

Photoinduced Copper-Catalyzed Asymmetric C–O Cross-Coupling

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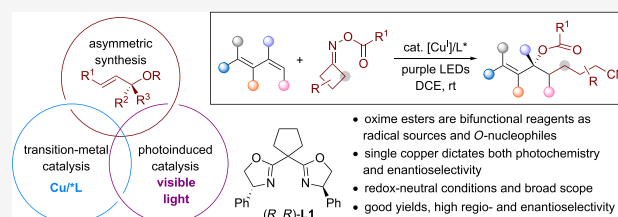


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ABSTRACT: The construction of carbon–heteroatom bonds is one of the most active areas of research in organic chemistry because the function of organic molecules is often derived from the presence of heteroatoms. Although considerable advances have recently been achieved in radical-involved catalytic asymmetric C–N bond formation, there has been little progress in the corresponding C–O bond-forming processes. Here, we describe a photoinduced copper-catalyzed cross-coupling of readily available oxime esters and 1,3-dienes to generate diversely substituted allylic esters with high regio- and enantioselectivity (>75 examples; up to 95% ee). The reaction proceeds at room temperature under excitation by purple light-emitting diodes (LEDs) and features the use of a single, earth-abundant copper-based chiral catalyst as both the photoredox catalyst for radical generation and the source of asymmetric induction in C–O coupling. Combined experimental and density functional theory (DFT) computational studies suggest the formation of π -allylcopper complexes from redox-active oxime esters as bifunctional reagents and 1,3-dienes through a radical–polar crossover process.



INTRODUCTION

The scaffolds of organic compounds mainly consist of carbon–carbon bonds, but their functions are often derived from the presence of various heteroatoms. In the toolbox of medicinal chemists, the assembly of carbon–heteroatom bonds accounts for almost half of the top ten major categories of chemical reactions employed in drug discovery.^{1,2} Not surprisingly, the development of more efficient and sustainable methods for the construction of carbon–heteroatom bonds, particularly C–N and C–O bonds, continues to be the focus of a considerable proportion of modern synthetic efforts. With the evolution of radical chemistry and transition-metal catalysis, radical-involved cross-coupling is emerging as a particularly straightforward strategy for the construction of various carbon–heteroatom bonds.^{3–6} The remarkable findings of Fu and Peters demonstrated that photoinduced asymmetric copper catalysis provides a robust and reliable method for enantioselective C–N coupling of racemic tertiary alkyl chlorides with amines under mild conditions (Figure 1).^{7,8} Subsequent work by Liu^{9–11} and Liu¹² showed that certain chiral ligands (phosphoric acid, bisoxazolines) and directing groups substantially improved the catalytic activity of copper and opened up a much broader substrate scope of radical precursors and N-nucleophiles. Notably, MacMillan's¹³ organocatalytic photoredox-based approach, Zhang's Co(II)-based metalloradical catalysis,¹⁴ and Nagib's¹⁵ radical relay chaperone strategy also provided a range of complementary strategies for direct enantioselective N-centered radical-mediated sp^3 C–N bond formation. Despite these considerable advances, there has been little progress related to corresponding radical-

	sp^3 C–N cross-coupling	vs	sp^3 C–O cross-coupling
intermolecular	sp^3 C-radical + amines ^{7,8} sp^3 C-radical + azides ¹² N-radical + sp^3 C-H ¹³		sp^3 C-radical + alcohols ¹⁹ only a single example with enamides rarely explored
intramolecular	sp^3 C-radical + thioureas ^{9–11} sp^3 C-radical + imidate ¹⁵ metalloradical + sp^3 C-H ¹⁴		sp^3 C-radical + carboxylic acids ^{16,17} sp^3 C-radical + oximes ¹⁸

Figure 1. Qualitative overview of the radical-involved sp^3 C–N and sp^3 C–O cross-coupling.

involved C–O bond-forming processes. Even with several recent noteworthy exceptions of alkene-based intramolecular enantioselective C–O bond-forming radical cyclizations from the groups of Buchwald^{16,17} and Liu,¹⁸ the development of new catalytic systems for radical-involved catalytic asymmetric intermolecular C–O coupling remains an unsolved and long-standing challenge.^{19,20}

Copper-catalyzed asymmetric allylic substitution provides a less expensive and potentially equally efficient approach for the construction of valuable enantiopure allylic compounds compared to the dominant Pd-, Rh-, and Ir-based catalytic systems.^{21,22} The key intermediates, $[\sigma + \pi]$ -allylcopper(III) or

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π -allylcopper(III) complexes, are mostly formed through ionic mechanisms involving nucleophilic organometallic species and electrophilic allylic systems possessing a leaving group (Figure 2a).²³ Despite being powerful, however, the use of highly

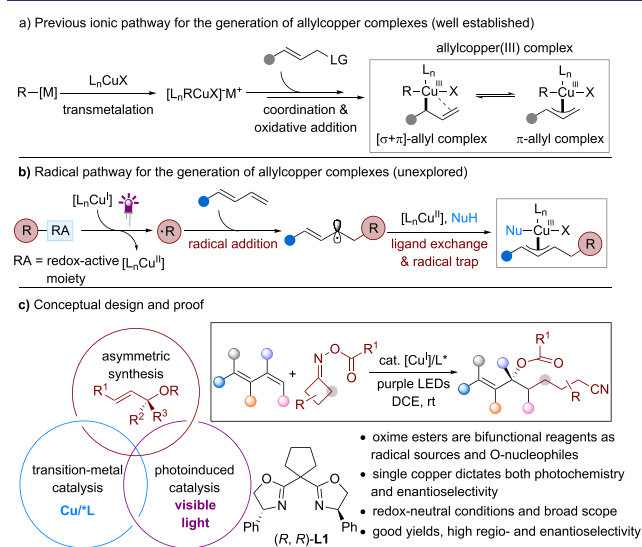


Figure 2. Strategic development for the formation of π -allylcopper complexes and new reaction design. (a) Previous thermal ionic pathway. (b) Outline of a radical pathway (unexplored). (c) Conceptual design and proof (this work, catalytic asymmetric sp^3 C–O coupling enabled by radical formation of π -allylcopper complexes). This work features the use of a single chiral copper catalyst both as photo- and coupling catalysts and oxime esters as bifunctional reagents. This protocol enables efficient incorporation of a cyanoalkyl moiety and sp^3 C–O bond formation with good functional group tolerance and excellent regio- and enantioselectivity, leading to many valuable chiral allylic esters.

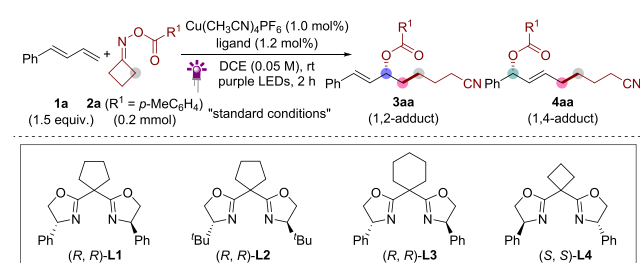
reactive and moisture-sensitive reagents (e.g., organomagnesium, organolithium, organoaluminum, organozinc, or milder organoboron reagents) and prefunctionalized allylic systems considerably limits the substrate range. Notably, application of this strategy to heteroatom nucleophiles as coupling partners has not been realized in copper-catalyzed asymmetric allylic alkylation. Recent advances in copper-catalyzed photoredox and radical chemistry have shown that photoexcited copper catalysts can not only generate highly reactive radical species from various redox-active precursors but also trap these open-shell species to enable asymmetric coupling.^{24–26} Liu showed that copper(II)-bound N-centered radicals could cleave the allylic sp^3 C–H bond of alkenes in a site-specific manner via hydrogen atom transfer to generate allylic radicals.²⁷ This method allows site- and enantioselective allylic C–H cyanation. Quite recently, the groups of Glorius,^{28–32} Gevorgyan,³³ and Shi³⁴ demonstrated that alkyl radicals, which are generated from *N*-hydroxyphthalimide esters or alkyl halides under photoredox catalysis, can be sequentially trapped by 1,3-dienes and palladium, chromium, or titanium catalysts to generate the corresponding electrophilic or nucleophilic π -allylmetal complexes. Employing these intermediates, they achieved a range of aminoalkylation and dialkylation reactions of 1,3-dienes. However, in most of these transformations, the control of both the regio- and stereoselectivity of these radical transformations remains a formidable challenge. Drawing inspiration from these breakthroughs and based on our long-standing interest in photo-

induced copper catalysis,³⁵ we questioned whether π -allylcopper complexes could also be formed by a radical pathway to surmount the aforementioned limitations often encountered in traditional copper-catalyzed ionic asymmetric allylic substitution (Figure 2b). Specifically, we hypothesized that a photoexcited Cu(I) complex might reduce a redox-active radical precursor via a single electron transfer (SET) process to generate a radical species and a Cu(II) species. Then, interception of such a radical species by a feedstock 1,3-diene would give a new allyl radical that might be readily trapped by the initially formed Cu(II) species to generate a π -allylcopper(III)/nucleophile complex in the presence of a nucleophilic reagent. Finally, this high-valent Cu(III) species is prone to undergo reductive elimination to form a new C–O chemical bond with concomitant formation of Cu(I) catalyst.^{36,37} To date, exploration of this strategy in the development of asymmetric allylic sp^3 C–O coupling, particularly intermolecular variants, has not been documented.^{38–40}

Because of their availability from ketones and carboxylic acids as well as their susceptibility to SET reduction, oxime esters have been widely used as cyanoalkyl radical precursors in various radical cross-coupling reactions.^{41–43} Based on our design plan (Figure 2b), we hypothesized that π -allylcopper(III) complexes might be generated by combining oxime esters and 1,3-dienes under photoinduced copper catalysis. However, at the beginning of this study, we were not certain that oxime esters can serve as bifunctional reagents, as both radical sources and O-nucleophiles, or whether regio- and stereocontrol can be realized by using a chiral ligand in such a radical–polar crossover process.^{44,45} Here, we describe a radical strategy for the formation of π -allylcopper(III) complexes and the achievement of highly regio- and enantioselective asymmetric C–O cross-coupling under photoinduced copper catalysis (Figure 2c). The protocol lies at the intersection of several significant fields of modern chemical catalysis. The obtained enantioenriched 1,2-cyanoalkylesterification products of 1,3-dienes are important building blocks in both synthetic and medicinal chemistry.

RESULTS AND DISCUSSION

Reaction Optimization. On the basis of our conceptual design, we began the study by examining the cross-coupling reaction of 1-phenylbutadiene **1a** and oxime ester **2a** under visible-light-induced copper catalysis (Table 1). The major challenge was to control both the regio- (1,2- vs 1,4-adduct) and enantioselectivity. After extensive screening of the reaction parameters, we discovered that irradiation of the cross-coupling partners with purple LEDs at room temperature for 2 h in the presence of $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (1.0 mol %) and a chiral bisoxazoline ligand **L1** (1.2 mol %) gave the best results, affording the desired 1,2-adduct **3aa** in 79% isolated yield with 94% enantiomeric excess (ee) (entry 1) (Supporting Information, Table S1–5). Notably, the competitive side product 1,4-adduct **4aa** was not detected. The reaction efficiency appeared to be sensitive to the solvents and copper salts. For instance, the use of THF and DMF led to a significant decrease in yield (entries 2 and 3). While employment of $\text{Cu}(\text{OTf})_2$ gave comparable results,⁴⁶ the reaction did not proceed when using CuI, with **2a** being fully recovered (entries 4 and 5). The substitution patterns of the ligands also played an essential role. Compared to ligand **L1**, ligands **L2–L4** resulted in substantially lower reaction

Table 1. Effects of Variations in the Reaction Parameters and Conditions^a

entry	variation	yield (%) ^b	ee ^c
1 ^d	none	88 (79)	94
2 ^e	use of THF, 16 h	21 (33)	86
3 ^e	use of DMF, 16 h	0 (99)	-
4 ^e	use of CuI	0 (99)	-
5	use of Cu(OTf) ₂	81	94
6 ^e	ligand (R,R)-L2	15 (16)	9
7	ligand (R,R)-L3	61	88
8	ligand (S,S)-L4	69	-82
9 ^e	blue LEDs	5 (63)	91
10 ^e	no light	0 (99)	-
11 ^e	no ligand (R,R)-L1	0 (22)	-
12 ^e	no Cu(CH ₃ CN) ₄ PF ₆	0 (99)	-
13	added water (0.1 equiv)	84	94

^aReaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), Cu(CH₃CN)₄PF₆ (1.0 mol %), ligand **L1** (1.2 mol %), 1,2-dichloroethane (DCE) (4.0 mL), 2 × 20 W purple LEDs ($\lambda_{\text{max}} = 390$ nm), at room temperature. ^bYields were determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. ^cDetermined by HPLC analysis on a chiral stationary phase. ^dIsolated yield. ^eRecovery of **2a**.

efficiency and enantioselectivity (entries 6–8). Interestingly, the reaction that was performed under irradiation by blue LEDs ($\lambda_{\text{max}} = 460$ nm) proceeded sluggishly, with **3aa** being obtained in only 5% yield with 91% ee (entry 9).

Control experiments established that each component is critical to the desired cross-coupling reaction (entries 10–12). Remarkably, without ligand **L1**, the majority of oxime ester **2a** was consumed but led to a messy mixture. Our concern that allylic radicals initially formed upon radical addition might isomerize to oxidize labile benzylic radicals to lead to the 1,4-adduct appeared to be unfounded, as evidenced by the exclusive formation of the 1,2-adduct. In terms of the method practicality, Cu(CH₃CN)₄PF₆ and chiral bisoxazoline ligands are commercially available, and the protocol is not moisture-sensitive (entry 13). Until now, oxime esters have been mainly used as cyanoalkyl radical sources, with the generation of a stoichiometric carboxylic anion as a byproduct. In contrast, this protocol allows waste carboxylic anions to be used as O-nucleophiles, leading to atom-economic incorporation of oxime esters.

Substrate Scope of Cyclobutanone Oxime Esters.

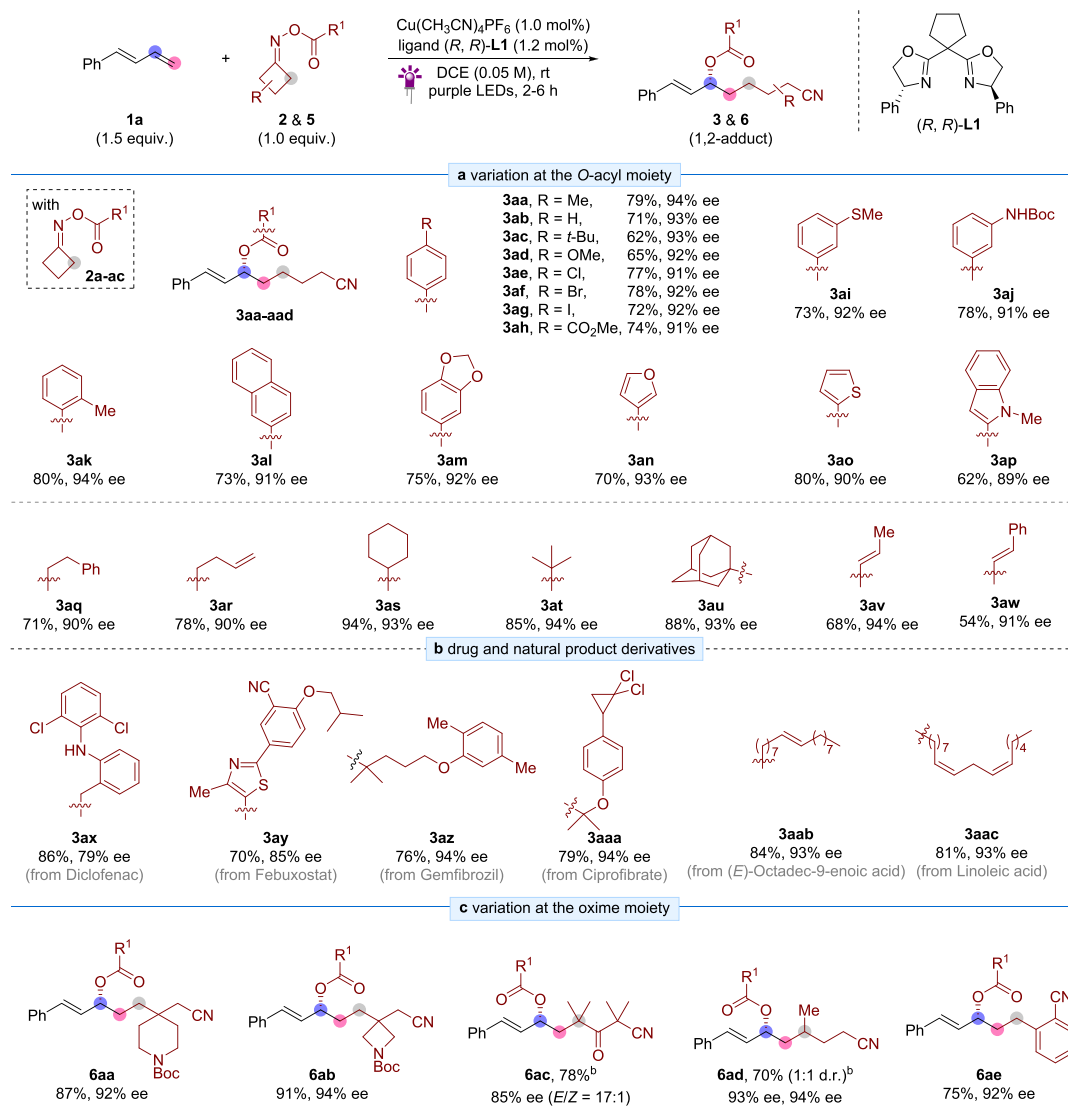
With the optimized conditions in hand, we examined the substrate scope with respect to the two coupling partners on a 0.2 mmol scale. First, the scope of oxime esters was tested by varying the *O*-acyl moiety (Table 2a). Aside from **2a**, aryl-carboxylic-acid-derived oxime esters **2b–h** bearing various neutral (H), electron-donating (e.g., *t*-Bu, OMe), or electron-withdrawing (e.g., Cl, Br, I, CO₂Me) groups at the *para*-position of the aromatic ring were all suitable partners for the

cross-coupling. Desired products **3ab–ah** were obtained in generally good yields (62–78%) with excellent enantioselectivity (91–93% ee). Notably, the halogen atoms (Cl, Br, I) may be subjected to further synthetic manipulations (in particular, transition-metal-catalyzed cross-coupling reactions) at the halogenated positions (products **3ae–ag**). Moreover, oxime esters **1i–k** with functional groups at the *meta*- or *ortho*-position also reacted well, affording **3ai–ak** in 73–80% yields with 91–94% ee and indicating that steric hindrance did not affect the transformation. Reactions with substrates possessing a fused aromatic ring (**2l**) or heteroaromatic ring (**2m–p**) were also amenable to this process, giving the corresponding coupled products **3al–ap** in good yields with consistently excellent enantioselectivity (89–93% ee). Then, we proceeded to examine the generality of this asymmetric cross-coupling by using a range of aliphatic carboxylic-acid-derived oxime esters. For instance, oxime esters **2q–w** derived from cyclobutanone and primary, secondary (cyclohexyl), tertiary (e.g., *t*-butyl and adamantyl acids), and α,β -unsaturated acids were all well accommodated under the current catalytic system. Thus, the expected allylic ester products **3aq–aw** were isolated in good yields ranging from 54% to 94% with 90–94% ee.

Markedly, as shown in Table 2b, oxime esters **2x–z** and **2aa** derived from drugs diclofenac, febuxostat, gemfibrozil, and ciprofibrate were converted into their corresponding 1,2-cyanoalkylacyloxylation products **3ax**, **3ay**, **3az**, and **3aaa**, respectively, with good yields and satisfactory enantioselectivity. Naturally occurring acid-derived oxime esters **2ab–ac** were also suitable for coupling, providing the expected products with good yields and stereoselectivity. These results showed the robustness and utility of the developed reaction.

Finally, we investigated the effect of varying the oxime moiety on the efficiency and enantioselectivity of the reaction with **1a** (Table 2c). The reaction of 3,3-disubstituted oxime esters **5a** and **5b** proceeded smoothly to afford the expected products **6aa** and **6ab** in high yields with 92% and 94% ee, respectively. Sterically more demanding **5c** was also well tolerated to give **6ac** with modest reaction statistics. 2-Methyl-substituted oxime ester **5d** also efficiently participated in the reaction to produce a good yield of **6ad** with high ee values, but the d.r. was 1:1 because of the initial nonenantioselective addition of cyanoalkyl radicals. Notably, benzocyclobutenone-derived oxime ester **5e** also proved to be suitable for the reaction, leading to product **6ae** in 75% yield with 92% ee.

Substrate Scope of 1,3-Dienes. Next, a representative set of 1,3-dienes was evaluated to further investigate the generality of this cross-coupling (Table 3). First, it was found that the 1-aryl- and heteroaryl-substituted 1,3-dienes were all competent reaction partners. For example, substrates **1b–g** bearing either alkyl or electron-withdrawing groups (e.g., F, Cl, Br, CF₃) at the *para*-position of the phenyl ring were well tolerated, furnishing the corresponding allylic esters **7ba–ga** in 60–73% yields with 87–92% ee. Again, as shown in the reactions of **1h–m**, variations in the substitution pattern and steric hindrance of the aromatic ring had little effect on both the reaction efficiency and enantioselectivity. As such, the expected products **7ha–ma** were isolated in 70–80% yields with 87–95% ee, regardless of the electronic properties of the substituent. The reaction of 1-(2-naphthyl)-substituted 1,3-diene **1n** also proceeded smoothly to produce **7na** in 53% yield with 88% ee. Additionally, 1,3-dienes **1o** and **1p** with 3-furanyl or 3-thiophenyl groups were well tolerated, furnishing the relative products **7oa** and **7pa** in good yields with 88% and

Table 2. Scope of the Oxime Esters Tolerated in Photoinduced Copper-Catalyzed Asymmetric C–O Cross-Coupling^a

^aReaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), Cu(CH₃CN)₄PF₆ (1.0 mol %), ligand **L1** (1.2 mol %), 1,2-dichloroethane (DCE) (4.0 mL), 2 × 20 W purple LEDs (λ_{max} = 390 nm), room temperature; isolated yields. ^bWith Cu(CH₃CN)₄PF₆ (2.0 mol %), ligand **L1** (2.4 mol %), and 3.0 equiv of **1a**.

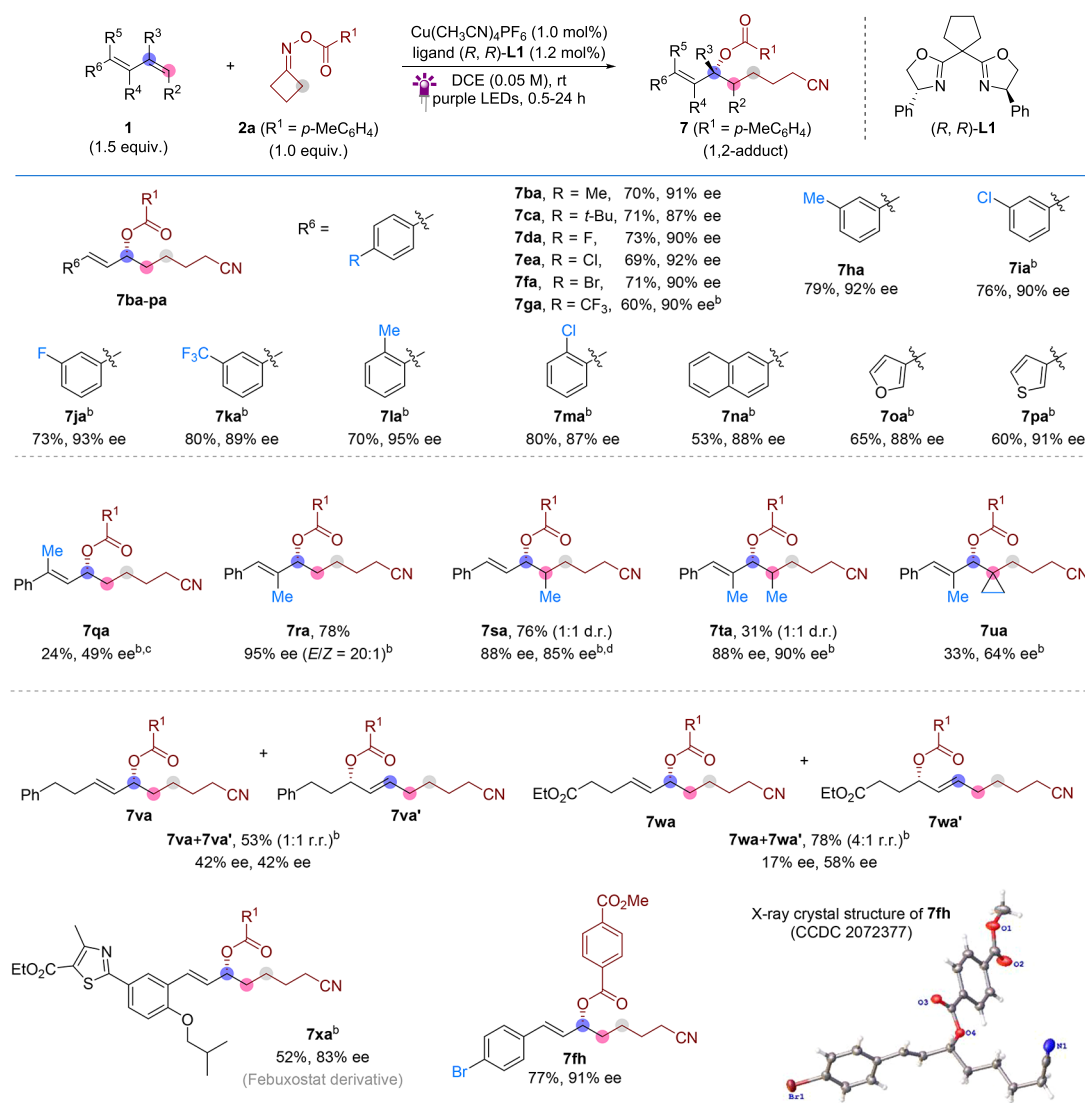
91% ee, respectively. Notably, as shown in the cases of **1q–s**, 1,1-disubstituted 1,3-dienes and those bearing a methyl group at the C2 or C4 position were also proven to be suitable coupling partners. The expected products **7ra** and **7sa** were obtained with good yields and satisfactory enantioselectivity, while **7qa** was isolated with moderate yield due to low conversion. The 1:1 d.r. of **7sa** was a result of the initial nonenantioselective radical addition of the cyanoalkyl radical. Remarkably, tri- (**1t**) and tetra-substituted (**1u**) 1,3-dienes could also work well under the standard conditions, giving the corresponding products **7ta** and **7ua** with moderate yields and good enantioselectivity.

Challenging alkyl-substituted 1,3-dienes such as **1v** and **1w** could also participate in the desired cross-coupling. In both cases, however, mixtures of 1,2- and 1,4-adducts were isolated in good yields but with moderate regio- and enantioselectivity, probably because of the steric similarity at the C-2 and C-4 positions of this type of 1,3-dienes. We are currently investigating modifications to the chiral ligand, which will

provide better stereocontrol for these alkyl-substituted 1,3-dienes. X-ray crystallographic analysis of product **7fh**, produced in the reaction of 1,3-diene **1f** and oxime ester **2h** with 77% yield and 91% ee, confirmed the (*R*)-configuration of the newly formed absolute stereochemistry. Thus, all other cross-coupling products were tentatively assigned by analogy to **7fh**. Remarkably, a biologically relevant molecule, febuxostat-derived 1,3-diene **1x**, could also couple with **2a** efficiently to give the desired product **7xa** in 52% yield with 83% ee.

Substrate Scope of Cyclopentanone Oxime Esters.

According to our design, an allylic radical might be involved in the formation of the π-allylcopper complex, which was supposed to be formed upon the addition of a cyanoalkyl radical to 1,3-diene. Thus, we envisioned that if 2-styrenyl-substituted cycloketoxime esters could undergo SET-reduction-mediated ring opening to give allylic radicals under the current catalytic system then asymmetric C–O cross-coupling might also occur between such allyl radical species and the leaving group–carboxylic anion. As such, the reaction would

Table 3. Scope of 1,3-Dienes Tolerated in Photoinduced Copper-Catalyzed Asymmetric C–O Cross-Coupling^a

^aReaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (1.0 mol %), ligand **L1** (1.2 mol %), 1,2-dichloroethane (DCE) (4.0 mL), 2 × 20 W purple LEDs ($\lambda_{\text{max}} = 390$ nm), room temperature; isolated yields. ^bWith $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (2.0 mol %), ligand **L1** (2.4 mol %), and 3.0 equiv of **1**. ^c*E*/*Z*-**1q** = 10:1. ^d*E*/*Z*-**1s** = 3:1.

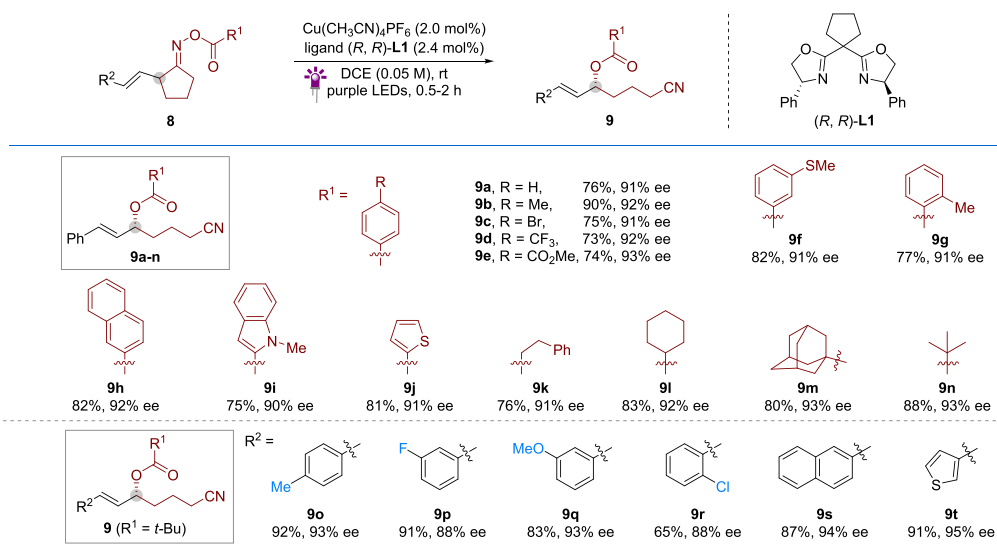
provide an atom-economic process for catalytic asymmetric fragmentation/rearrangement of cycloketoxime esters. As highlighted in Table 4, the reaction indeed proceeded well, and the standard catalytic system had broad substrate scope. A range of aryl-carboxylic-acid-derived cycloketoxime oxime esters **8a–g** with an electron-donating or electron-withdrawing substituent at the *para*-, *meta*-, or *ortho*-position of the phenyl ring all smoothly underwent the desired reaction. Corresponding products **9a–g** were obtained with generally good yields (73–90%) and excellent enantioselectivity (91–93% ee). Moreover, substrates **8h** and **8i**, containing (hetero)arene-annulated systems, and **8j**, with a 2-thiophenyl group, were also suitable for the reaction, with the relative products **9h–j** being formed with comparable results. As shown in the synthesis of **9k–n**, primary (**8k**) and secondary (**8l**), as well as sterically very demanding carboxylic-acid-derived cycloketoxime esters (**8m** and **8n**), were also well tolerated without loss of reaction efficiency or enantioselectivity (91–93% ee). We also briefly examined the effect of the R² group on the reaction. As shown

in the reactions of **8o–t** with R² being an aryl or heteroaryl group, although the change in their electronic properties had some effect on the reaction efficiency, the expected products **9o–t** could still be obtained with high to excellent ee values.

Synthetic Applications. A 5.0 mmol-scale reaction of **2a** produced comparable results (**3aa**, 1.22 g, 73% yield, 93% ee), indicating the scalability of the process (Figure 3a). Moreover, the alkene moiety of product **3aa** allows further synthetic manipulation. For example, the carbon–carbon double bond in **3aa** could easily undergo hydrogenation to give **10** in good yield without loss of enantioselectivity (Figure 3b). Irradiation of **3aa** with blue LEDs in the presence of photocatalyst $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ enabled isomerization of (*E*)-**3aa** to its (*Z*)-form **11** without a deleterious effect on the enantiopurity (Figure 3c).

Mechanistic Studies. Next, we conducted a series of experiments to shed light on the mechanism. First, we obtained UV–vis absorption spectra of each reaction component and confirmed that the $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6/\text{L1}$ complex was the only

Table 4. Preliminary Attempts to Achieve Photoinduced Copper-Catalyzed Ring-Opening Asymmetric C–O Coupling of Cyclopentanone Oxime Esters^a



^aReaction conditions: **8** (0.2 mmol), Cu(CH₃CN)₄PF₆ (2.0 mol %), ligand **L1** (2.4 mol %), 1,2-dichloroethane (DCE) (4.0 mL), 2 × 20 W purple LEDs (λ_{max} = 390 nm), at room temperature; isolated yields.

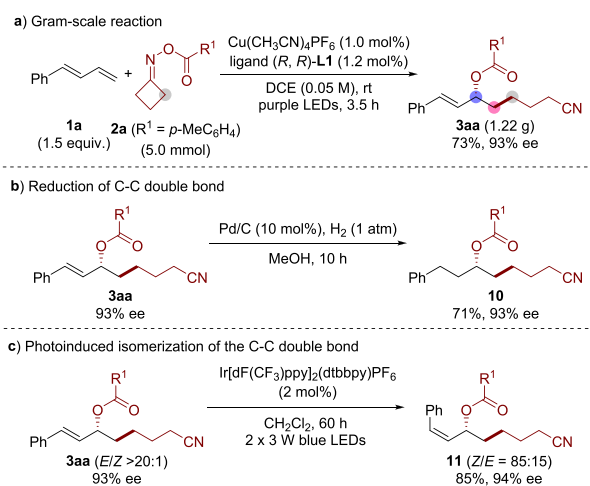


Figure 3. Synthetic utility. (a) Gram-scale synthetic capability. (b) Pd/C-catalyzed reduction of the carbon–carbon double bond. (c) Photoinduced isomerization of the carbon–carbon double bond.

visible-light-absorbing species. Stern–Volmer studies of Cu(CH₃CN)₄PF₆/L1 with oxime ester **2a** supported that a photoexcited Cu(I) complex could reduce **2a** by SET (see Supporting Information Figure S9). A study of the effect of the enantiopurity of ligand **L1** on the enantioselectivity of product **3aa** demonstrated an obvious linear effect (see Supplementary Figure S10). This observation suggested that the active catalyst species for chiral induction in C–O cross-coupling was consistent with a 1:1 ratio of the copper catalyst and chiral bisoxazoline ligand **L1**.

The premade Cu(I)/L1 complex demonstrated the similar outcomes in the model reaction. We also studied the photophysical and electrochemical properties of an in situ formed Cu(I)/L1 complex. The lifetime of the photoexcited state of *Cu(I)/L1 was also determined (*t*₁ = 0.95 ns; *t*₂ = 3.79 ns; *t*₃ = 15.02 ns). The measured potentials of the photoexcited state of *Cu(I)/L1 (−2.39 V vs SCE) and **2a** (−2.22 V vs

SCE) suggest that SET reduction of **2a** by *Cu(I)/L1 is thermodynamically feasible (see section 6.9 in the Supporting Information).

To gain additional insight into the mechanism, we then carried out a series of control experiments (Figure 4). When the commonly used radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and PhSeSePh were added to the model reaction of **1a** and **2a** under standard conditions, the formation of the desired product **3aa** was completely inhibited in both cases. The radical-trapping adducts **12** and **13** could be detected by high-resolution mass spectrometry (HRMS) and isolated in quantitative yield (Figure 4a). These results suggest the possible involvement of cyanoalkyl radical **2a-B**, which should be formed from iminyl radical **2a-A** through β-C–C bond cleavage.⁴³ In addition, when radical clock substrate **14** reacted with **2a**, the cyclopropyl group was completely opened to give product **15** in modest yield with 83% ee (Figure 4b). Thus, this radical clock experiment provides further evidence of a radical process. To understand the behavior of the O-nucleophile-carboxylic anion formed upon SET reduction of the oxime ester, crossover experiments with two different oxime esters were performed (Figure 4c). When equimolar amounts of oxime esters **2h** and **5a** were employed, four cross-coupling products were isolated with similar yields and enantioselectivities. In particular, the formation of formal three-component cross-coupled products **3aa** and **16** implied that the copper-catalyzed C–O bond-forming step should occur through out-of-cage coupling of the radical intermediate and carboxylic anion.

DFT Computational Studies. To obtain a deeper understanding of the photoinduced copper-catalyzed asymmetric C–O cross-coupling, several elementary steps involving regioselectivity and stereoselectivity were evaluated through density functional theory (DFT) calculations at the SMD⁴⁷ (DCE)/M06⁴⁸/[6-311++G(d,p)]/SDD⁴⁹ (Cu)//M06/[6-31G(d)/LanL2DZ⁵⁰ (Cu)] level. Inspired by our previous study,⁴³ the time-dependent DFT (TD DFT) calculations demonstrated that the Cu(I) complex can be excited under

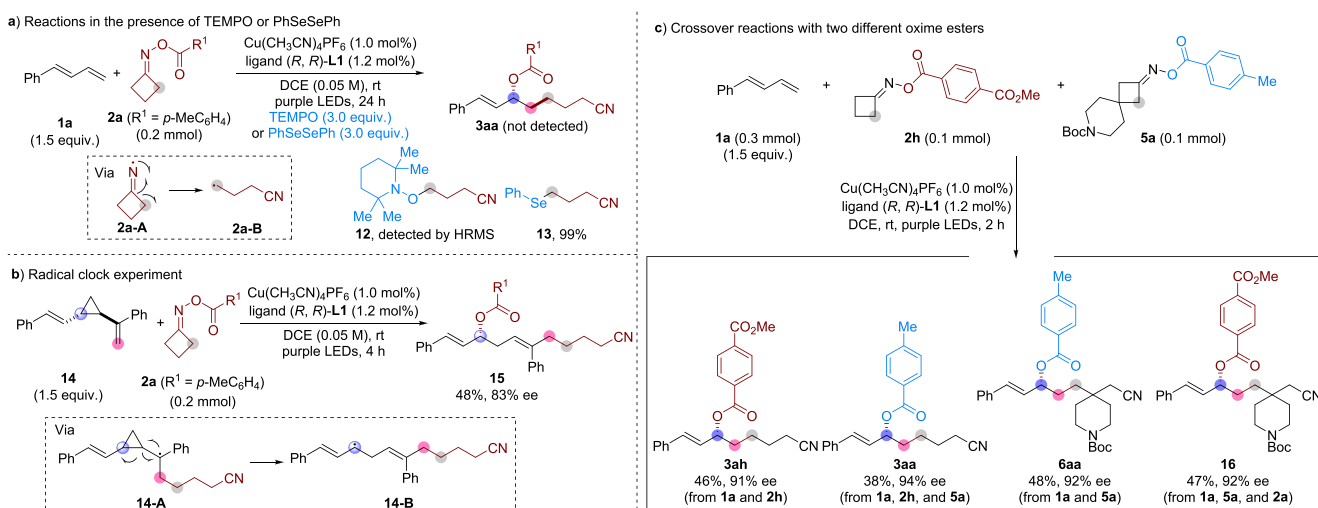


Figure 4. Mechanistic studies. (a) Reactions in the presence of radical scavengers. (b) Radical clock experiment. (c) Crossover experiments with two different oxime esters.

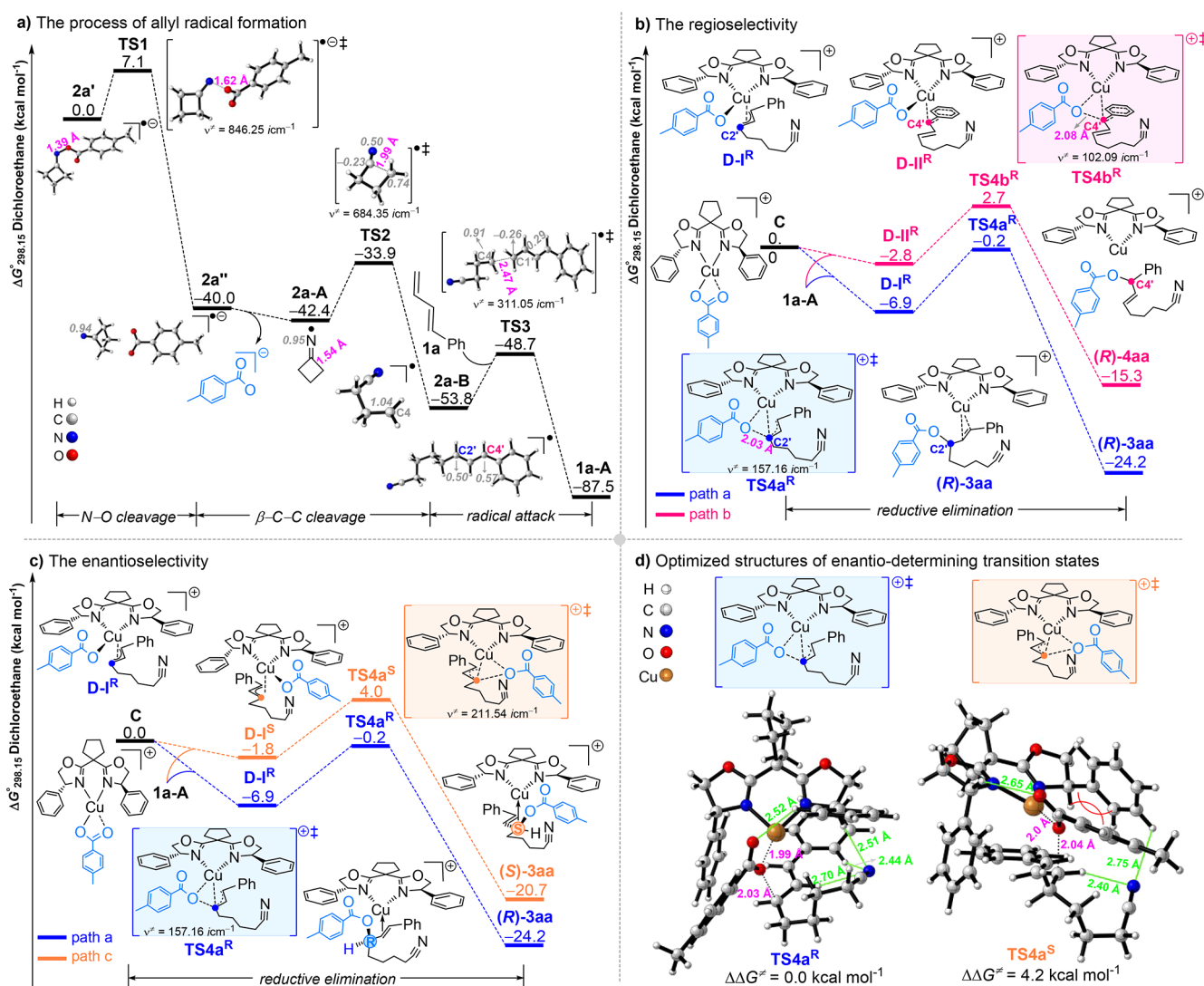


Figure 5. Results of density functional theory (DFT) calculations (all values are in kilocalories per mole). (a) Process of allyl radical formation. (b) Formation of the allylcopper complex and the regioselectivity of the C–O cross-coupling reaction. (c) Enantioselectivity of the C–O cross-coupling reaction. (d) Optimized structures of enantio-determining transition states.

irradiation with purple LEDs (see Supporting Information, section 8.1, Figures S16 and S17 and Table S6). Then, the photoexcited triplet $^3\text{Cu(I)}$ complex can be oxidatively quenched by oxime ester **2a** via SET to generate radical anion **2a'** and a ground-state Cu(II) cation. As shown in Figure 5a, the resultant radical anion **2a'** undergoes three key elementary steps, N–O bond cleavage, $\beta\text{-C-C}$ bond cleavage, and radical addition to **1a**, to provide the allyl radical (**1a-A**). **TS1**, **TS2**, and **TS3** are the corresponding transition states for these three steps with Gibbs activation energies (ΔG^{\ddagger}) of 7.1, 8.5, and 5.1 kcal mol $^{-1}$, respectively. In **TS1**, the N–O bond is elongated to 1.62 Å from 1.39 Å in **2a'**, which indicates that the N–O bond is breaking. When the N–O bond breaks, the spin densities of the resultant N–O cleaved intermediate **2a''** are mainly localized on N at 0.94. Then, the iminyl radical (**2a-A**) is dissociated from **2a''** with a negative Gibbs free energy change (ΔG°) of -2.4 kcal mol $^{-1}$. In **TS2**, the $\beta\text{-C-C}$ bond of **2a-A** is activated to 1.99 Å from 1.54 Å in **2a-A**, which means that the cyanoalkyl radical (**2a-B**) has formed. When the $\beta\text{-C-C}$ bond is cleaved, the spin density becomes mainly localized on the terminal C4 of **2a-B** with 1.04. In **TS3**, the C1'–C4 distance is shortened to 2.47 Å, which indicates that the C1'–C4 bond is gradually forming. When **2a-B** attacks the terminal position of 1-phenylbutadiene (**1a**), the spin densities become mainly localized on C2' and C4' of radical intermediate **1a-A** at 0.50 and 0.57, respectively. Overall, allyl radical formation occurs with a small energy barrier of 8.5 kcal mol $^{-1}$ and a negative ΔG° value of -87.5 kcal mol $^{-1}$. Subsequently, as shown in Figure 5b, two possible C–O bond-forming reductive eliminations were investigated: one is C2'–O reductive elimination from the stable π -allylcopper complex **D-I^R** to provide 1,2-adduct (*R*)-**3aa** (path a), whereas the other is C4'–O reductive elimination from π -benzylcopper complex **D-II^R** to obtain 1,4-adduct (*R*)-**4aa** (path b). **TS4a^R** and **TS4b^R** are the corresponding transition states for these two steps, with ΔG^{\ddagger} values of 6.7 and 9.6 kcal mol $^{-1}$, respectively. The C2'–O distance is shortened to 2.03 Å in **TS4a^R** from 2.82 Å in **D-I**, while the C4'–O distance is shortened to 2.08 Å in **TS4b^R** from 3.08 Å in **D-II^R**; these distance changes indicate that the C2'–O and C4'–O bonds are forming. The former path (a) occurs much more favorably (by 2.9 kcal mol $^{-1}$) than the latter path (b) due to the stable π -allylcopper interaction. Thus, the 1,2-adduct is a major product whose formation is favored both thermodynamically and kinetically, which is in line with the regioselectivity observed experimentally. To determine the origin of high enantioselectivity, the locations of two favorable enantio-determining C2'–O reductive eliminations leading to (*R*)-**3aa** and (*S*)-**3aa** were determined, as shown in Figure 5c. Starting from Cu(II) benzoate complex **C**, allyl radical **1a-A** is electrophilically captured by the Cu(II) center from the *Re*-face and *Si*-face to generate *R*-type and *S*-type carbon-centered chiral Cu(III) intermediates **D-I^R** and **D-I^S**, respectively. **D-I^R** is more stable than **D-I^S** by 5.1 kcal mol $^{-1}$. Then, the C2'–O reductive elimination of **D-I^R** and **D-I^S** occurs through **TS4a^R** and **TS4a^S** to provide the asymmetric C–O cross-coupling products (*R*)-**3aa** and (*S*)-**3aa**. **TS4a^R**, leading to the *R*-configured product, is lower than **TS4a^S**, leading to the *S*-configured product, by 4.2 kcal mol $^{-1}$, which is qualitatively in agreement with the observed 94% ee ((*R*)-**3aa**) (Figure 5d). To understand the reason why the *R*-configured product shows excellent enantioselectivity, further structural analysis from the perspective of the steric effect suggests that the steric hindrance

between the aryl group of the chiral ligand and the carboxylic group of the substrate may be responsible for determining the enantioselectivity of the *R*-configured product.

To shed more light on the intermediacy of the radical intermediates, EPR experiments were performed (Figure 6a).

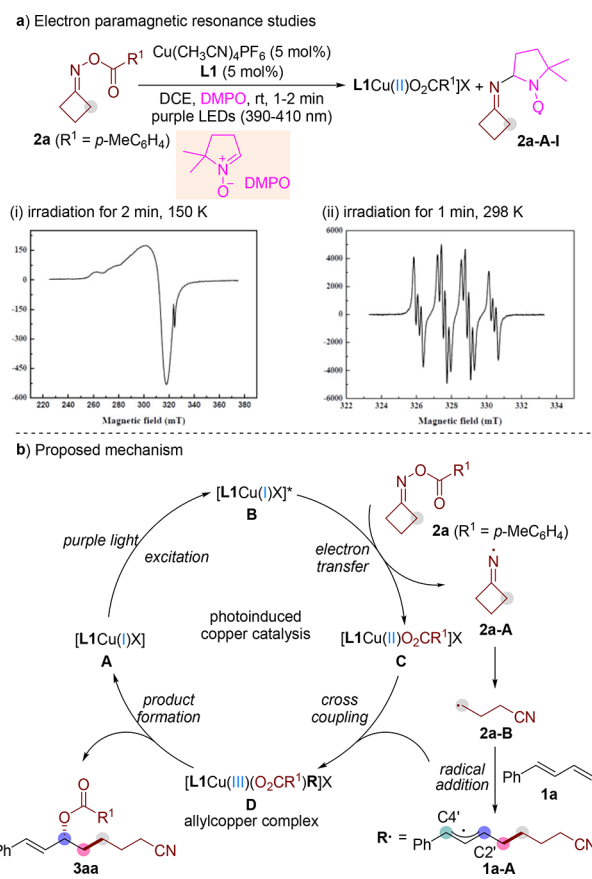


Figure 6. Electron paramagnetic resonance (EPR) studies and proposed mechanism. (a) Electron paramagnetic resonance studies. (i) EPR spectra of Cu(II) (X band, 9.045 GHz, $g_{\parallel} = 2.31$, $g_{\perp} = 2.07$) and (ii) EPR spectra of spin adduct **2a-A-I** (X band, 9.045 GHz, $g = 2.0036$). (b) Proposed catalytic cycle.

A solution of **2a** and **L1/Cu(I)**(CH_3CN) $_4\text{PF}_6$ in DCE produced obvious Cu(II) signals under visible-light irradiation (Figure 6a (i)). An iminyl-radical-trapping adduct **2a-A-I** was also probed by adding the radical trap 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) (Figure 6a (ii)). These results indicate the involvement of iminyl radicals, and their formation can occur through only a photoinduced copper(I)-catalyzed SET process.

Based on these mechanistic studies, we proposed a potential mechanism for this transformation with the model reaction as an example (Figure 6b). First, irradiation of a L1Cu(I)X complex (**A**) by purple light could lead to its excited state $[\text{L1Cu(I)X}]^*$ (**B**), which would then engage in a SET process with redox-active oxime ester **2a** to generate iminyl radical **2a-A** and L1Cu(II) species with the release of a carboxylic anion (R^1CO_2^-). Meanwhile, coordination of the waste carboxylic anion (R^1CO_2^-) with the L1Cu(II) species could result in a copper–nucleophile complex (**C**). Next, iminyl radical **2a-A** undergoes facile $\beta\text{-C-C}$ bond cleavage to form cyanoalkyl radical **2a-B**, which adds to the terminal position of diene **1a** to furnish radical species **1a-A**. At this stage, radical **1a-A** might

associate with Cu(II) complex **C** to form π -allyl Cu(III) complex **D** (specifically energetically favorable **D-I^R**, as shown in Figure 5).⁵¹ However, π -allyl Cu(III) complex **D** might exist in equilibrium with hybrid allylic Cu(II) radicals, which cannot be ruled out at the current stage. Finally, sp³ C–O bond formation could occur enantioselectively to afford product **3aa** and regenerate the LCu(I)X complex (**A**). During the optimization study, it was also found that Cu(OTf)₂ also proved to be a suitable catalyst. On the basis of the previous reports,⁵² we reasoned that the Cu(II) salt could be possibly in situ converted into Cu(I) species by homolytic cleavage of the O–Cu(II) bond or disproportionation, thus initiating the SET reduction of oxime esters.

CONCLUSIONS

In conclusion, we have developed a photoinduced copper-catalyzed intermolecular asymmetric C–O cross-coupling reaction that enables the overall transformation of readily available oxime esters and 1,3-dienes to the corresponding diversely substituted chiral allylic esters with high regio- and enantioselectivity. This redox-neutral reaction proceeds at room temperature under visible-light irradiation and features the use of a copper-based chiral catalyst as both a photoredox catalyst for radical generation and a source of asymmetric induction in C–O cross-coupling. Key to the success of this transformation is the establishment of a general strategy for the formation of π -allylcopper complexes through a radical pathway under visible-light irradiation. This strategy provides an alternative to the in situ generation of π -allylcopper(III) complexes typically from nucleophilic organometallic reagents and prefunctionalized allylic systems. Overall, considering that photochemistry can generate various reactive intermediates that would otherwise be difficult to produce under thermal conditions,⁵³ many exciting extensions of this radical strategy to other related catalytic asymmetric cross-couplings can be envisaged.⁵⁴

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c06535>.

Experimental procedures and characterization data for all the products (PDF)

Accession Codes

CCDC 2072377 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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