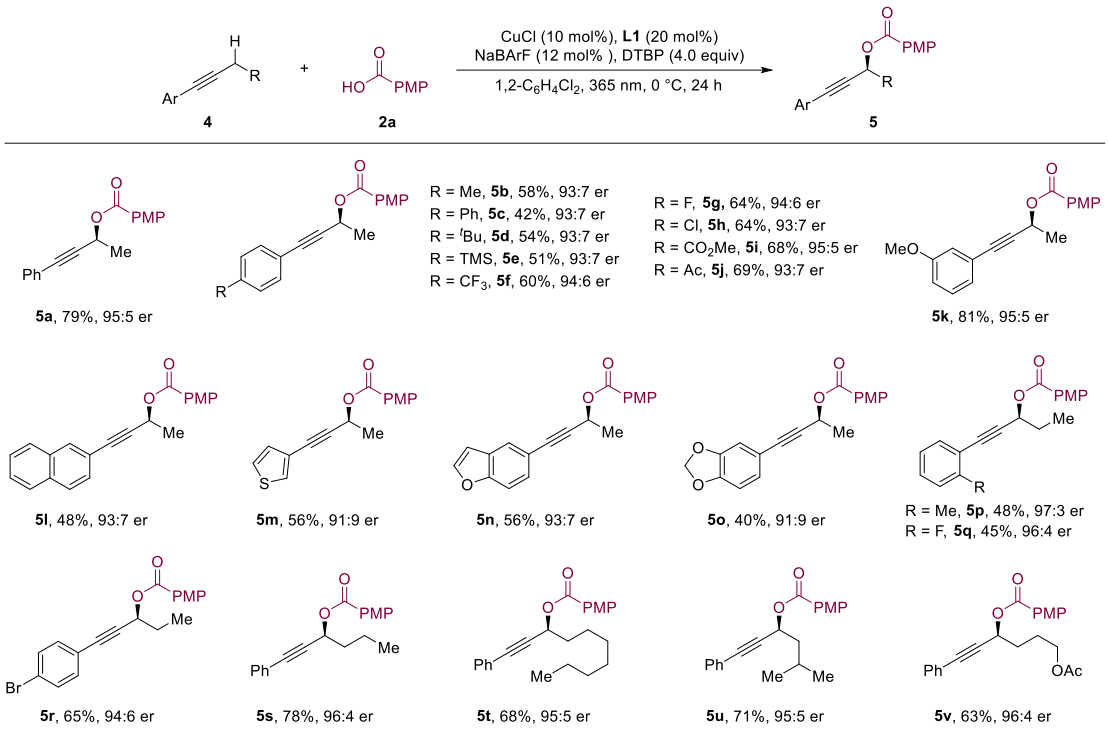

Fig. 3 | Enantioselective oxidative coupling of alkyne C(sp^3)–H bonds with carboxyl acids.

Applications. To demonstrate the potential of enantioselective oxidative coupling reaction in organic synthesis, we applied our method to the derivatization of bioactive molecules, which is a commonly used strategy for drug discovery (Fig. 4). Medicines containing a carboxylic acid group, such as ibuprofen, naproxen, probenecid, and gemfibrozil, reacted with (*E*)-but-1-en-1-ylbenzene to produce the corresponding allyl esters (**3ao**–**3ar**) with high diastereoselectivity or enantioselectivity. The natural product ursolic acid has three allyl sites, and only one site (**3as** and **3at**) reacts with *p*-methoxybenzoic acid, showing an excellent site-selectivity. The alkynes derived from tigogenin (**5w**) and dihydrocholesteol (**5x**) can be coupled with acid to form propargyl C–H bond oxidation products with high enantioselectivity. These examples underscored the high efficiency of the enantioselective oxidative coupling of C(sp^3)–H bonds with carboxylic acids—the direct synthesis of chiral esters from alkenes and alkynes—and their broad applicability in bioactive molecule synthesis and drug discovery.

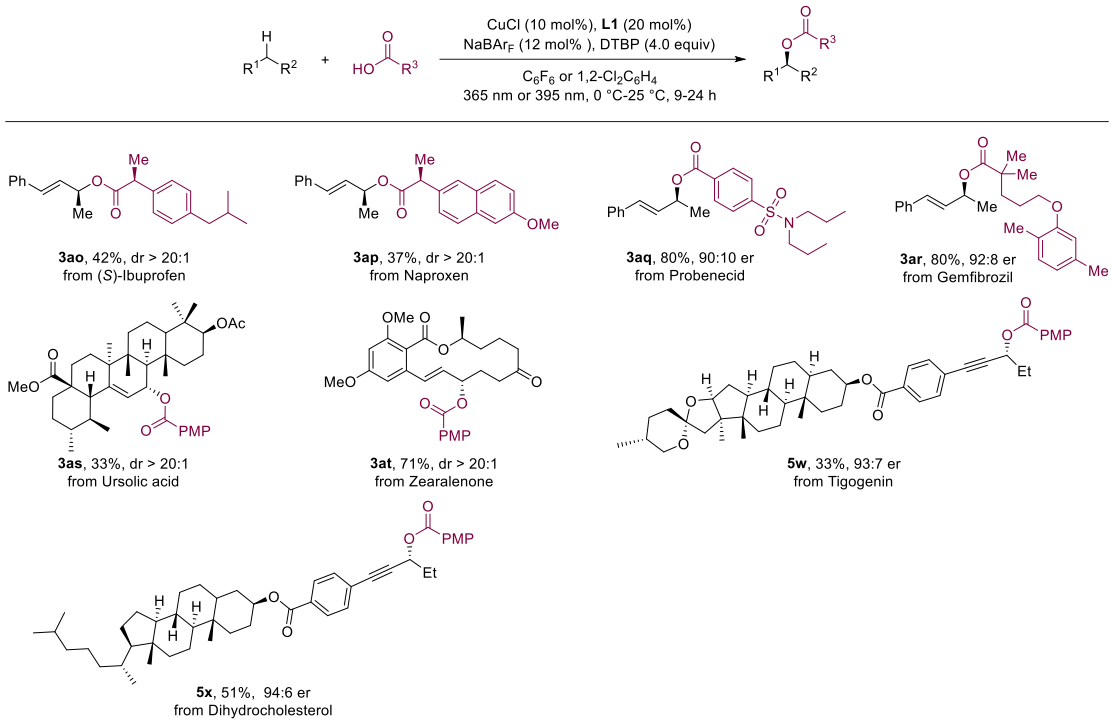

Fig. 4 | Applications of enantioselective C(sp^3)–H bond oxidation in the derivatization of bioactive molecules.

Mechanism studies. Although the mechanism of copper-catalyzed alkene oxidation reactions like the Kharasch reaction has been proposed, some key issues have not been clarified. In particular, the Cu^{III} intermediates frequently mentioned in the mechanism have not been experimentally confirmed (*53*,*54*). To elucidate the mechanism of the oxidative coupling of C(sp^3)–H bonds with carboxylic acids, we conducted radical trapping experiments using 2,2,6,6-tetramethyl-1-oxylpiperidine (TEMPO). The inhibition of the reaction by TEMPO indicated that radicals are involved in the reaction (Fig. 5A). The kinetic isotope effect experiments showed that the k_H/k_D ratios of the three reactions are 3.1 and 3.3, respectively (Fig. 5B), suggesting that the hydrogen atom abstraction from the C(sp^3)–H bond may be a rate-limiting step. We prepared the complexes Cu^{II}-O^{t}Bu and Cu^{II}-OBz, called **Int-I** and **Int-II** respectively, and used them to catalyze the reaction to obtain the desired product (Fig. 5C), which indicates that the reaction went through the intermediates **Int-I** and **Int-II**. A series of electron paramagnetic resonance (EPR) measurements were performed to identify the various free radicals in the reaction. The EPR spectra of intermediates **Int-I**, **Int-II,** and catalyst prepared in-situ showed the presence of Cu^{II} (Fig. 5D). We are excited to have detected Cu^{III} intermediate in the reaction solution by low-temperature EPR analysis (Fig. 5E), which is the first experimental confirmation of the presence of Cu^{III} in a Cu-catalyzed reaction. We also verified by EPR analysis that the *tert*-butoxy radicals were mainly generated by the photodecomposition of DTBP (Fig. 5F). Finally, the light on/off experiments showed that ceasing irradiation halted the reaction (Fig. 5G), indicating that the reaction does not involve the radical chain mechanism.

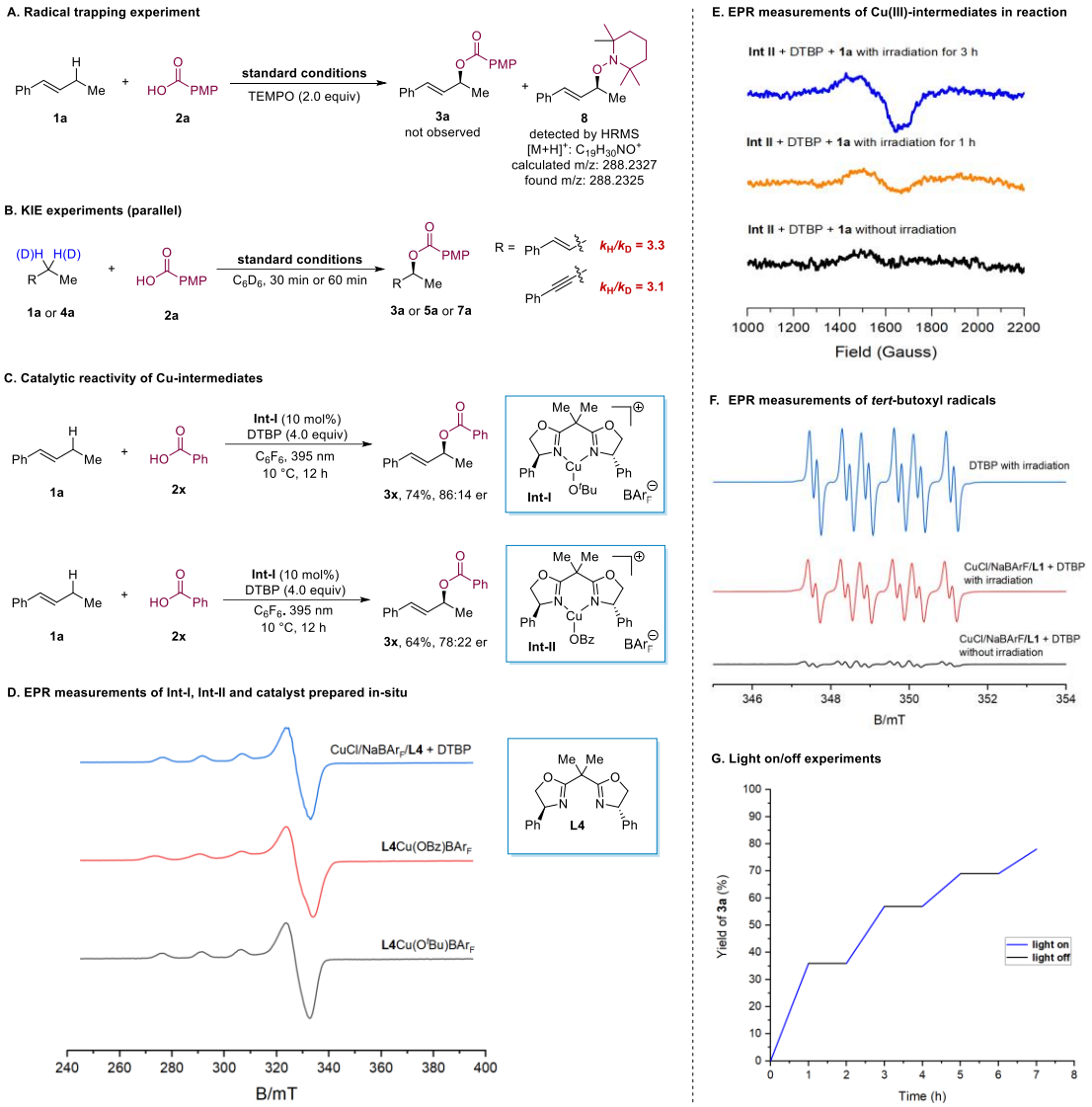

Fig. 5 | Mechanism studies. A, Radical trapping experiment. **B**, Kinetic isotope effect (KIE) experiments. **C**, Catalytic reactivity of Cu-intermediates. **D**, EPR measurements of **Int-I**, **Int-II**, and the catalyst prepared in-situ. **E**, EPR measurements of Cu^{III}-intermediates in reaction. **F**, EPR measurements of *tert*-butoxyl radicals. **G**, Light on/off experiments.

DFT calculation. DFT calculations were conducted to gain a better understanding of the reaction mechanism. The results are shown in Fig. 6. Starting from the Cu^{I} catalyst, the complexation with *tert*-butoxy radical to form Cu^{II}-O^{t}Bu intermediate **Int-I** and subsequent ligand substitution with carboxylic acid to form Cu^{II}-OBz intermediate **Int-II** are both significantly exergonic. Radical addition of **1a** to the Cu^{II} center to form a Cu^{III} intermediate **Int-III** requires an energy barrier of 7.6 kcal/mol via an open-shell singlet (OSS) transition state **TS-III-OSS**. The Cu^{III} intermediate **Int-III** lies 2.4 kcal/mol above the Cu^{II}-OBz intermediate **Int-II**. Intermediate **Int-III** then undergoes an outer-sphere reductive elimination process via **TS-S-allylic-RA** with a barrier of 4.6 kcal/mol to form **Int-IV**. Finally, radical addition of another ^{t}BuO radical to **Int-IV** facilitates its dissociation to afford product **3a** while recycling the catalyst to **Int-1**. Besides, the generation of **1a** radical requires an energy barrier of 9.8 kcal/mol, which is the rate-determining step in the proposed mechanism and is consistent with kinetic isotope effect experiments.

Both enantio- and regioselectivity achieved by using **L1** are well reproduced with this mechanism. As shown in Fig. 6B, TS-R-allylic-RA and TS-S-benzylic-RA are 3.9 kcal/mol and 5.8 kcal/mol less stable than TS-S-allylic-RA, respectively. These calculated results agree well with experimental findings on enantioselectivity (96:4 er) and regioselectivity. The enantioselectivity likely arises from stronger steric repulsions in transition state structures leading to unfavored products compared with TS-S-allylic-RA. Indeed, changing the ligand from **L1** to a simplified ligand **L4** leads to decreased enantioselectivity (Table. S1–S4), and the calculated results show a consistent trend (Fig. S17), which further supports the reliability of the proposed mechanism.

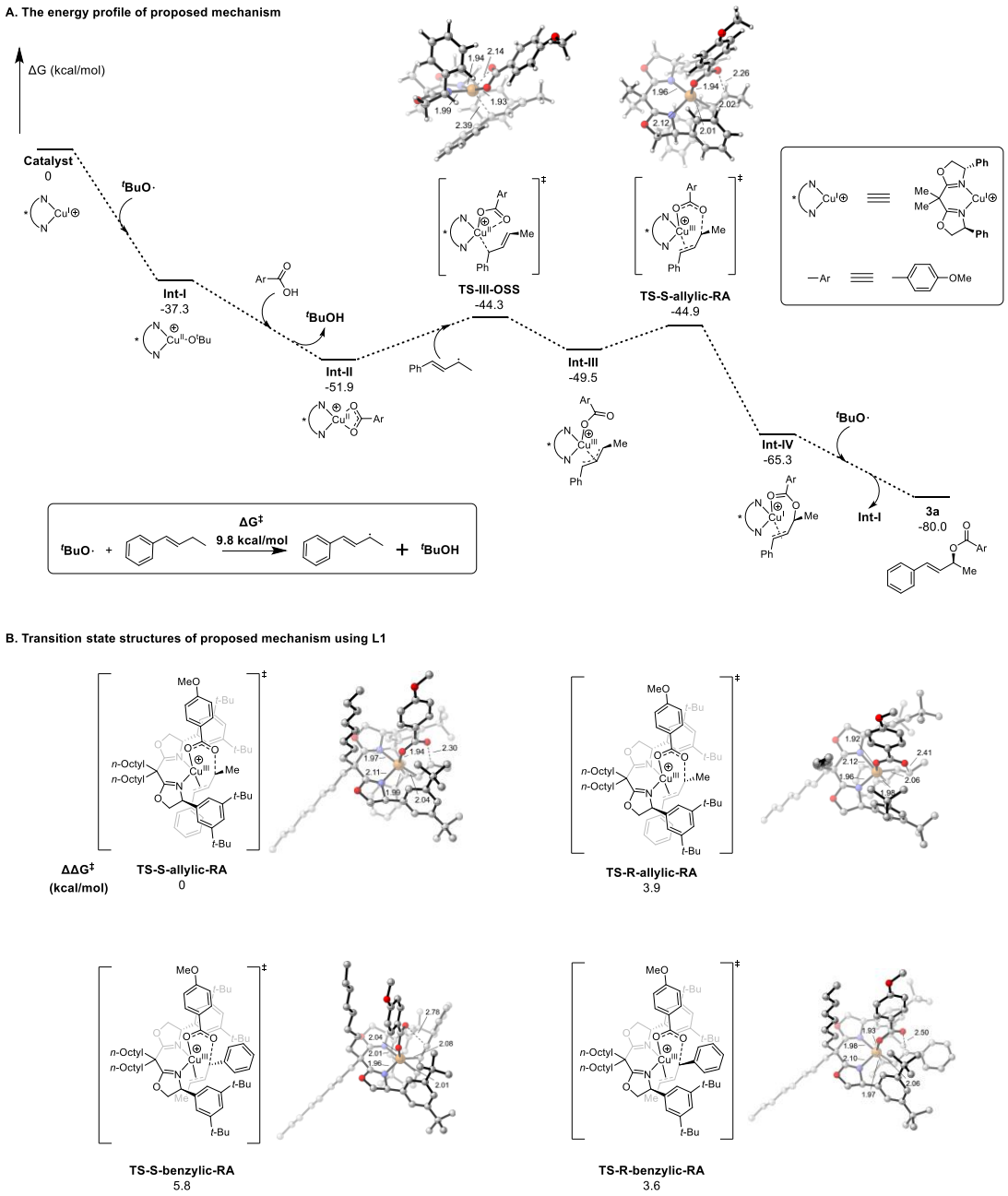

Fig. 6 | A, Energy profile of proposed mechanism, **B**, Transition state structures of the proposed mechanism using **L1**. H atoms are hidden for better clearance. Numbers in figures of optimized structures of transition states denote key bond lengths. Unit: Å.

Our DFT simulations also explained the importance of BAr_F^- as the counter ion for separating Cu^I center and Cl^- ion. In Fig. S18, if the Cu^I center is coordinated by a Cl^- ion, starting from **Catalyst-Cl**, the overall reaction to afford **3a** is still downhill. However, the transition state **TS-S-Cl** necessitates an energy barrier of 18.2 kcal/mol for reductive elimination to afford **3a** while recycling **Catalyst-Cl**. The significantly high energy barrier handicaps the overall reaction so that the yield is low (16%) without $NaBAr_F$, as shown in Fig. 1B. Besides the proposed reaction pathway, other possible coordination structures are also tested (Fig. S19). However, energy changes for forming such structures are significantly more positive compared with that of **TS-III-OSS**.

On the basis of our experimental findings, DFT calculations, and literature reports (*15*, *16*, *56*–*59*) we propose that the enantioselective oxidative coupling of C(sp^3)–H with carboxylic acids proceed by the mechanism shown in Fig. 7. In the reaction, irradiation decomposes DTBP to *tert*-butoxy radicals, which react with Cu^I complex to form Cu^{II}-O^{t}Bu intermediate **Int-I** and abstract a hydrogen atom from the substrate to form allyl radical. The **Int-I** undergoes a ligand exchange reaction with acid to generate Cu^{II}-OBz intermediate **Int-II**, which combines with allyl radical to generate intermediate **Int-III**. Intramolecular coupling of the acyl and allyl groups on the catalyst results in the intermediate **Int-IV**. The intermediate **Int-IV** reacts with the *tert*-butoxy radical to produce allyl ester and regenerate catalyst **Int-I**.

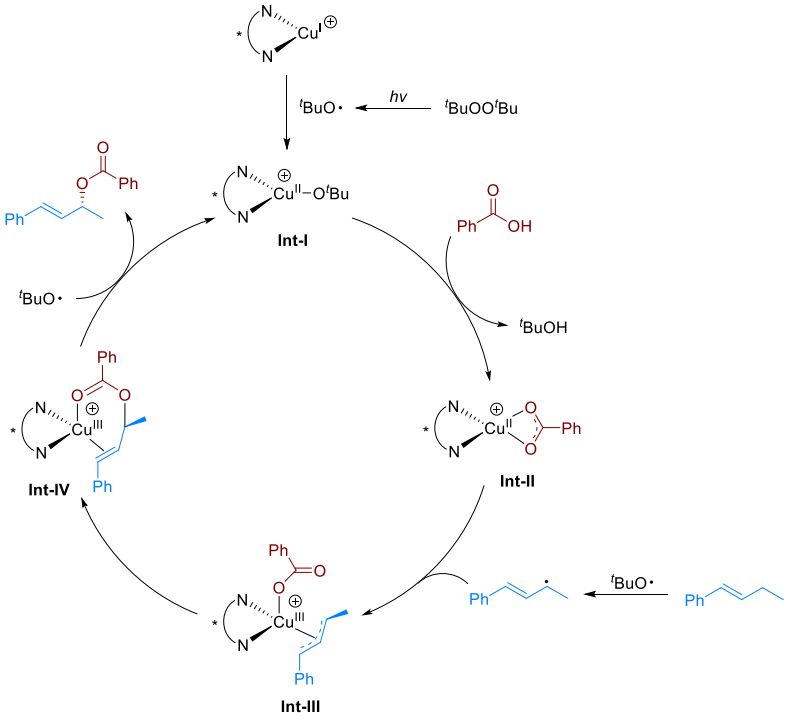

Fig. 7 | Proposed mechanism.

In summary, we have developed a cationic copper catalysis approach that enables the enantioselective oxidative coupling of allylic and propargyl C(sp^3)–H bonds with carboxylic acids under blue light. This method not only broadens the asymmetric Kharasch reaction to encompass open-chain alkenes and alkynes, but also eliminates the need for peroxy esters as oxygen nucleophiles. Utilizing this method, we successfully synthesized various chiral esters directly from readily accessible C(sp^3)–H substrates, achieving good to high enantioselectivities. Our research

opens new avenues for the asymmetric functionalization of unactivated C(sp^3)–H bonds. Furthermore, the identification of Cu^{III} intermediate not only deepens understanding of copper-catalyzed reaction but also lays a solid foundation for its exploration and application in a wide field of chemistry.

Methods

Enantioselective oxidative coupling of (*E*)-but-1-en-1-ylbenzene with *p*-methoxybenzoic acid

In an argon atmosphere, CuCl (1.0 mg, 0.01 mmol), **L1** (15.1mg, 0.02 mmol), $NaBAr_F$ (10.6 mg, 0.012 mmol), C_6F_6 (2 mL) were mixed in a vial. The mixture was stirred for 15 min, and *p*-methoxybenzoic acid (15.2 mg, 0.1 mmol) and (*E*)-but-1-en-1-ylbenzene (40 mg, 0.3 mmol) and DTBP (75 uL, 0.4 mmol) were added into the vial. The mixture was stirred at 10 °C (internal temperature) under the irradiation of 12 W 395 nm LEDs. After stirring for 9 h, the reaction mixture was quenched by exposure to air. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel to obtain product **3a** in 82% yield with 96:4 er.

References and Notes:

1. T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, Enantioselective C(sp^3)–H bond activation by chiral transition metal catalysts. *Science* **359**, eaao4798 (2018). doi: 10.1126/science.aao4798

2. C. Zhang, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, Catalytic Enantioselective C(sp^3)–H Functionalization Involving Radical Intermediates. *Nat Commun* **12**, 475 (2021). doi: 10.1038/s41467-020-20770-4

3. D. L. Golden, S.-E. Suh, S. S. Stahl, Radical C(sp^3)–H functionalization and cross-coupling reactions. *Nat Rev Chem* **6**, 405–427 (2022). doi: 10.1038/s41570-022-00388-4

4. Z. Zhang, P. Chen, G. Liu, Copper-catalyzed radical relay in C(sp^3)–H functionalization. *Chem. Soc. Rev.* **51**, 1640–1658 (2022). doi: 10.1039/D1CS00727K

5. X. Chen, S. Kramer, Photoinduced Transition-Metal-Catalyzed Enantioselective Functionalization of Non-acidic C(sp^3)−H Bonds. *Chem Catal.* **4**, 100854 (2024). doi: 10.1016/j.checat.2023.100854

6. G.-Q. Xu, W. D. Wang, P.-F. Xu, Photocatalyzed Enantioselective Functionalization of C(sp^3)–H Bonds. *J. Am. Chem. Soc.* **146**, 1209–1223 (2024). doi: 10.1021/jacs.3c06169

7. K. P. Bryliakov, Transition Metal-Catalyzed Direct Stereoselective Oxygenations of C(sp^3)–H Groups. *ACS Catal.* **13**, 10770–10795 (2023). doi: 10.1021/acscatal.3c02282

8. M. C. White, J. Zhao, Aliphatic C–H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **140**, 13988–14009 (2018). doi: 10.1021/jacs.8b05195

9. Y. Liu , T. You, H.-X. Wang, Z. Tang, C.-Y. Zhou, C.-M. Che, Iron- and Cobalt-Catalyzed C(sp3)–H Bond Functionalization Reactions and Their Application in Organic Synthesis. *Chem. Soc. Rev.* **49**, 5310–5358 (2020). doi: 10.1039/D0CS00340A

10. J. Cramer, C. P. Sager, B. Ernst, Hydroxyl Groups in Synthetic and Natural-Product-Derived Therapeutics: A Perspective on a Common Functional Group. *J. Med. Chem.* **62**, 8915–8930 (2019). doi: 10.1021/acs.jmedchem.9b00179

11. S. N. Charlton, M. Hayes, A. Oxygenating Biocatalysts for Hydroxyl Functionalisation in Drug Discovery and Development. *ChemMedChem* **17**, e202200115 (2022). doi: 10.1002/cmdc.202200115

12. W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, Enantioselective Cyanation of Benzylic C–H Bonds via Copper-Ccatalyzed Radical relay. *Science* **353**, 1014–1018 (2016). doi: 10.1126/science.aaf7783

13. J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin, G. Liu, Site-Specific Allylic C–H Bond Functionalization with a Copper-Bound *N*-Centred Radical. *Nature* **574**, 516–521 (2019). doi: 10.1038/s41586-019-1655-8

14. P. Xu, J. Xie, D.-S. Wang, X. P. Zhang, Metalloradical Approach for Concurrent Control in Intermolecular Radical Allylic C−H Amination. *Nat. Chem.* **15**, 498–507 (2023). doi: 10.1038/s41557-022-01119-4

15. L. Dai, Y.-Y. Chen, L.-J. Xiao, Q.-L. Zhou, Intermolecular Enantioselective Benzylic C(sp^3)–H Amination by Cationic Copper Catalysis. *Angew. Chem. Int. Ed.* **62**, e202304427 (2023). doi: 10.1002/anie.202304427

16. X. Chen, Z. Lian, S. Kramer, Enantioselective Intermolecular Radical Amidation and Amination of Benzylic C−H Bonds via Dual Copper and Photocatalysis. *Angew. Chem. Int. Ed.* **62**, e202217638 (2023). doi: 10.1002/anie.202217638

17. J. M. Lee, E. J. Park, S. H. Cho, S. Chang, Cu-Facilitated C–O Bond Formation Using *N*-Hydroxyphthalimide: Efficient and Selective Functionalization of Benzyl and Allylic C–H Bonds. *J. Am. Chem. Soc.* **130**, 7824–7825 (2008). doi: 10.1021/ja8031218

18. B. Zhang, S.-F. Zhu, Q.-L. Zhou, Copper-Catalyzed Benzylic Oxidation of C(sp^3)–H Bonds. *Tetrahedron* **69**, 2033–2037 (2013). doi: 10.1016/j.tet.2012.12.046

19. T. K. Salvador, C. H. Arnett, S. Kundu, N. G. Sapiezynski, J. A. Bertke, M. Raghibi Boroujeni, T. H. Warren, Copper-Catalyzed sp^3 C–H Etherification with Acyl Protected Phenols. *J. Am. Chem. Soc.* **138**, 16580–16583 (2016). doi: 10.1021/jacs.6b09057

20. L. Tanwar, J. Börgel, T. Ritter, Synthesis of Benzylic Alcohols by C–H Oxidation. *J. Am. Chem. Soc.* **141**, 17983–17988 (2019). doi: 10.1021/jacs.9b09496

21. H. Hu, S.-J. Chen, M. Mandal, S. M. Pratik, J. A. Buss, S. W. Krska, C. J. Cramer, S. S. Stahl, Copper-Catalysed Benzylic C–H Coupling with Alcohols via Radical Relay Enabled by Redox Buffering. *Nat. Catal.* **3**, 358–367 (2020). doi: 10.1038/s41929-020-0425-1

22. B. J. Lee, K. S. DeGlopper, T. P. Yoon, Site-Selective Alkoxylation of Benzylic C–H Bonds by Photoredox Catalysis. *Angew. Chem. Int. Ed.* **59**, 197–202 (2020). doi: 10.1002/anie.201910602

23. A. Palone, G. Casadevall, S. Ruiz-Barragan, A. Call, S. Osuna, M. Bietti, M. Costas, C–H Bonds as Functional Groups: Simultaneous Generation of Multiple Stereocenters by Enantioselective Hydroxylation at Unactivated Tertiary C–H Bonds. *J. Am. Chem. Soc.* **145**, 15742–15753 (2023). doi: 10.1021/jacs.2c10148

24. A. Call, G. Capocasa, A. Palone, L. Vicens, E. Aparicio, N. Choukairi Afailal, N. Siakavaras, M.

E. López Saló, M. Bietti, M. Costas, Highly Enantioselective Catalytic Lactonization at Nonactivated Primary and Secondary γ-C–H Bonds. *J. Am. Chem. Soc.* **145**, 18094–18103 (2023). doi: 10.1021/jacs.3c06231

25. R. G. Pearson, J. Songstad, Application of the Principle of Hard and Soft Acids and Bases to Organic Chemistry. *J. Am. Chem. Soc.* **89**, 1827–1836 (1967). doi: 10.1021/ja00984a014

26. S. Alvarez, Coordinating Ability of Anions, Solvents, Amino Acids, and Gases towards Alkaline and Alkaline-Earth Elements, Transition Metals, and Lanthanides. *Chem. Eur. J.* **26**, 4350 – 4377 (2020). doi: 10.1002/chem.201905453

27. N. M. Camasso, M. H. Pérez-Temprano, M. S. Sanford, C(sp^3)–O Bond-Forming Reductive Elimination from Pd^{IV} with Diverse Oxygen Nucleophiles. *J. Am. Chem. Soc.* **136**, 12771–12775 (2014). doi: 10.1021/ja507056u

28. L. T. Pilarski, P. G. Janson, K. J. Szabó, Palladium-Catalyzed Selective Acyloxylation Using Sodium Perborate as Oxidant. *J. Org. Chem.* **76**, 1503–1506 (2011). doi: 10.1021/jo1024199

29. H.-Z. Yu, Y.-Y. Jiang, Y. Fu, L. Liu, Alternative Mechanistic Explanation for Ligand-Dependent Selectivities in Copper-Catalyzed *N*- and *O*-Arylation Reactions. *J. Am. Chem. Soc.***132**, 18078–18091 (2010). doi: 10.1021/ja104264v

30. G. Yang, Y. Ma, J. Xu, Biomimetic Catalytic System Driven by Electron Transfer for Selective Oxygenation of Hydrocarbon. *J. Am. Chem. Soc.* **126**, 10542–10543 (2004). doi: 10.1021/ja047297b

31. S. Chakrabarty, Y. Wang, J. C. Perkins, A. R. H. Narayan, Scalable Biocatalytic C–H Oxyfunctionalization Reactions. *Chem. Soc. Rev.* **49**, 8137–8155 (2020). doi: 10.1039/D0CS00440E

32. J. Dong, E. Fernández-Fueyo, F. Hollmann, C. E. Paul, M. Pesic, S. Schmidt, Y. Wang, S. Younes, W. Zhang, Biocatalytic Oxidation Reactions: A Chemist's Perspective. *Angew. Chem. Int. Ed.* **57**, 9238–9261 (2018). doi: 10.1002/anie.201800343

33. J. T. Groves, P. Viski, Asymmetric Hydroxylation by a Chiral Iron Porphyrin. *J. Am. Chem. Soc.* **111**, 8537–8538 (1989). doi: 10.1021/ja00204a047

34. K. Hamachi, R. Irie, T. Katsuki, Asymmetric Benzylic Oxidation Using a Mn-Salen Complex as Catalyst. *Tetrahedron Lett.* **37**, 4979–4982 (1996). doi: 10.1016/0040-4039(96)00984-7

35. R. Zhang, W.-Y. Yu, T.-S. Lai, C.-M. Che, Enantioselective Hydroxylation of Benzylic C–H Bonds by D_4-symmetric Chiral Oxoruthenium Porphyrins. *Chem. Commun.* 1791–1792 (1999). doi: 10.1039/A904100A

36. H. Srour, P. Le Maux, G. Simonneaux, Enantioselective Manganese-Porphyrin-Catalyzed Epoxidation and C–H Hydroxylation with Hydrogen Peroxide in Water/Methanol Solutions. *Inorg. Chem.* **51**, 5850–5856 (2012). doi: 10.1021/ic300457z

37. R. V. Ottenbacher, E. P. Talsi, K. P. Bryliakov, Highly Enantioselective Undirected Catalytic Hydroxylation of Benzylic CH_2 Groups with H_2O_2. *J. Catal*. **390**, 170–177 (2020). doi: 10.1016/j.jcat.2020.08.005

38. F. Burg, M. Gicquel, S. Breitenlechner, A. Pothig, T. Bach, Site- and Enantioselective C-H Oxygenation Catalyzed by a Chiral Manganese Porphyrin Complex with a Remote Binding Site. *Angew. Chem., Int. Ed.* **57**, 2953–2957 (2018). doi: 10.1002/anie.201712340

39. M. Milan, M. Bietti, M. Costas, Enantioselective Aliphatic C–H Bond Oxidation Catalyzed by Bioinspired Complexes. *Chem. Commun.* **54**, 9559–9570 (2018). doi: 10.1039/c8cc03165g

40. Q. Sun, W. Sun, Catalytic Enantioselective Methylene C(sp^3)–H Hydroxylation Using a Chiral Manganese Complex/Carboxylic Acid System. *Org. Lett.* **22**, 9529–9533 (2020). doi: 10.1021/acs.orglett.0c03585

41. M. S. Kharasch, G. Sosnovsky, The Reactions of *t*-Butyl Perbenzoate and Oefins—A Stereospecific Reaction. *J. Am. Chem. Soc.* **80**, 756 (1958). doi: 10.1021/ja01536a062

42. M. S. Kharasch, G. Sosnovsky, N. C. Yang, Reactions of *tert*-Butyl Peresters. I. The Reaction of Peresters with Olefins. *J. Am. Chem. Soc.* **81**, 5819–5824 (1959). doi: 10.1021/ja01530a067

43. A. S. Gokhale, A. B. E. Minidis, A. Pfaltz, Enantioselective Allylic Oxidation Catalyzed by Chiral Bisoxazoline-Copper Complexes. *Tetrahedron Lett.* **36**, 1831–1834 (1995). doi: 10.1016/0040-4039(95)00140-8

44. M. B. Andrus, A. B. Argade, X. Chen, M. G. Pamment, The Asymmetric Kharasch Reaction. Catalytic Enantioselective Allylic Acyloxylation of Olefins with Chiral Copper(I) Complexes and *tert*-Butyl Perbenzoate. *Tetrahedron Lett.* **36**, 2945–2948 (1995). doi: 10.1016/0040-4039(95)00444-h

45. K. Kawasaki, S. Tsumura, T. Katsuki, Enantioselective Allylic Oxidation Using Biomimetic Tris(oxazolines)-Copper(II) Complex. *Synlett* 1245–1246 (1995). doi: 10.1055/s-1995-5260

46. J. Eames, M. Watkinson, Catalytic Allylic Oxidation of Alkenes Using an Asymmetric Kharasch–Sosnovsky Reaction. *Angew. Chem. Int. Ed.* **40**, 3567–3571 (2001). doi: 10.1002/1521-3773(20011001)40:19<3567::AID-ANIE3567>3.0.CO;2-C

47. M. B. Andrus, Z. Zhou, Highly Enantioselective Copper−Bisoxazoline-Catalyzed Allylic Oxidation of Cyclic Olefins with *tert*-Butyl *p*-nitroperbenzoate. *J. Am. Chem. Soc.* **124**, 8806–8807 (2002). doi: 10.1021/ja026266i

48. Z. Zhou, M. B. Andrus, Naphthyl-substituted Bisoxazoline and Pyridylbisoxazoline–Copper(I) Catalysts for Asymmetric Allylic Oxidation. *Tetrahedron Lett.* **53**, 4518–4521 (2012). doi: 10.1016/j.tetlet.2012.06.010

49. L. Aldea, I. Delso, M. Hager, M. Glos, J. I. García, J. A. Mayoral, O. A. Reiser, Reusable Enantioselective Catalytic System for the Kharasch–Sosnovsky Allylic Oxidation of Alkenes Based on a Ditopic Azabis(oxazoline) Ligand. *Tetrahedron*, **68**, 3417–3422 (2012). doi: 10.1016/j.tet.2011.10.009

50. B. Zhang, S.-F. Zhu, Q.-L. Zhou, Copper-Catalyzed Enantioselective Allylic Oxidation of Aacyclic Olefins. *Tetrahedron Lett.* **54**, 2665–2668 (2013). doi: 10.1016/j.tetlet.2013.03.046

51. S. Hu, L. P. Hager, Highly Enantioselective Propargylic Hydroxylations Catalyzed by Chloroperoxidase. *J. Am. Chem. Soc.* **121**, 872–873 (1999). doi: 10.1021/ja983612g

52. J. Xi, X. Zhu, H. Bao, Copper-Catalyzed Enantioselective Radical Esterification of Propargylic C–H Bonds. *Synthesis* **56**, 1393–1400 (2024). doi: 10.1055/a-2240-5349

53. A. J. Sterling, N. R. Ciccia, Y. Guo, J. F. Hartwig, M. Head-Gordon, Mechanistic Insights into the Origins of Selectivity in a Cu-Catalyzed C–H Amidation Reaction. *J. Am. Chem. Soc.***146**, 6168–6177 (2024). doi: 10.1021/jacs.3c13822

54. Y. Weng, Y. Jin, J. Wu, X. Leng, X. Lou, F. Geng, B. Hu, B. Wu, Q. Shen, Oxidative Substitution of Organocopper(II) by a Carbon-Centered Radical. *J. Am. Chem. Soc.* (2024). doi: 10.1021/jacs.4c07552

55. B. L. Tran, M. Driess, J. F. Hartwig, Copper-Catalyzed Oxidative Dehydrogenative Carboxylation of Unactivated Alkanes to Allylic Esters via Alkenes. *J. Am. Chem. Soc.* **136**, 17292−17301 (2014). doi: 10.1021/ja510093x

56. C.-Y. Cai, X.-L. Lai, Y. Wang, H.-H. Hu, J. Song, Y. Yang, C. Wang, H.-C. Xu, Photoelectrochemical Asymmetric Ccatalysis Enables Site- and Enantioselective Cyanation of Benzylic C–H Bonds. *Nat. Catal.* **5**, 943–951 (2022). doi: 10.1038/s41929-022-00855-7

57. W. Zhang, L. Wu, P. Chen, G. Liu, Enantioselective Arylation of Benzylic C−H Bonds by Copper-Catalyzed Radical Relay. *Angew. Chem. Int. Ed.* **58**, 6425–6429 (2019). doi: 10.1002/anie.201902191

58. L. Liu, K.-X. Guo, Y. Tian, C.-J. Yang, Q.-S. Gu, Z.-L. Li, L. Ye, X.-Y. Liu, Copper-Catalyzed Intermolecular Enantioselective Radical Oxidative C(sp3)−H/C(sp)−H Cross-Coupling with Rationally Designed Oxazoline-Derived N,N,P(O)-Ligands. *Angew. Chem. Int. Ed.* **60**, 26710–26717 (2021). doi: 10.1002/anie.202110233

59. L. Fu, Z. Zhang, P. Chen, Z. Lin, G. Liu, Enantioselective Copper-Catalyzed Alkynylation of Benzylic C–H Bonds via Radical Relay. *J. Am. Chem. Soc.* **142**, 12493–12500 (2020). doi: 10.1021/jacs.0c05373

Acknowledgements: We thank the National Key R&D Program of China (2022YFA1504302), the National Natural Science Foundation of China (22188101, 91956000, 92256301), the Fundamental Research Funds for the Central Universities, and the Haihe Laboratory of Sustainable Chemical Transformations for financial support. **Author contributions:** Q.L.Z. conceived the study; X.M.L., F.L., L.J.X. and Q.L.Z. designed the experiments and analyzed the data; X.M.L. and F.L. performed the reactions and mechanistic studies; L.D., N.-Q.J., and L.-Y X. did some of the reactions. J.Y.L. made some of the substrates; Y. Y. measured EPR spectra; T.W. and X.-S.X. performed DFT calculations; X.M.L., F.L., L.J.X., and Q.L.Z. wrote the paper. **Competing interests:** The authors declare no competing interests. **Data availability:** The authors declare that all data generated in this study are available within the article and the Supplementary Materials.