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Copper-catalyzed enantioselective synthesis of γ-butenolides via radical diversification of allenoic acid

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Chiral γ-butenolides, which are widely prevalent in natural products and pharmaceuticals, necessitate synthetic methods that precisely control both stereochemistry and substituent diversity. In this study, we report a Cu/PyBim-catalyzed asymmetric lactonization of 2,3-allenoic acids initiated by sulfonyl or phosphonyl radicals. This strategy facilitates the direct construction of enantioenriched γ-butenolides featuring modular endocyclic double bond substituents, thereby circumventing the traditional reliance on prefunctionalized substrates. Synthetic applications of the obtained chiral γ-butenolide are emphasized and mechanistic experiments are investigated.

γ-Butenolides represent a class of compounds characterized by a five-membered cyclic lactone backbone, which features an α,β-unsaturated ester unit in its core structure[1]. This structural motif is prevalent in various natural products, such as plant defensins and microbial secondary metabolites, as well as in pharmaceutical compounds, including antitumor and cardiovascular drugs (Fig. 1)[2–6]. The unique cyclic enone system of γ-butenolides not only imparts significant biological activities, including electrophilicity and covalent bonding capabilities, but also positions them as crucial intermediates for the synthesis of complex chiral molecules. Furthermore, the diversity of substituents on the double bond and the precise control of chiral centers directly influences their pharmacological activities and selectivity. Consequently, the development of efficient and highly enantioselective synthetic methodologies remains a central challenge in this area.

Current enantioselective syntheses of γ-butenolides strategically employ on furan-derived precursors (e.g., 2-silyloxyfurans[7–9], conjugated[8,10–12]/deconjugated butenolides[13–24]), achieving precise stereochemical control through sophisticated catalytic systems such as transition-metal complexes or organocatalysts (Fig. 2a). While effective, these strategies inherently limit structural diversification due to the furan frameworks. Notably, approaches utilizing non-furan substrates to access chiral γ-butenolides remain underexplored, with only sporadic reports addressing the challenges (Fig. 2b). For instances, Maruoka et al.[25] demonstrated the intramolecular cascade oxidation/lactonization of β,γ-unsaturated carboxylic acids into enantioenriched γ-butenolides, utilizing a chiral selenium catalyst. Zhang et al.[26] developed an efficient synthesis of chiral γ-butenolides through the gold-catalyzed cycloisomerization of allylic ynolates. Li et al.[27] synthesized a series of chiral γ-alkenyl butenolides via Ni(0)-catalyzed enantioselective [3 + 2] cycloaddition reactions, which involved enones/imines and cyclopropenones, with C–C bond activation as a pivotal step. Meanwhile, Hu et al.[28] directly synthesized enantiomer enriched γ-butenolides through the highly enantioselective trapping of carboxylic oxonium ylides with imines. Furthermore, Feng et al.[29] successfully constructed chiral γ-butenolides via cascade allylation and lactonization reactions. Despite these advances, direct enantioselective C–O bond formation via radical intermediates—a strategy enabling modular substitution and stereochemical control—remains unexplored in γ-butenolide synthesis.

Recent breakthroughs in stereoselective bond formation at radical intermediates have revolutionized the synthesis of chiral molecules[30–41]. Inspired by pioneering work[42–49] on enantioselective C–O bond construction via carbon radical intermediates, we aimed to extend this strategy to access enantioenriched γ-butenolides through intramolecular stereocontrolled radical cyclization. Leveraging the inherent reactivity of 2,3-allenoic acids[50–60]—versatile precursors for γ-butenolide derivatization—we developed a Cu/PyBim-catalyzed asymmetric lactonization platform (Fig. 2c). This method employs sulfonyl or phosphonyl radicals to initiate a cascade process, enabling simultaneous control over enantioselectivity and endocyclic double bond

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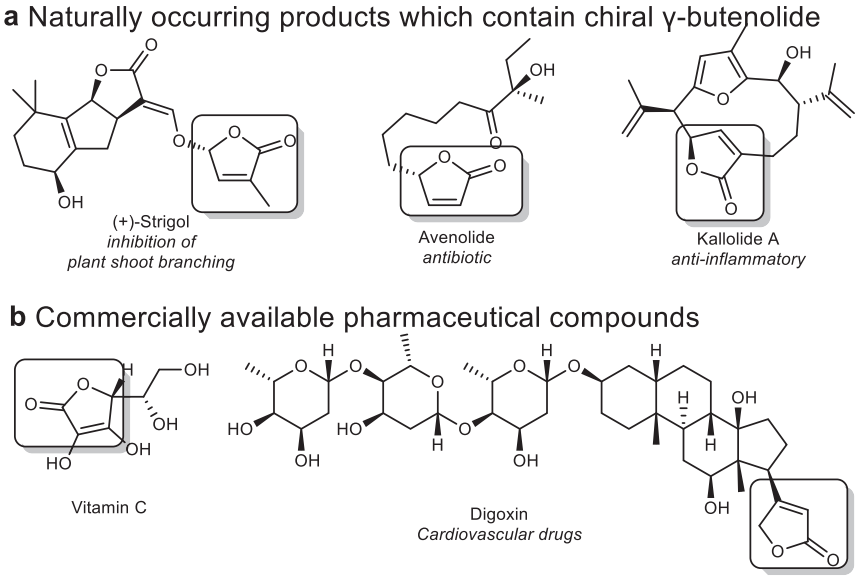

Fig. 1 | Pharmaceuticals and natural products containing chiral γ-butenolide cores. a Naturally occurring products which contain chiral γ-butenolide. **b** Commercially available pharmaceutical compounds.

substitution. This approach directly establishes a modular pathway for the synthesis of chiral γ-butenolides with diverse functional group versatility.

Results

Initial ligand screening was performed with 2-methyl-4-phenylbuta-2,3-allenoic acid (**1a**) and 4-bromophenyldiazonium tetrafluoroborate (**2a**) as model substrates under $Cu(OAc)_2$ catalysis (Table 1; full ligand screening data in Table S1, Supplementary information). Guided by our earlier work[47,48], oxazoline derivatives (**L1**–**L7**) were first explored, with **L3** providing **3a** in 68% yield and 83:17 er. Notably, substitution with the PyBim ligand **L8** dramatically enhanced both catalytic efficiency and enantioselectivity, yielding **3a** in 72% yield and 93.5:6.5 er. Subsequent structural modifications of the PyBim framework (**L9**–**L20**) failed to surpass **L8**. Crucially, tosyl protection of the imidazole N–H moiety in **L8** nearly abolished reactivity. Further adjustments to catalysts, solvents, and temperatures (entries 2–8) yielded no substantial improvement.

With optimized conditions in hand, the substrate generality of the asymmetric synthesis of sulfonyl γ-butenolides was investigated using diverse aryl diazonium salts and 2,3-allenoic acids (Fig. 3). Aryl diazonium salts bearing electron-withdrawing and electron-donating substituents (**3a**–**3i**) proved broadly compatible, furnishing products in 40–79% yield with 88.5:11.5–95:5 er. Notably, substrate **2d**, containing a terminal C≡C bond—typically prone to radical addition—reacted efficiently to afford **3d** in 49% yield and 95:5 er, underscoring the method's functional group tolerance. In addition to para-substituted aryl diazonium salts, ortho- (**3j**), meta- (**3k**), 3,5-disubstituted (**3l**), and 1-naphthyl (**3m**) diazonium salts also demonstrated good compatibility achieving yields from 68% to 79% yield and 88:12 to 93:7 er. Systematic variation of the R^3 substituents in 2,3-allenoic acids demonstrated exceptional versatility. Linear alkyl chains (**4a**–**4c**), cyclopropyl (**4d**), and benzyl groups (**4e**) delivered products in 53–87% yield with 91:9–96:4 er. Para-substituted aromatic derivatives—spanning electron-donating (Me, OEt, OPh, OCF_3; **4f**–**4h, 4m**) and electron-withdrawing (Ph, F, Br, CF_3; **4i**–**4l**) groups—achieved 70–92% yield and 85.5:14.5–96.5:3.5 er. Meta-substituted analogues (F, Cl, Br, CF_3, 3,5-difluoro, 3-fluoro-5-chloro; **4n**–**4s**) exhibited 58%–89% yield and 90:10– 94:6 er. Heteroaromatic (thiophene, **4u**) and polycyclic (naphthalene, **4t**) substrates performed admirably, yielding products in 81–88% yield with 92.5:7.5–95.5:4.5 er. Strikingly, installing a methyl (**4v**) or ethyl (**4w**) group at R^2 efficiently generated a chiral tetra-substituted carbon center in 66–93% yield, albeit with reduced enantiocontrol (73:27–77.5:22.5 er).

Having demonstrated the versatility of sulfonyl radical precursors in accessing γ-butenolides with diverse electronic and steric profiles, we subsequently investigated the scope of phosphonyl radical precursors to further enhance the structural and functional diversity of this privileged scaffold (Fig. 4). By using the LPO-initiated phosphonyl radicals from diphenylphosphine oxide, we successfully synthesized a series of chiral phosphonyl γ-butenolides. Fourteen 2,3-allenoic acids (**6a**–**6n**) bearing diverse substituents reacted efficiently, delivering products in 58–90% yield with 60:40–96:4 er. Diarylphosphine oxides with electronically varied aryl groups—including methyl (**6o**), methoxy (**6p**), fluoro (**6q**), chloro (**6r**), and bromo (**6s**)—exhibited excellent compatibility, affording products in 75–86% yield and 91.5:8.5–93:7 er, thereby demonstrating robust tolerance to steric and electronic modulation.

Synthetic applications of sulfonyl chiral γ-butenolides and phosphonyl chiral γ-butenolides have been demonstrated and are shown in Fig. 5. After recrystallization, γ-butenolide **3e** obtained by the gram-scale reaction, could be obtained with a 99:1 er. The carbonyl group of **3e** was selectively reduced with diisobutylaluminum hydride agent, yielding the hemiacetal **7**. Compound **7** can be further reduced with Et_3SiH and $BF_3{\cdot}Et_2O$, resulting in the formation of a 2-aryl-3,4-dihydrofuran derivative. The recrystallized chiral phosphonyl-substituted γ-butenolide **6a** (98:2 er) can be reduced from pentavalent to trivalent phosphine (**9**) by using trichlorosilane as the reductant. Additionally, compound **9** can be further transformed into the corresponding phosphanimine (**12**), phosphine sulfide (**11**), and phosphine selenide (**10**). Notably, the stereoselectivity of all these transformations is well preserved.

To investigate the reaction mechanism, control experiments were conducted (Fig. 6). Notably, the formation of product **3e** was not observed upon the addition of 2,2,6,6-tetramethylpiperidine-1-yloxy (TEMPO) to the reaction mixture (Fig. 6a), indicating the free radical nature of the reaction. The enantiomeric excess of ligand **L8** showed a linear correlation with the enantiomeric excess of **3e**, suggesting that the active catalytic species is a mono-copper complex with a single chiral ligand (Fig. 6c). To further confirm the active catalyst, **L8**Cu(II)

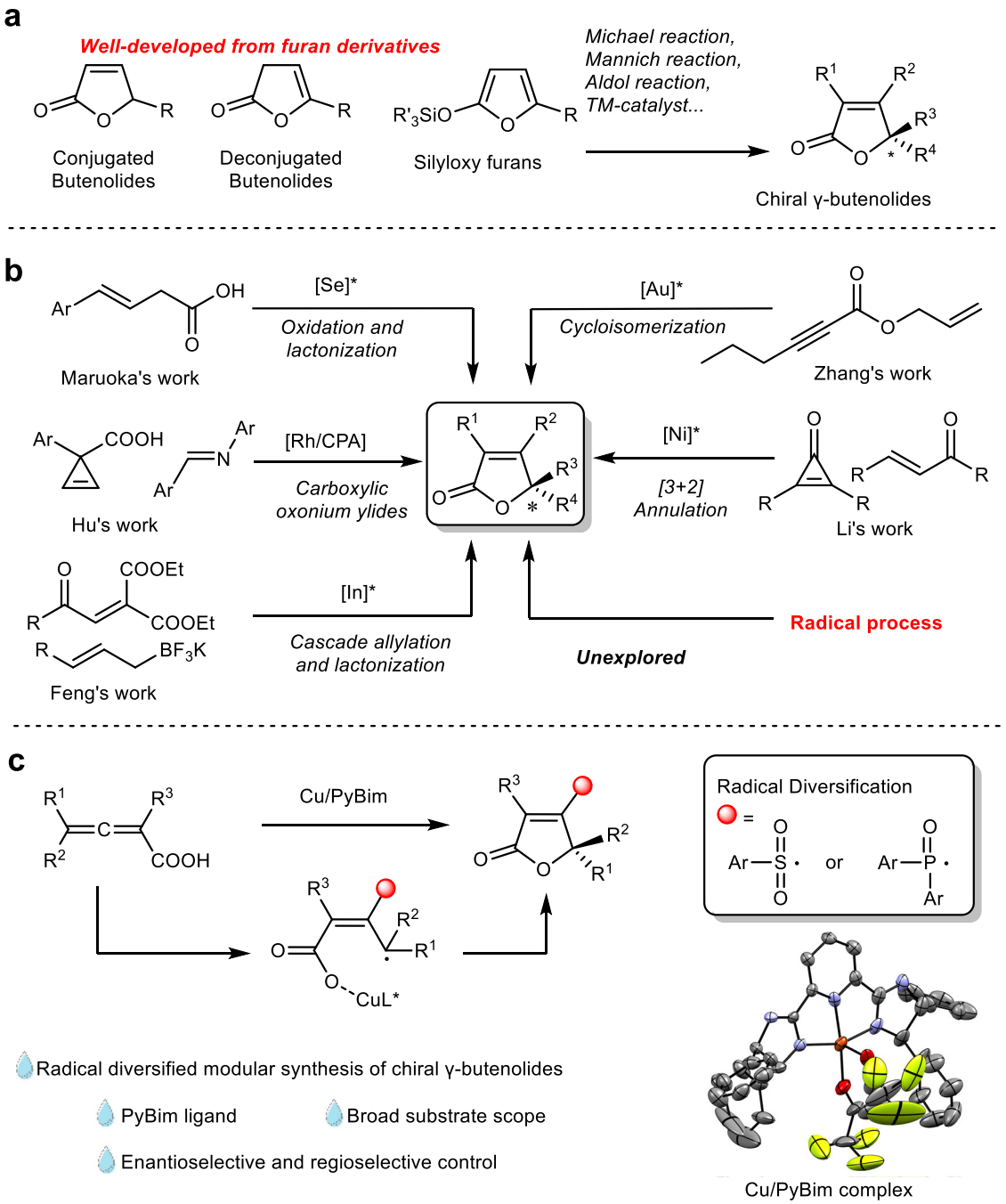

Fig. 2 | Synthesis of chiral γ-butenolide and this work. a Construction of chiral γ-butenolides from furan derivatives. **b** Construction of chiral γ-butenolides from non-furan derivatives. **c** Synthesis of chiral γ-butenolides via radical diversification of allenoic acids (this work).

(**A**) was synthesized and characterized using X-ray single-crystal diffraction (Fig. 6b). Catalyst **A** demonstrated similar reactivity to the standard reaction conditions with ligand **L8**, implying that **A** is likely the initial active catalyst. A Hammett analysis was performed to examine the electronic effects of the 2,3-allenoic acid substrate on the reaction rate (Fig. 6d). A linear correlation was observed between $\log(k_X/k_H)$ and Hammett's constant (σ), with a small negative ρ value (−0.23). This observation suggests that a slight partial positive charge develops in the transition state of the turnover-limiting step.

Based on the results of mechanistic experiments, a potential reaction mechanism has been proposed (Fig. 7). Initially, the mono-ligand Cu(I) complex (**I**) and the aryl diazonium salt undergo a single-electron transfer (SET), generating a Cu(II) complex (**II**) and an aryl radical (**III**). The aryl radical then reacts with SO_2 from $Na_2S_2O_5$ to form an aryl sulfonyl radical (**IV**). This aryl sulfonyl radical (**IV**) subsequently attacks 2,3-allenoic acid, leading to the formation of a resonance-stabilized species, the π-allyl radical (**V**), which benefits from enhanced stability due to resonance delocalization. The radical intermediate (**V**) is then oxidized and undergoes intramolecular cyclization by Cu(II) complex (**II**), resulting in the formation of the desired chiral γ-butenolide and the regeneration of the reactive Cu(I) complex (**I**). Despite the different radical species involved, we anticipate that phosphonylation reactions will proceed through a similar mechanism. The proposed reaction mechanism for the phosphonyl radical pathway is shown in Fig. S2 (Supplementary information).

In conclusion, we have developed a Cu/PyBim-catalyzed asymmetric radical lactonization strategy that enables the direct synthesis of enantioenriched γ-butenolides from readily available 2,3-allenoic

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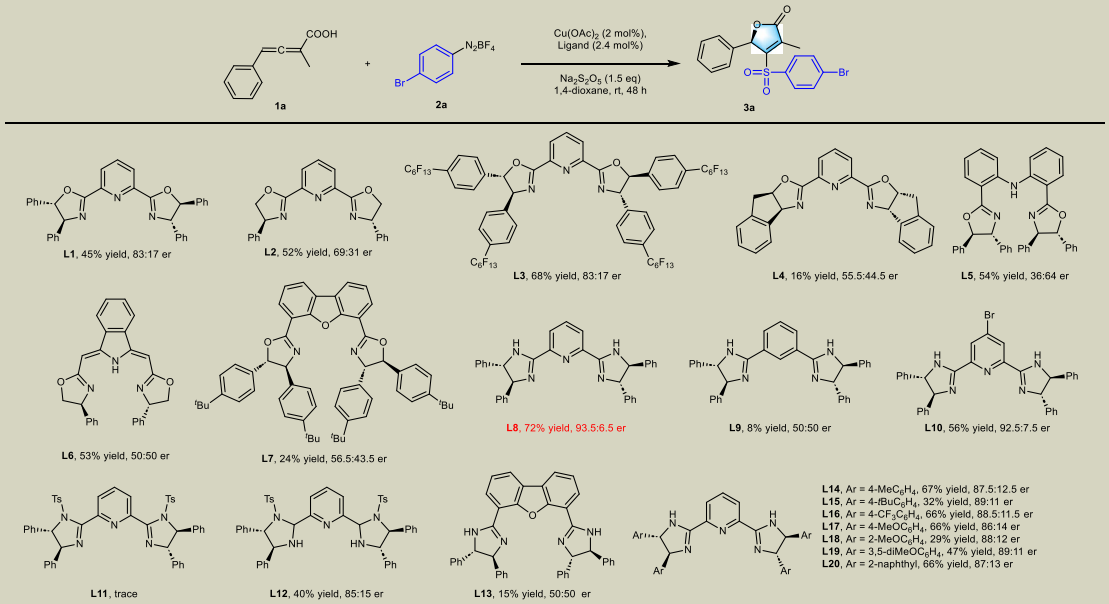
Table 1 | Reaction condition optimizations



Entry	Change from standard conditions	Yield (%)	er
1	None	72	93.5:6.5
2	$CuBr_2$ instead of $Cu(OAc)_2$	50	92.5:7.5
3	THF instead of 1,4-dioxane	32	91.5:8.5
4	Under 60 °C, 8 h	76	90.5:9.5
5	50 °C, 15 h	64	92:8
6	40 °C, 24 h	62	92:8
7	10 °C, 48 h	64	94:6
8	−20 °C, 120 h	10	93:7

Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), $Na_2S_2O_5$ (0.15 mmol, 1.5 equiv), $Cu(OAc)_2$ (2.0 mol%) and **L8** (2.4 mol%) in solvent (0.1 M) at room temperature for 48 h under a nitrogen atmosphere.

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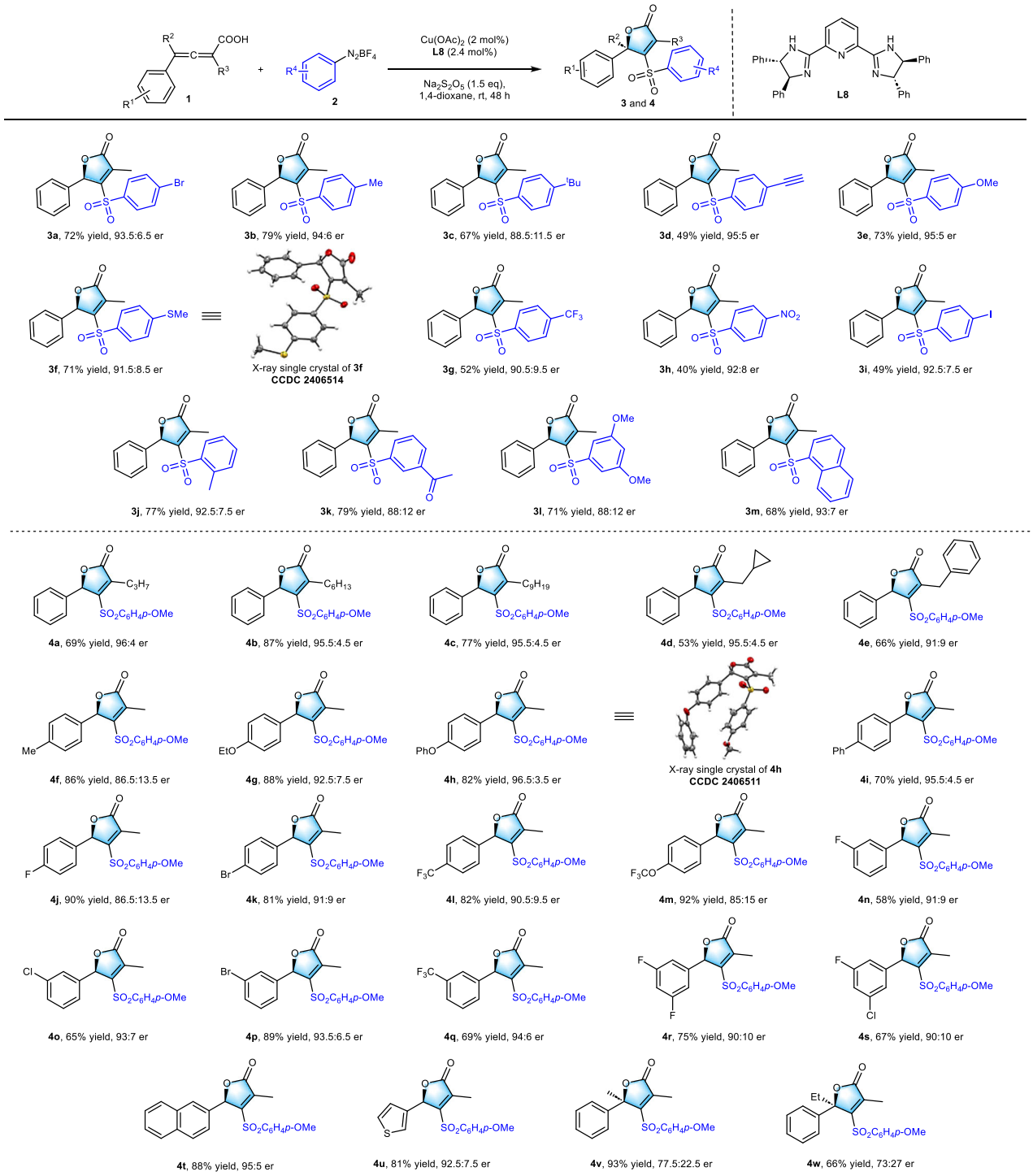

Fig. 3 | Substrate scope of sulfonyl radical. Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), $Na_2S_2O_5$ (0.3 mmol, 1.5 equiv), $Cu(OAc)_2$ (2.0 mol%) and **L8** (2.4 mol%) in 1,4-dioxane (0.1 M) at room temperature for 48 h under a nitrogen atmosphere.

acids. By leveraging sulfonyl and phosphonyl radicals as both initiators and functional group carriers, this method achieves simultaneous control over stereochemistry and substituent diversity at the endocyclic double bond, overcoming the limitations of traditional furan-based approaches. The reaction is characterized by high yields, good enantioselectivity, and excellent functional group compatibility. Successful gram-scale reactions and a series of subsequent transformations highlight the practical applicability of this approach. Key mechanistic insights, supported by radical trapping experiments and Hammett analysis, reveal a radical pathway initiated by aryl sulfonyl/phosphonyl radicals, followed by stereodetermining cyclization orchestrated by the Cu/PyBim complex.

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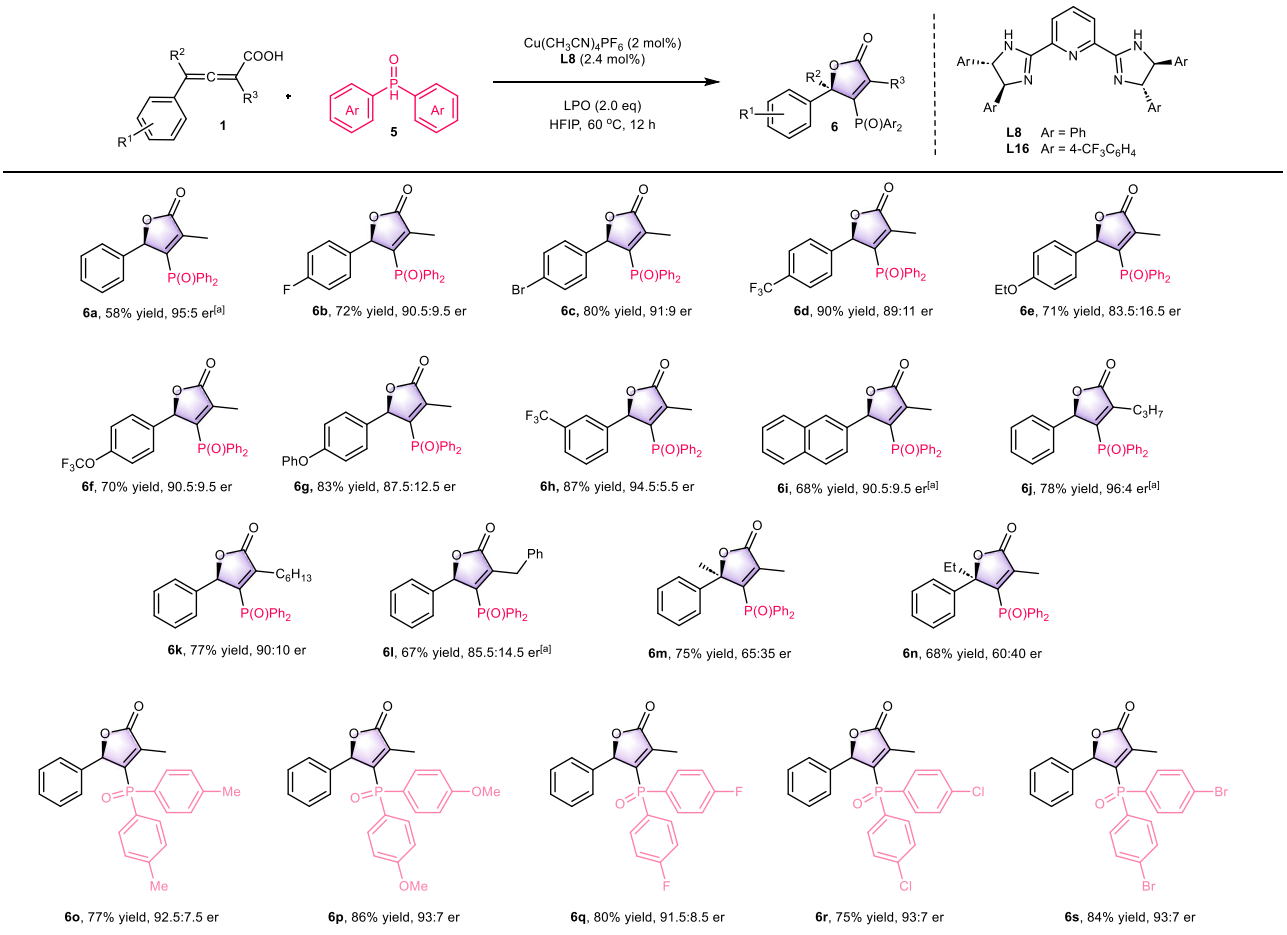

Fig. 4 | Substrate scope of phosphonyl radical. Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **5** (0.4 mmol, 2.0 equiv), LPO (0.4 mmol, 2.0 equiv), $Cu(CH_3CN)_4PF_6$ (2.0 mol %) and **L8** (2.4 mol%) in HFIP (0.1 M) at 60 °C for 12 h under a nitrogen atmosphere. [a] **L16** instead of **L8**.

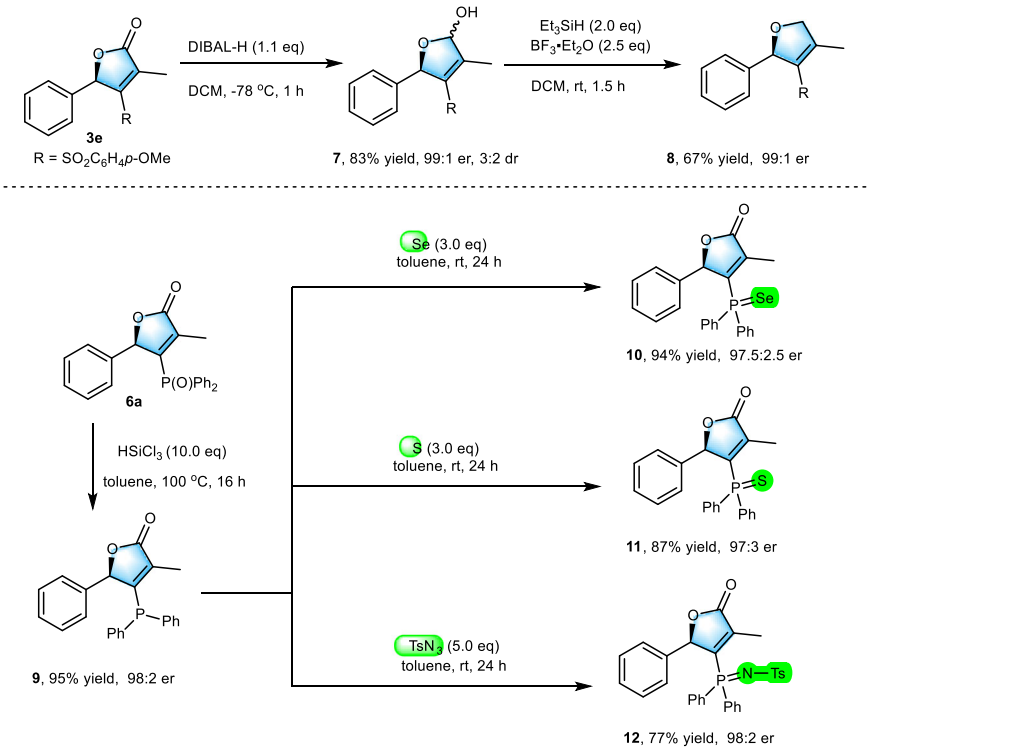

Fig. 5 | Synthetic applications. The transformation of chiral γ-butenolides.

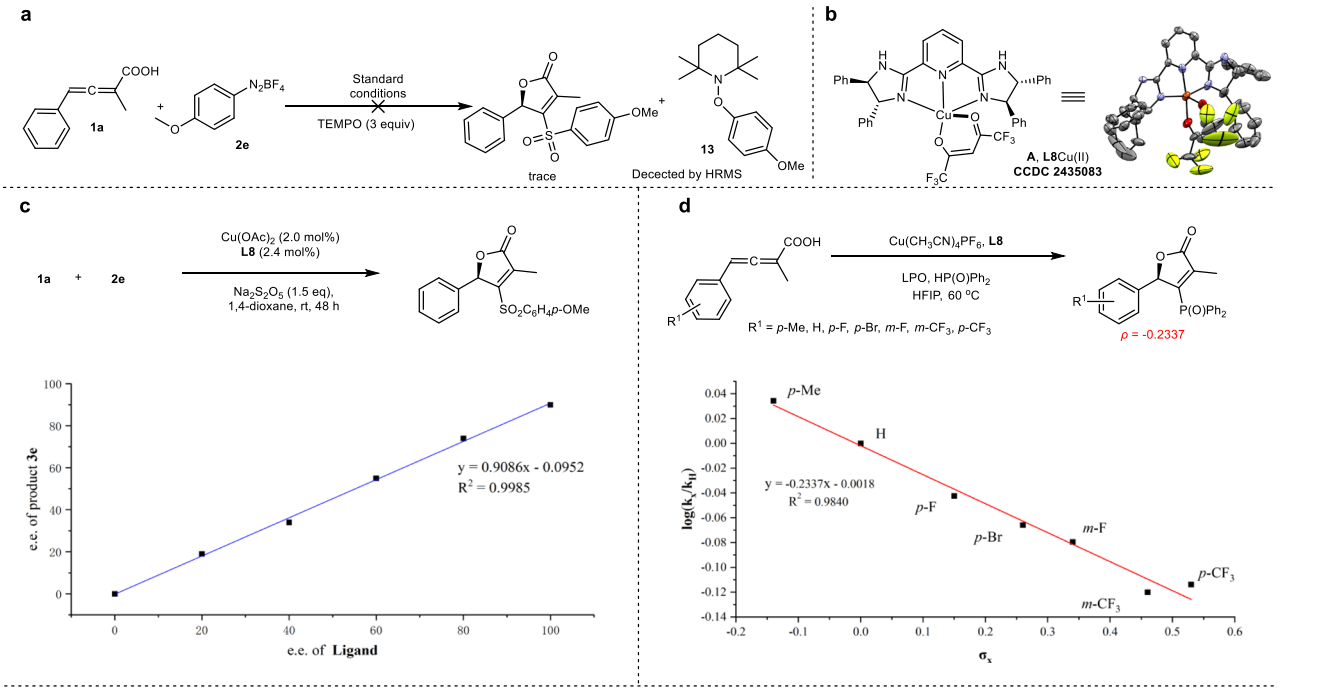

Fig. 6 | Mechanistic studies. a Radical trapping experiment. **b** Single crystal. **c** Non-linear effect study. **d** Hammett analysis.

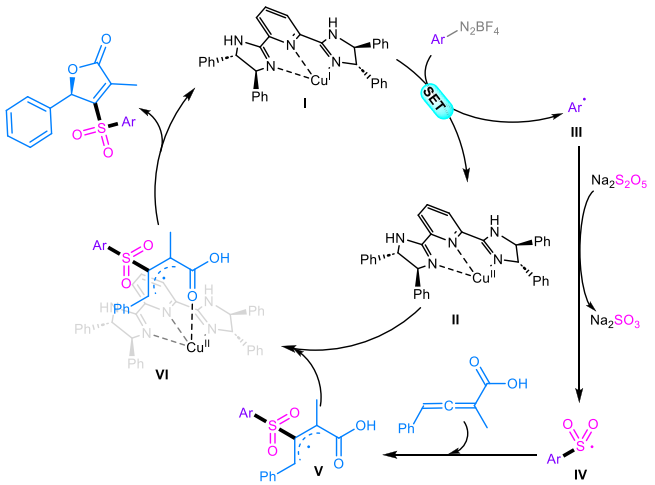

Fig. 7 | Possible reaction mechanism. The proposed catalytic cycle for the synthesis of chiral γ-butenolides through the radical diversification of allenoic acids.

Methods

General method for synthesis of chiral sulfonyl γ-butenolides

In a flame-dried Schlenk tube, $Cu(OAc)_2$ (0.004 mmol, 2 mol%) and ligand **L8** (0.0048 mmol, 2.4 mol%) were dissolved in DCM (1.0 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 30 mins. Then, the solvent was evaporated under reduced pressure, aryldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv), $Na_2S_2O_5$ (0.3 mmol, 1.5 equiv), 2,3-Allenoic acid (0.2 mmol, 1.0 equiv) and 1,4-dioxane (0.1 M) were sequentially added. The reaction mixture was stirred at room temperature for 48 h under a nitrogen atmosphere. After reaction completion, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the product.

General method for synthesis of chiral phosphonyl γ-butenolides

In a flame-dried Schlenk tube, $Cu(CH_3CN)_4PF_6$ (0.004 mmol, 2 mol%) and ligand **L8** or **L16** (0.0048 mmol, 2.4 mol%) were dissolved in DCM (1.0 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 30 min. Then, the solvent was evaporated under reduced pressure, diarylphosphine oxide (0.4 mmol, 2.0 equiv), LPO (0.4 mmol, 2.0 equiv), 2,3-Allenoic acid (0.2 mmol, 1.0 equiv) and HFIP (0.1 M) were sequentially added. The reaction mixture was stirred at 60 °C for 12 h under a nitrogen atmosphere. After reaction completion, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the product.

Data availability

The data generated in this study have been deposited in the Supplementary Information file. The experimental procedures, data of NMR, and HRMS have been deposited in the Supplementary Information file. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC: 2406514), (CCDC:2406511) and (CCDC: 2435083). These data could be obtained free of charge from The Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/data_request/cif). All data are available from the corresponding author upon request.

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Author contributions

H. Bao and C. Ye directed the investigations. H. Bao and C. Ye prepared the paper. B. Han and Z. Nie performed the synthetic experiments and analyzed the experimental data. All authors contributed to the writing of this paper.

Competing interests

The authors declare no competing interests.

Additional information

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