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Cu-catalyzed enantioconvergent oxygen-centered radical cyclization

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Radical asymmetric cyclization has emerged as a powerful strategy for constructing ring structures. Despite significant progress in carbon-centered radical cyclization, the catalytic asymmetric cyclization of oxygen-centered radicals, key species in many biological processes, remains challenging owing to their high oxidizing power and electrophilicity. Herein, we report an enantioconvergent oxygen-centered radical cyclization *via* Cu-catalyzed asymmetric C(sp^3)–O oxidative coupling between the tertiary C(sp^3)–H bond and the oxime O–H bond of racemic γ-ketoximes. This radical reaction proceeds efficiently under aerobic and mild conditions, affording a wide range of valuable isoxazolines bearing a fully substituted stereocenter in good yields with excellent enantioselectivity. Mechanistic studies were conducted to elucidate the origin of enantiocontrol, and the synthetic utility of the method was demonstrated through the late-stage transformation of isoxazolines into polyhydroxy building blocks.

Introduction

Radical cyclization represents a powerful strategy for constructing ring structures, offering advantages such as mild reaction conditions, high reactivity, excellent chemoselectivity, and broad functional group tolerance.[1–7] However, achieving a catalytic asymmetric version remains a daunting challenge due to the difficulty in the enantioselective control of highly reactive radical species.[8–15] To address this issue, conceptually new methodologies for asymmetric radical cyclization have been developed during the past few decades.[16–18] Among these innovative approaches, major advances have been made in carbon (C)-centered radical cyclization (Fig. 1A, left),[19–28] whereas heteroatom-centered radical cyclization remains underexplored.[29–31] Oxygen (O)-centered radicals are key reactive species in many biological processes, such as the biosynthesis of prostaglandins and phytoprostanes.[32] Their high oxidizing power and electrophilicity distinguish them from alkyl radical analogues.[33,34] Typical reactions of O-centered radicals include hydrogen-atom transfer (HAT) and β-fragmentation to form a C–O bond (Fig. 1A, right).[35–38] Theses competing pathways significantly hinder the development of O-centered radical cyclization reactions, particularly in catalytic asymmetric versions.[39–42]

Iminoxyl radicals, also known as oxime radicals, are a unique subclass of O-centered radicals.[43,44] As the single electron spin is delocalized over both the O and N atoms, iminoxyl radicals are more stable than alkoxy radicals (Fig. 1B).[45–47] In addition, the relatively low bond-dissociation energy (BDE, ~76–85 kcal mol^{-1}) of O–H bonds inhibits the HAT process,[11c] thereby facilitating radical cyclization.[48–51] Although the physical properties such as the structure, stability, and spectra of oxime radicals have been extensively studied, their synthetic potential has long been underestimated.[52–55] Recently, Han *et al.* reported the iminoxyl radical-promoted dioxygenation, oxyamination, and diamination of alkenes.[56–64] Despite these racemic advances, catalytic asymmetric iminoxyl radical cyclization has not been reported. To address this gap, we herein present an asymmetric O-centered radical cyclization of iminoxyl radicals *via* Cu-catalyzed intramolecular C(sp^3)–O oxidative coupling between the tertiary C(sp^3)–H bond and the oxime O–H bond of racemic γ-ketoximes (Fig. 1C). This radical reaction proceeds under aerobic and mild conditions in an enantioconvergent manner, providing a wide range of valuable isoxazolines[65–71] bearing a fully substituted stereocenter in good yield with excellent enantioselectivity. DFT calculations have been performed to elucidate the origin of enantiocontrol, and the utility of this method was demonstrated through the synthesis of chiral polyhydroxy building blocks.

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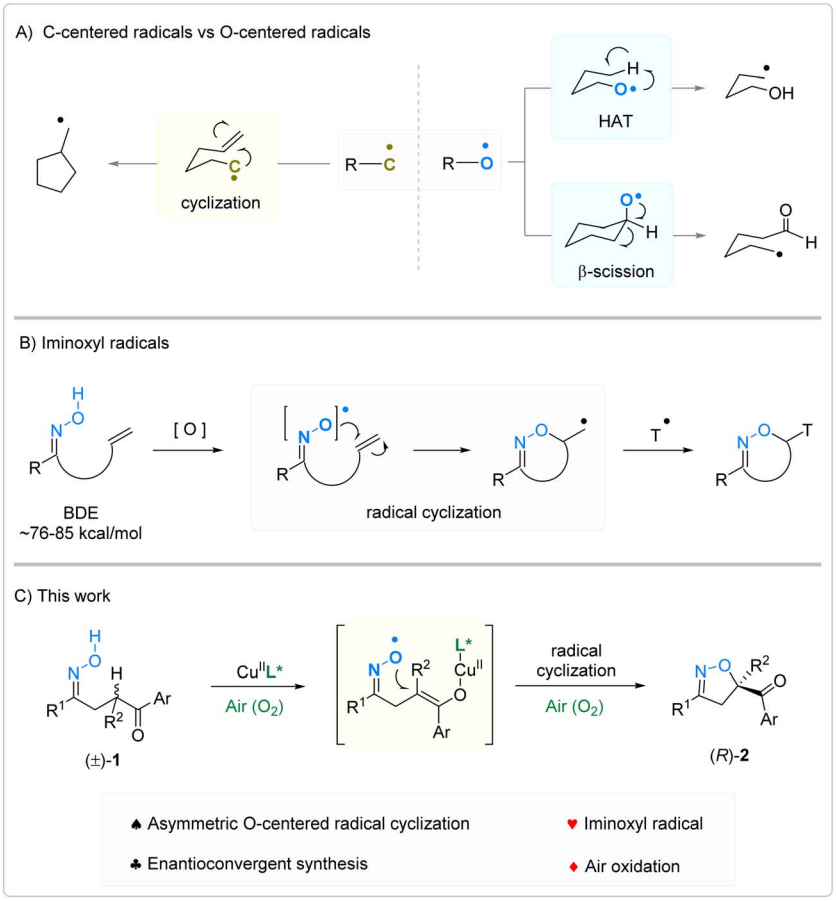


Fig. 1 Radical asymmetric cyclization.

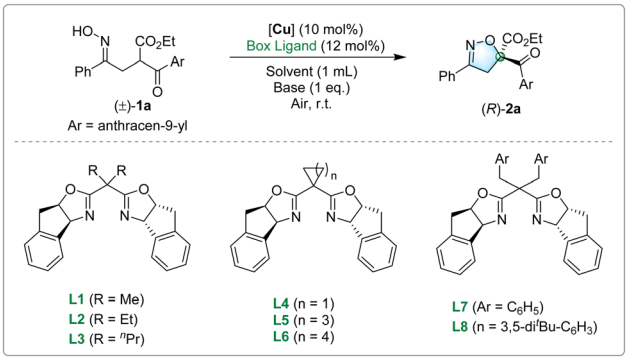
Results and discussion

We commenced the study with a model reaction of racemic ketoxime **1a** (Table 1). Under the initial conditions—10 mol% $Cu(OTf)_2$, 12 mol% ligand **L1** in EtOAc at room temperature under air for 72 h—the desired cyclization product **2a** was obtained in moderate yield with 62% ee (entry 1). Screening of commercially available box ligands (entries 2–8) revealed that **L3** afforded the best results (entry 3). Subsequent evaluation of copper salts and solvents did not yield further improvements (entries 9–14). Accordingly, $Cu(OTf)_2$ was the best metal catalyst, and EtOAc was the optimal solvent. Notably, the choice of base significantly influenced enantioselectivity. While K_2CO_3 led to a significant decrease in enantioselectivity (entry 15), weaker bases improved enantioselectivity (entries 16–18). Consequently, the following reaction conditions were identified as optimal: (±)-**1a** (0.05 mmol), $Cu(OTf)_2$ (10 mol%), **L3** (12 mol%) and HCO_2Na (1.0 eq.) in EtOAc (1 mL) at room temperature (r.t.) in an air atmosphere for 72 h, which provided isoxazoline **2a** in 88% yield with 95% ee.

With the best reaction conditions, we next evaluated the reaction scope. As shown in Fig. 2, the Cu-catalyzed radical $C(sp^3)$–O oxidative coupling reaction demonstrated broad applicability across a diverse range of racemic ketoximes **1**, affording the corresponding isoxazoline products **2** in good yields with consistently excellent enantioselectivities (all >93% ee). Varying the ester group from CO_2Et (**2a**) to CO_2Me (**2b**), $CO_2{}^nPr$ (**2c**), $CO_2{}^iPr$ (**2d**), $CO_2{}^nBu$ (**2e**), and CO_2Bn (**2f**) had a negligible impact on both yield and enantioselectivity. Furthermore, the oxime moiety tolerated a variety of aryl groups (Ar^1). The position (*o*,*m*, or *p*) and the electron nature (electron-donating or electron-withdrawing) of the substituents on the benzene ring had no significant effect on the ee values of the products (**2g–2t**). However, strong electron-withdrawing substituents such as NO_2 and CF_3 led to lower yields for **2m** and **2n**. Additionally, the reaction also accommodated disubstituted phenyl (**2u** and **2v**), naphthyl (**2w**), and heteroaryl (**2x** and **2y**) groups under standard conditions.

We further expanded the substrate scope by modifying the aryl group (Ar) on the ketone motif (Fig. 3). This structural variation proved crucial, significantly influencing the reaction outcome. Replacing the anthracenyl (**2a**) group with naphthyl

Table 1 Reaction optimization[a]



Entry[a]	[Cu]	Ligand	Solvent	Base	Yield[b] (%)	ee[c] (%)
1	$Cu(OTf)_2$	**L1**	EtOAc	Na_2CO_3	84	62
2	$Cu(OTf)_2$	**L2**	EtOAc	Na_2CO_3	85	64
3	$Cu(OTf)_2$	**L3**	EtOAc	Na_2CO_3	89	75
4	$Cu(OTf)_2$	**L4**	EtOAc	Na_2CO_3	77	53
5	$Cu(OTf)_2$	**L5**	EtOAc	Na_2CO_3	70	55
6	$Cu(OTf)_2$	**L6**	EtOAc	Na_2CO_3	41	50
7	$Cu(OTf)_2$	**L7**	EtOAc	Na_2CO_3	68	55
8	$Cu(OTf)_2$	**L8**	EtOAc	Na_2CO_3	50	41
9	$Cu(CH_3CN)_4BF_4$	**L3**	EtOAc	Na_2CO_3	44	23
10	CuBr	**L3**	EtOAc	Na_2CO_3	65	52
11	CuI	**L3**	EtOAc	Na_2CO_3	53	38
12	$Cu(OTf)_2$	**L3**	CH_2Cl_2	Na_2CO_3	85	70
13	$Cu(OTf)_2$	**L3**	Toluene	Na_2CO_3	63	51
14	$Cu(OTf)_2$	**L3**	THF	Na_2CO_3	83	50
15	$Cu(OTf)_2$	**L3**	EtOAc	K_2CO_3	70	27
16	$Cu(OTf)_2$	**L3**	EtOAc	$NaHCO_3$	84	82
17	$Cu(OTf)_2$	**L3**	EtOAc	CH_3CO_2Na	86	91
18	$Cu(OTf)_2$	**L3**	EtOAc	HCO_2Na	88	95

[a] Unless otherwise indicated, the reaction conditions were as follows: **1a** (0.05 mmol), [Cu] (10 mol%), **L** (12 mol%) and base (1.0 eq.) were added to a specified solvent (1 mL) at room temperature (r.t.) in an air atmosphere for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

(**2z**) and phenyl (**2a′** and **2b′**) groups led to a gradual decline in both yield and enantioselectivity. This trend correlates with the diminished ability of these less conjugated arenes to stabilize the proposed radical intermediate **Int-A**, supporting the involvement of a radical pathway. The observed trend in yield and enantioselectivity (**2a** > **2z** > **2a′**/**2b′**) can be rationalized by the superior ability of the extended anthracenyl π-system to stabilize the radical intermediate **Int-A/D** and to engage in multiple, stabilizing non-covalent interactions with the chiral ligand in the favored transition state **TS1**, as revealed by our DFT analysis (Fig. 6a). In this regard, we found that 2-alkoxy-substituted naphthyl groups offered an optimal balance, effectively stabilizing the radical while maintaining high stereocontrol. Indeed, a broad series of alkoxy groups were all well accommodated, delivering **2c′**–**2m′** in 89–96% yield with 84–93% ee. The absolute configuration of **2k′** was determined by X-ray crystallographic analysis, and those of the other products were assigned by analogy. Furthermore, by using modified standard conditions (with Box ligand **L8**, siloxy groups, such as OTBS (**2n′**), OTIS (**2o′**) and OTBDPS (**2p′**), were tolerated. Finally, substrates bearing diverse functional groups on the naphthalene ring all underwent smooth cyclization, furnishing desired products **2q′**–**2v′** in good yields and with generally excellent enantioselectivities. While this methodology demonstrates a broad scope for aryl-substituted oximes, alkyl oximes proved to be challenging substrates under the current catalytic system, likely due to the inferior stabilization of the pivotal radical intermediates. The development of catalytic systems to accommodate aliphatic variants constitutes an important goal for future work.

To demonstrate the synthetic utility of the developed method, late-stage manipulations were performed (Fig. 4A). The reaction was successfully scaled up under standard conditions to afford isoxazoline **2a** without compromising

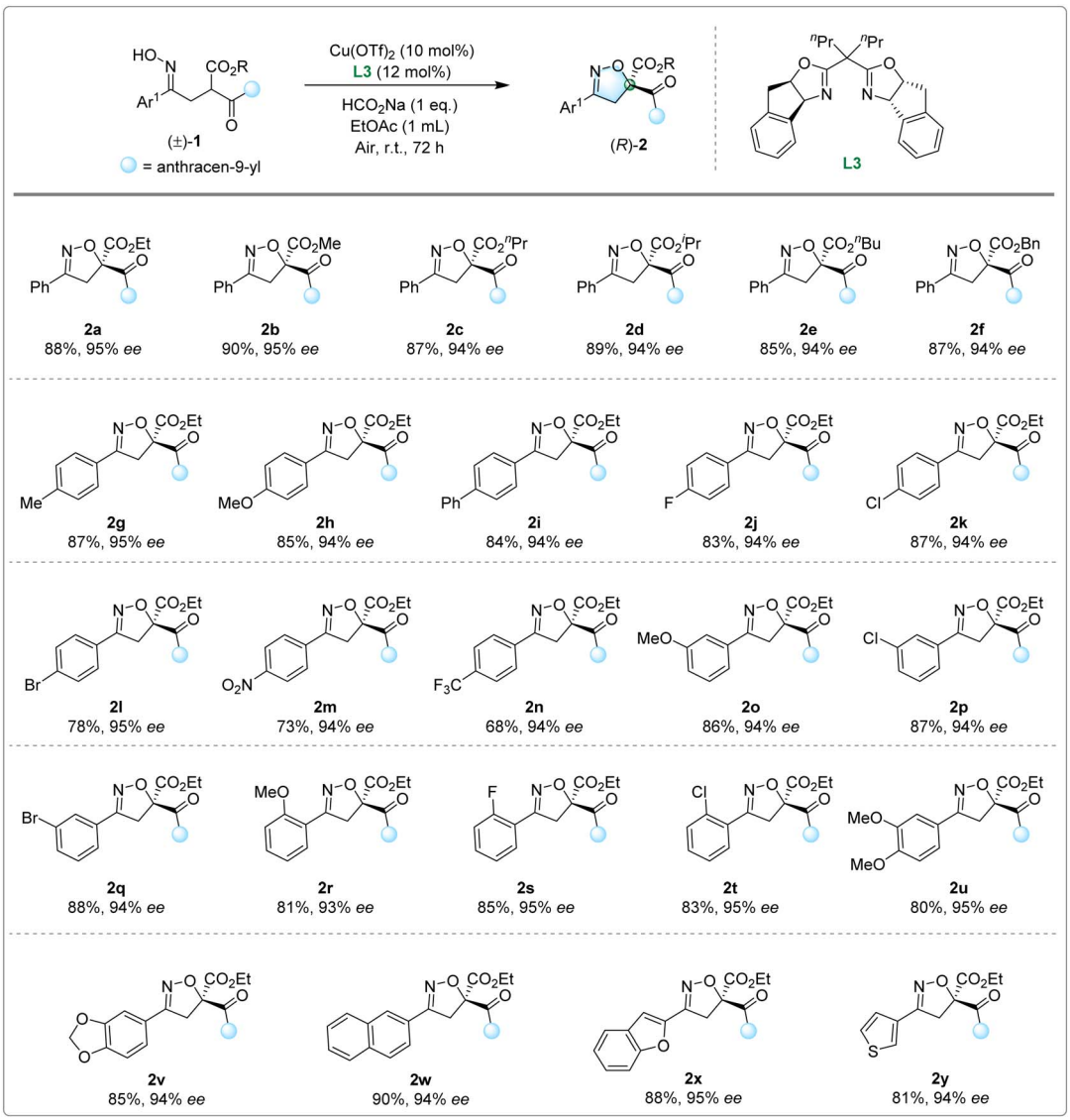


Fig. 2 Substrate scope. Reaction conditions: unless otherwise indicated, **1** (0.05 mmol), $Cu(OTf)_2$ (10 mol%), **L3** (12 mol%) and HCO_2Na (1.0 eq.) were added to EtOAc (1 mL) at room temperature (r.t.) in an air atmosphere for 72 h.

enantioselectivity (see the SI for details). Selective reduction of the ester group led to alcohol **3** in 80% yield without erosion of enantiomeric purity. Employing a RANEY® Ni/H_2 system cleaved the N–O bond efficiently, affording the 1,4-dicarbonyl compound **4** in 76% yield. Chemoselective reduction of the less hindered ketone with $NaBH_4$, followed by protection, gave triol carbonate **5** with >20 : 1 diastereoselectivity. To gain mechanistic insight, we conducted several control experiments (Fig. 4B). Replacing air with pure oxygen did not inhibit the reaction, whereas under a nitrogen atmosphere, the yield dropped significantly, suggesting that atmospheric oxygen serves as the terminal oxidant. Neither hydrazone **6** nor ketone **7** was reactive under standard conditions, highlighting the essential roles of the oxime functional group and activated α-H of the ketone. Electron paramagnetic resonance (EPR) spectroscopy was employed to probe radical intermediates. By adding a radical trap, 5,5-dimethyl-1-pyrroline N-oxide (DMPO), a characteristic signal for an oxy-centered radical was probed (Fig. 4C). Finally, a linear correlation between the enantiopurity of the ligand and the corresponding product was observed in a nonlinear effect study (Fig. 4D), consistent with a mechanism involving a monomeric copper complex containing a single box ligand.

Based on experimental evidence and prior literature,[72–76] a plausible mechanism for the Cu-catalyzed C–O oxidative coupling reaction was proposed (Fig. 5). The catalytic cycle

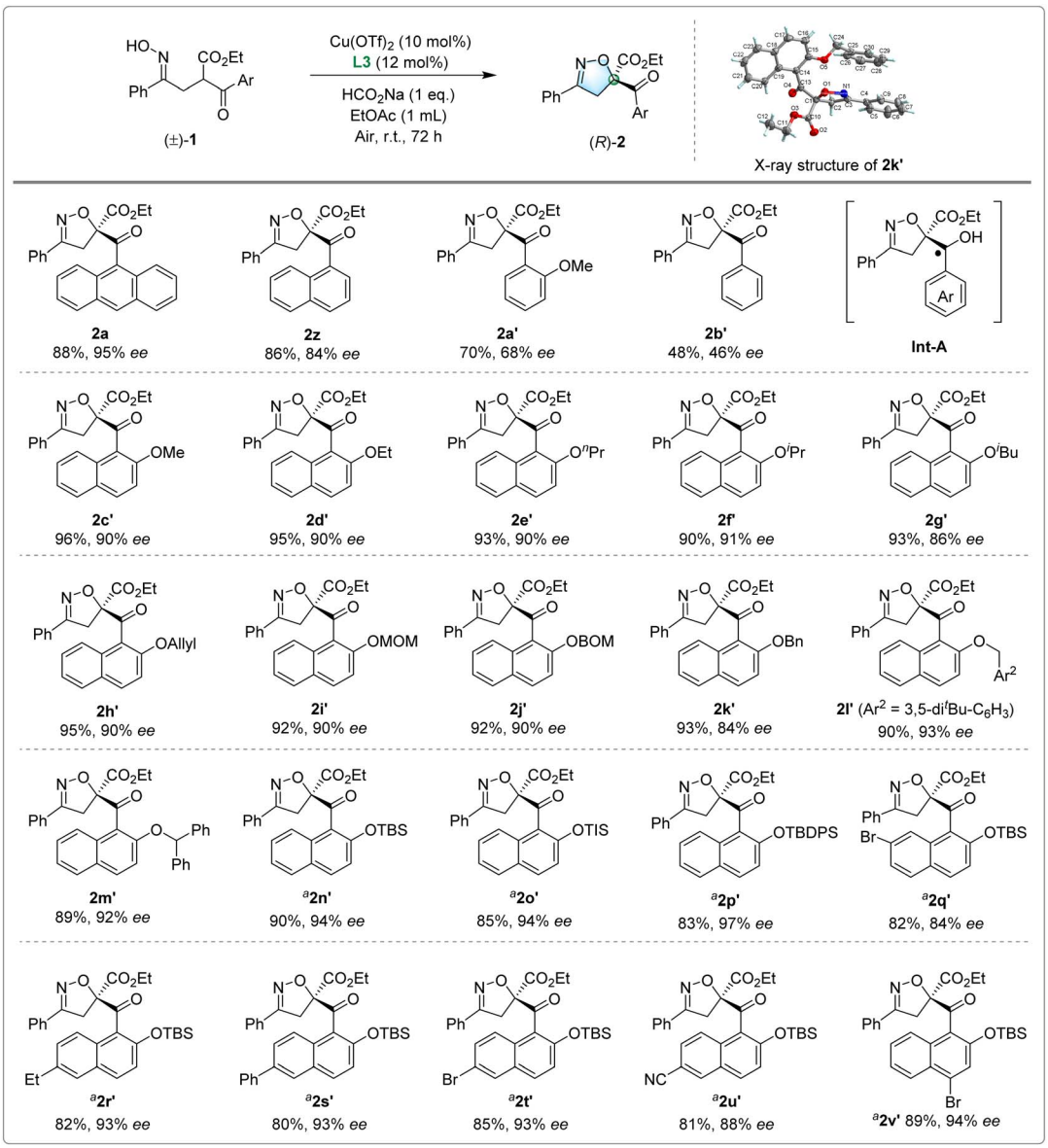


Fig. 3 Further substrate scope. Reaction conditions: unless otherwise indicated, 1 (0.05 mmol), $Cu(OTf)_2$ (10 mol%), **L3** (12 mol%) and HCO_2Na (1.0 eq.) were added to EtOAc (1 mL) at room temperature (r.t.) in an air atmosphere for 72 h. [a] **L8** was used.

begins with the coordination of the chiral Cu^{II} complex, generated from $Cu(OTf)_2$ and box-ligand **L3** under basic conditions, to racemic oxime (±)-**1a**, forming intermediate **A**. A sequential single-electron transfer (SET) then induces the homolysis of the resulting O–Cu^{II} bond, liberating the iminoxyl radical intermediate **B** alongside a Cu^{I}-complex. This radical is subsequently trapped by another molecule of the Cu^{II}-complex, forming intermediate **C**. Within **C**, the O-centered radical undergoes stereocontrolled 5-*exo-dig* cyclization, guided by the chiral ligand environment, to give the C-centered radical **D**. Homolysis of the O–Cu^{II} bond in intermediate **D** releases the enantioenriched isoxazoline **2a**, and regenerates the Cu^{I} species. Finally, oxidation of the Cu^{I}-complex by atmospheric oxygen closes the catalytic cycle by regenerating the active Cu^{II} complex.

Density functional theory (DFT) calculations were performed to elucidate the origin of enantioselectivity in the reaction. Two distinct transition states (**TS1** and **TS1′**, Fig. 6) were identified, corresponding to the formation of enantiomeric products. Energy decomposition analysis revealed that the energy difference between these transition states primarily originates from differential catalyst–substrate

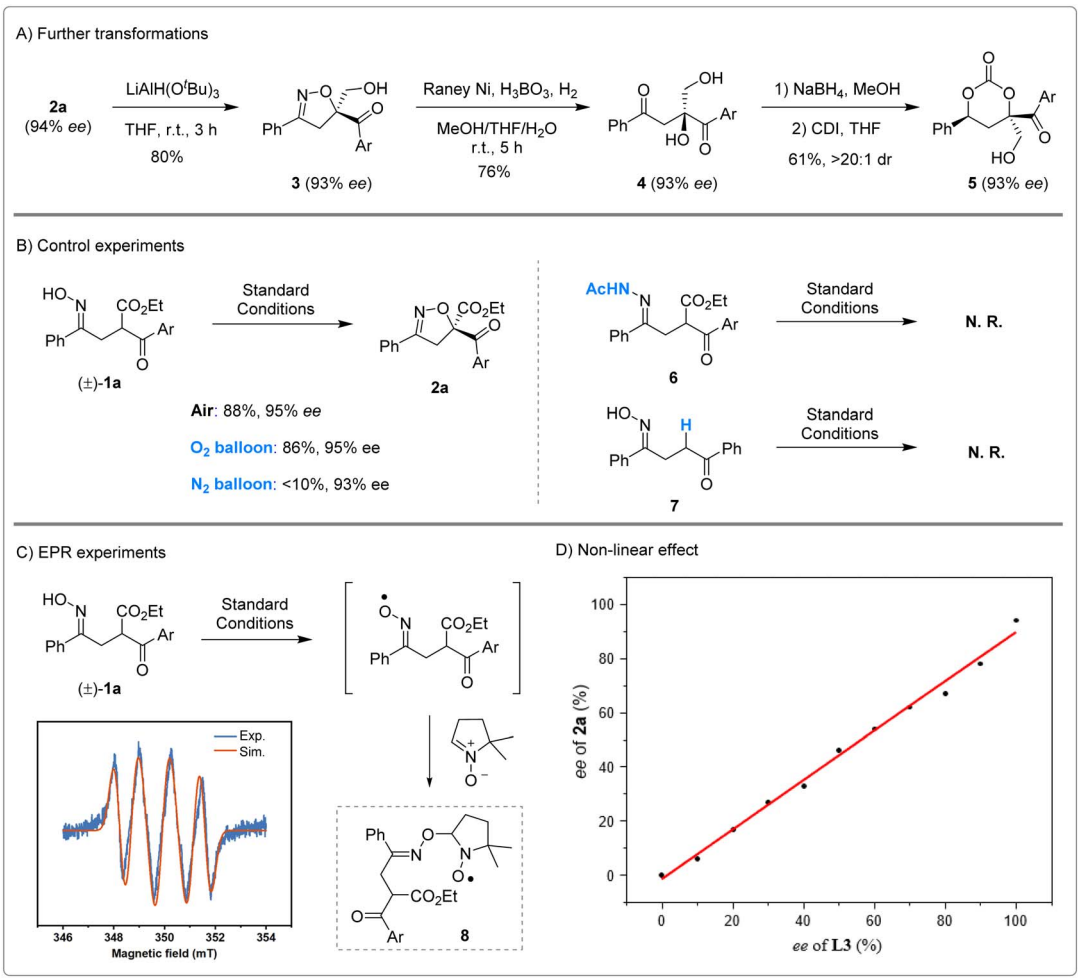


Fig. 4 Further elaborations. Ar = anthracen-9-yl.

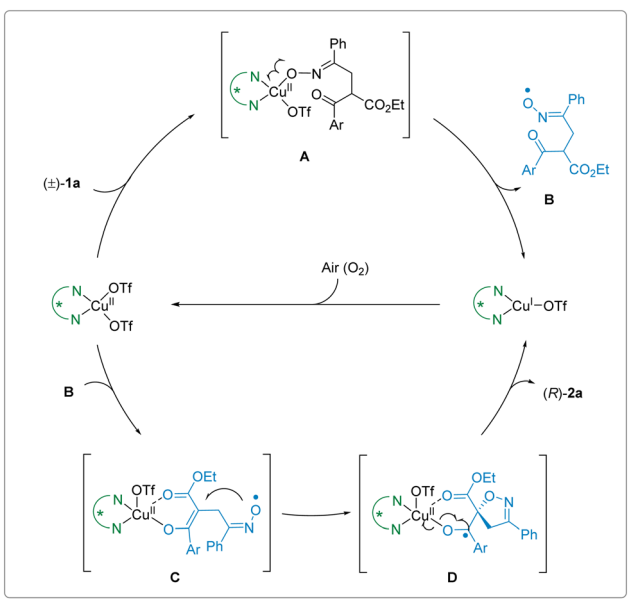


Fig. 5 Proposed mechanism.

interactions. Detailed structural analysis demonstrated significant differences in non-covalent interactions: **TS1** features multiple stabilizing C–H···O interactions ($b_1 = 2.347$ Å, $b_2 = 2.484$ Å, $b_3 = 2.404$ Å) and a C–H···π interaction ($b_4 = 2.956$ Å) between the catalyst and substrate fragment, while **TS1′** possesses only two C–H···O interactions ($b_5 = 2.159$ Å, $b_6 = 2.303$ Å). This disparity in stabilizing interactions accounts for the relative preference for **TS1**. All these interactions could be visualized from the NCI plot (see details in the SI). Furthermore, catalyst distortion energy contributes substantially to the higher energy of **TS1′**. Comparative analysis of dihedral angles revealed that the transformation from pre-intermediate **I1** ($\angle abcd = 18.8°$) to **TS1′** involves significant structural distortion ($\angle a''b''c''d'' = 12.4°$), whereas the corresponding angle in **TS1** remains nearly unchanged ($\angle a'b'c'd' = 20.0°$). These computational findings provide a coherent explanation for the observed enantioselectivity, as the higher energy barrier for **TS1′** effectively suppresses the competing pathway, in excellent agreement with experimental results.

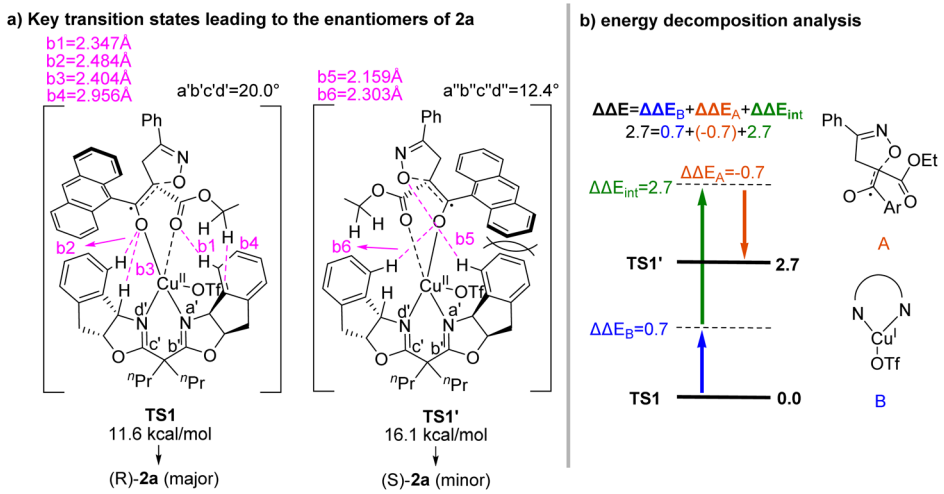


Fig. 6 The structural analysis and energy decomposition analysis of the key transition states leading to enantiomeric products.

Conclusions

In conclusion, we have developed a highly efficient Cu-catalyzed enantioconvergent oxygen-centered radical cyclization of iminoxyl radicals. Under aerobic and mild conditions, the asymmetric radical C(sp^3)–O oxidative coupling between the tertiary C(sp^3)–H bond and the oxime O–H bond of racemic γ-ketoximes proceeds smoothly, providing diverse isoxazolines bearing a fully substituted stereocenter in good yields with excellent enantioselectivity. Control experiments and DFT calculations were performed to explore the reaction mechanism and origin of enantiocontrol. The synthetic utility of this methodology was demonstrated through the late-stage conversion of isoxazolines into polyhydroxy building blocks.

Author contributions

Z. -Y. L., C. -Y. G., H. -M. G., L. -M. L., X. X. and B. G. performed and analyzed the experiments. C. -D. H. and S. -F. N. performed the DFT calculations. G. -J. M. conceived and designed the project. G. -J. M. overall supervised the project. All authors prepared this manuscript.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

CCDC 2434517 (**2k′**) contains the supplementary crystallographic data for this paper.[77]

The authors declare that the data relating to the characterization of products, experimental protocols and the computational studies are available within the article and its supplementary information (SI). Supplementary information is available. See DOI: **https://doi.org/10.1039/d5sc07101a**.

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