Enantioselective Oxidation of Benzylic C–H Bonds via Dual Photoredox and Copper Catalysis

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Abstract

Directly asymmetric oxidation of C(sp^3)–H bonds of organic molecules would radically alter current methods of synthesizing chiral alcohols and esters, which are widely existed in the structures of natural products, pharmaceuticals, and fine chemicals. The Kharasch–Sosnovsky reaction is commonly used process for oxidation of allylic C(sp^3)–H bonds of alkenes to yield allyl esters. However, its asymmetric variant is limited to cycloalkenes, and the enantioselectivity and efficiency of the reactions of open-chain alkenes are low. Moreover, asymmetric Kharasch–Sosnovsky reactions of alkanes remain a seemingly insurmountable challenge. However, we herein report a method for highly enantioselective oxidation of benzylic C(sp^3)–H bonds of arylalkanes by dual photoredox and copper catalysis. The method extends the scope of the Kharasch–Sosnovsky reaction to alkanes and, more importantly, uses alcohols or carboxylic acids instead of peroxides as oxygenated coupling partners. With this method, we obtained various chiral alcohols and esters with high enantioselectivity directly from readily available arylalkanes.

Main Text

The structural complexity of modern pharmaceuticals, which are characterized by numerous oxygenated aliphatic stereocenters, necessitates the use of innovative enantioselective catalytic processes to synthesize.[1,2] Among such processes, the enantioselective oxidation of aliphatic C–H bonds stands out as pivotal for directly introducing oxygen functionality into alkanes.[3,4,5,6,7,8,9,10,11,12] This approach is particularly suitable for constructing chiral oxygenated benzylic structures, which are prevalent in natural products and biologically active compounds and have therefore aroused widespread interest in the study of catalytic enantioselective oxidation of benzylic C–H bonds (Fig. 1a).[13,14] In nature, a key enzyme for this transformation is cytochrome P-450, which has an iron-porphyrin center that mediates the stereoselective oxidation of alkane C–H bonds.[15,16,17] To mimic cytochrome P-450, investigators have developed numerous optically active metal-porphyrin complexes to catalyze enantioselective oxidation of benzylic C–H bonds, but reactions mediated by these complexes show low enantioselectivity and a limited substrate scope (Fig. 1b).[18,19,20,21,22,23,24,25] The development of a useful method for catalytic enantioselective oxidation of benzylic C–H bonds requires overcoming the inherently low reactivity of C–H bonds, achieving precise enantiocontrol in structurally complex molecules, and avoiding overoxidation to generate ketones.

We reasoned that the Kharasch–Sosnovsky reaction might be useful for this purpose. This copper-

catalyzed reaction, first reported over six decades ago, was a milestone in C(sp^3)–H oxidation at the allylic positions of alkenes to yield valuable allyl esters[26,27] and is generally thought to proceed through a three-step radical-relay mechanism (Fig. 1c). Despite it has become an important method for the synthesis of allyl esters, enantioselective variants of the reaction did not receive much attention until 1995, when the first synthetically useful example was reported.[28,29,30] Recently, notable progress on enantioselective Kharasch–Sosnovsky reactions has been made,[31,32,33,34,35,36] but significant challenges persist. For instance, most of the existing catalytic systems are effective only for cycloalkenes such as cyclopentene and cyclohexene, and the enantioselectivity and efficiency of the reactions of open-chain alkenes are low. Moreover, and more critically, the peroxide used in the Kharasch–Sosnovsky reaction acts as both an oxidizing agent and an oxygen nucleophile, severely limiting the range of coupling partners that can be used. Therefore, the development of efficient, practical catalytic systems for enantioselective Kharasch–Sosnovsky reactions is urgently needed, especially for the oxidation of C–H bonds of alkanes.[37,38,39,40,41,42,43]

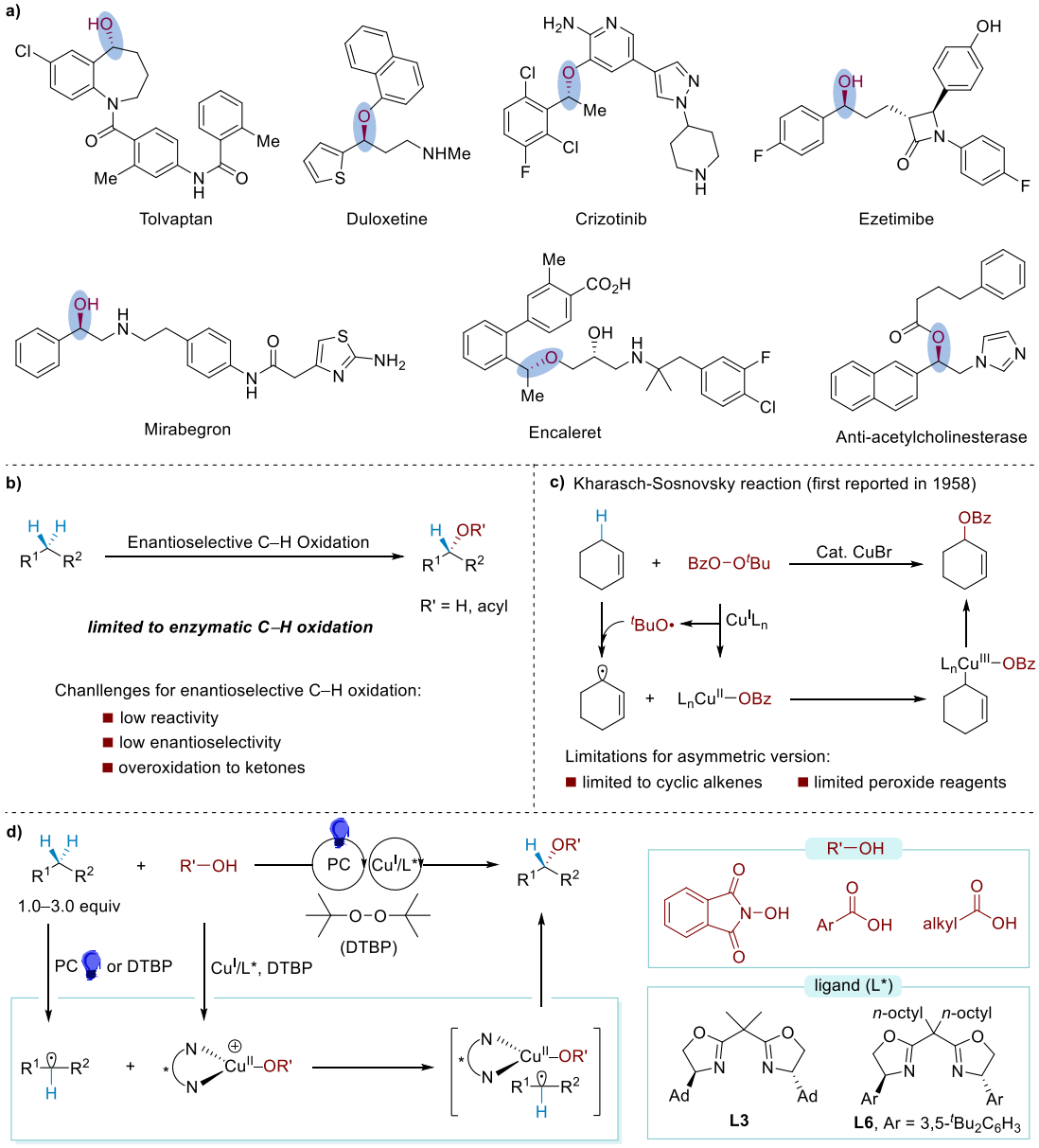
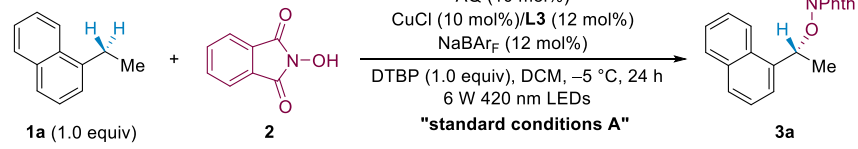


Fig. 1 | Overview of the strategies for enantioselective C(sp^3)–H oxidation. PC, photocatalyst. **a**, Chiral drugs containing oxygenated benzylic stereocenters. **b**, Challenges for enantioselective C(sp^3)–H oxidation. **c**, Kharasch–Sosnovsky reaction and mechanism. **d**, Design for enantioselective oxidation of benzylic C(sp^3)–H bonds via dual photoredox and copper catalysis.

Recently, our group[44] and Kramer group,[45] have developed a copper-catalyzed asymmetric amination of benzylic C–H bonds in high yield with high enantioselectivity. These studies encouraged us to explore the asymmetric oxidation of benzylic C–H bonds of arylalkanes. We herein present our newly developed method for enantioselective oxidation of benzylic C–H bonds with dual photoredox and copper catalysis and *N*-hydroxyphthalimide (NHPI) or carboxylic acids as coupling partners (Fig. 1d). This method addresses several key limitations of traditional Kharasch–Sosnovsky reactions; specifically, it uses arylalkanes instead of alkenes as substrates and alcohols and acids instead of peroxides as oxygen coupling partners, thereby extending the scope and practicality of the reaction.

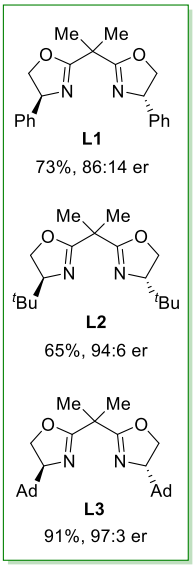
a)



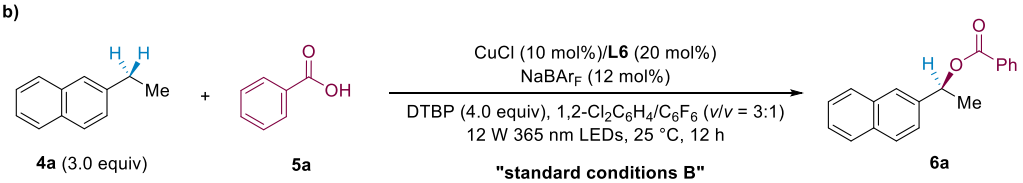
1a (1.0 equiv) **2** **3a**

entry	variation from the "**standard conditions A**"	yield (%)	enantiomer ratio (er)
1	none	91	97:3
2	without CuCl	10	50:50
3	without **L3**	26	50:50
4	without NaBAr$_F$	0	ND
5	without AQ	5	94:6
6	without DTBP	7	95:5
7	without hv	0	ND
8	Selectfluor instead of DTBP	11	81:19
9	NFSI instead of DTBP	0	ND

AQ:



b)



4a (3.0 equiv) **5a** **6a**

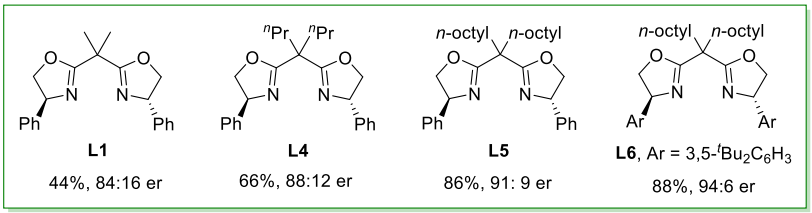


Fig. 2 | Development of enantioselective oxidation of benzylic C–H bonds. a, Enantioselective C–H oxidation of **1a** under standard conditions A. Variations from the standard conditions A. NPhth, *N*-phthalimido. **b**, Enantioselective C–H oxidation of **4a** under the standard conditions B.

We initiated our study by investigating conditions for oxidative coupling of 1-ethylnaphthalene (**1a**) and NHPI (2) (Fig. 2a). After extensive screening of copper sources, ligands, oxidants, photocatalysts, solvents, temperature settings, and light sources, we were delighted to discover that chiral copper catalysts, when combined with anthraquinone (AQ) as a photocatalyst, promoted enantioselective oxidation of the benzylic C–H bond of **1a** under mild conditions (–5 °C, 420 nm LEDs) to yield target product **3a** in high yield (91%) with outstanding enantioselectivity (97:3 enantiomer ratio [er]) (Fig. 2a, entry 1). Control experiments indicated that CuCl, ligand **L3**, $NaBAr_F$, AQ, di-*tert*-butyl peroxide (DTBP), and light were indispensable for the success of the reaction (entries 2–7). Among the oxidants evaluated, DTBP provided the best results; other oxidants, such as Selectfluor and *N*-fluorobenzenesulfonimide (NFSI), either gave low yield with low enantioselectivity or failed to yield the target product (entries 8 and 9). Ligand screening revealed that bisoxazoline ligands with bulky substituents showed higher enantioselectivity, and ligand **L3**, which contains adamantyl groups, gave the highest enantioselectivity (for details, see SI).

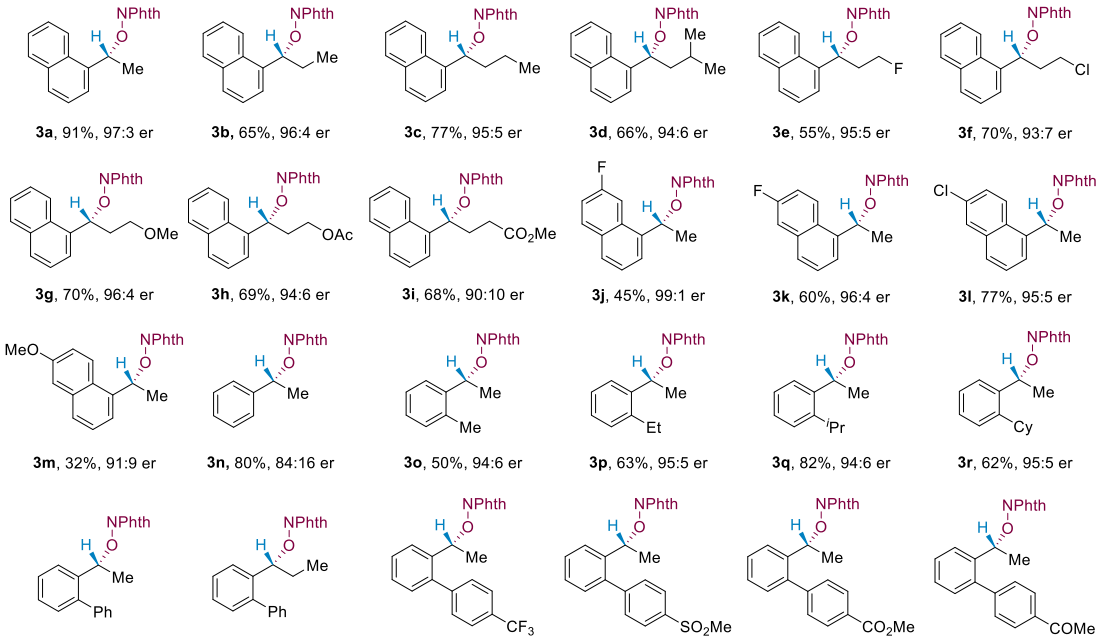
Subsequently, in the course of our study of enantioselective C–H oxidation of 2-ethylnaphthalene (**4a**) with benzoic acid (**5a**), we found that the results obtained under standard conditions A were unsatisfactory in terms of both yield and enantioselectivity (data not shown). This finding led us to try to refine the conditions by varying the reaction parameters, including the ligand, solvent, photocatalyst, temperature, and light source. The refined conditions were established to be as follows: 3:1 (v/v) 1,2-dichlorobenzene/hexafluorobenzene, CuCl (10 mol%), $NaBAr_F$ (12 mol%), ligand **L6** (20 mol%), benzoic acid (**5a**), 2-ethylnaphthalene (**4a**, 3.0 equiv), and DTBP (4.0 equiv) (Fig. 2b). These reaction components were irradiated with 12 W, 365 nm blue light at 25°C in an argon atmosphere for 12 h. Under these conditions (standard conditions B), the photocatalyst AQ was not needed.

Having optimized the conditions, we explored the substrate scope of the reaction (Fig. 3a). 1-Alkyl-substituted naphthalenes reacted with NHPI to yield the corresponding oxidation products (**3a**–**3d**) with high enantioselectivities (94:6–97:3 er) in 66–91% yields. Halogen atoms (**3e**, **3f**), an ether (**3g**), and esters (**3h**, **3i**) on the alkyl chain were tolerated, as were halogen atoms (7-F, **3j**; 6-F, **3k**; 6-Cl, **3l**) and a OMe group (**3m**) on the naphthyl ring. These functional groups offer opportunities for subsequent synthetic transformations. Ethylbenzene (**1n**) was also a suitable substrate, giving **3n** in 80% yield with 84:16 er. *Ortho*-dialkyl-substituted benzenes **1o**–**1r** yielded the corresponding mono-oxidation products, and the reaction occurred selectively on the CH_2 group of the alkyl chain. *Ortho*-phenyl-substituted alkylbenzenes also reacted with NHPI to afford the desired products (**3s**–**3x**) with high enantioselectivities (92:8–95:5 er); and functional groups on the phenyl substituent—trifluoromethyl (**3u**), methyl sulfonyl (**3v**), ester (**3w**), and ketone group (**3x**)—had negligible effects on the yield and enantioselectivity.

To assess the substrate scope of this enantioselective oxidation, we carried out reactions of a series of arylalkanes under standard conditions B (Fig. 3b). 2-Alkyl-substituted naphthalenes proved to be suitable substrates, yielding the desired ester products (**6a**–**6f**) with high enantioselectivities (93:7–96:4 er) in 52–82% yields. An ester (**6g**) and a chlorine atom (**6h**) on the alkyl chain of the substrate were tolerated. The reactions of dialkyl-substituted naphthalenes always gave the corresponding mono-oxidation products (**6i**–**6k**), and the enantioselectivities were good to excellent (88:12–98:2 er). Exploration of various carboxylic acid substrates showed that benzoic acid (**6a**) and substituted benzoic acids (**6b**, **6l**–**6t**) could react with 2-ethylnaphthalene to afford the target products with good enantioselectivities. The electronic and steric properties of the substituents on

the aromatic ring of the benzoic acid had little effect on the reaction yield or enantioselectivity. Aliphatic carboxylic acids could also be used as oxygen nucleophiles for enantioselective benzylic C(sp^3)–H oxidation reactions to afford the target products (**6u**–**6w**) with relatively good enantioselectivities. However, only acetic acid had a good yield, while 4-phenylbutyric acid and isobutyric acid had low yields. The heteroaromatic acids furoic acid (**6x**) and thiophenic acid (**6y**) were compatible with the reaction conditions.

a) with standard conditions A



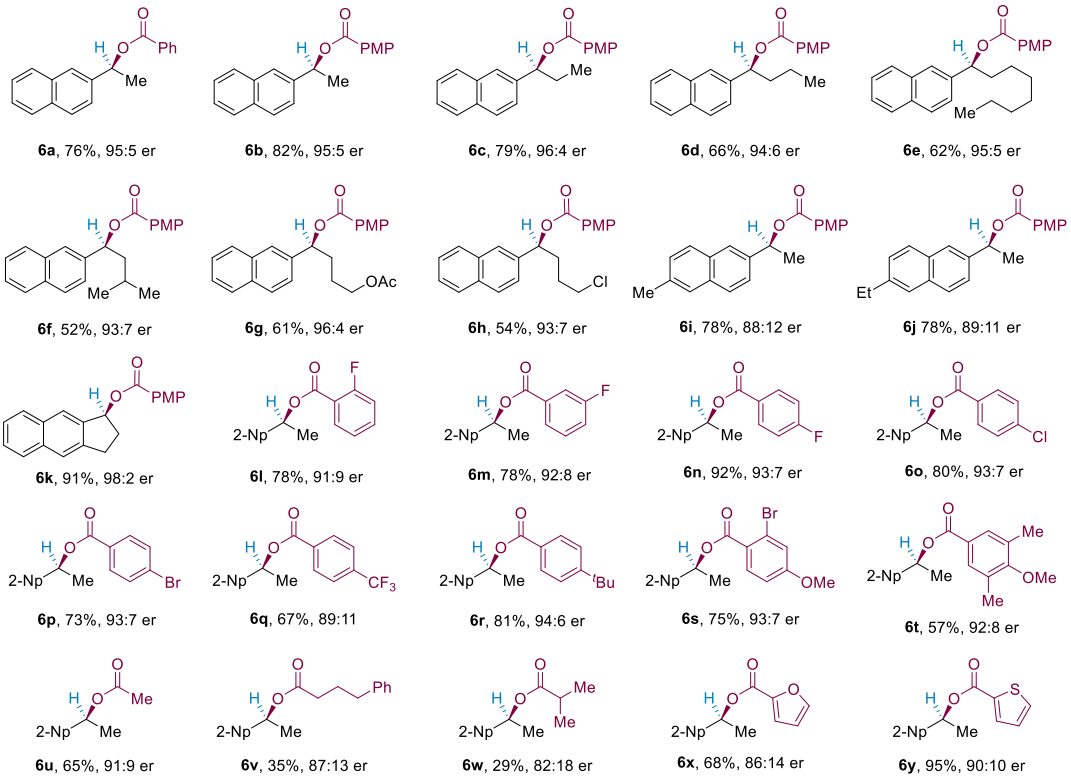
3a, 91%, 97:3 er; **3b**, 65%, 96:4 er; **3c**, 77%, 95:5 er; **3d**, 66%, 94:6 er; **3e**, 55%, 95:5 er; **3f**, 70%, 93:7 er

3g, 70%, 96:4 er; **3h**, 69%, 94:6 er; **3i**, 68%, 90:10 er; **3j**, 45%, 99:1 er; **3k**, 60%, 96:4 er; **3l**, 77%, 95:5 er

3m, 32%, 91:9 er; **3n**, 80%, 84:16 er; **3o**, 50%, 94:6 er; **3p**, 63%, 95:5 er; **3q**, 82%, 94:6 er; **3r**, 62%, 95:5 er

3s, 88%, 95:5 er; **3t**, 69% yield, 92:8 er; **3u**, 62%, 95:5 er; **3v**, 57%, 95:5 er; **3w**, 76%, 95:5 er; **3x**, 54%, 95:5 er

b) with standard conditions B



6a, 76%, 95:5 er; **6b**, 82%, 95:5 er; **6c**, 79%, 96:4 er; **6d**, 66%, 94:6 er; **6e**, 62%, 95:5 er

6f, 52%, 93:7 er; **6g**, 61%, 96:4 er; **6h**, 54%, 93:7 er; **6i**, 78%, 88:12 er; **6j** 78%, 89:11 er

6k, 91%, 98:2 er; **6l**, 78%, 91:9 er; **6m**, 78%, 92:8 er; **6n**, 92%, 93:7 er; **6o**, 80%, 93:7 er

6p, 73%, 93:7 er; **6q**, 67%, 89:11; **6r**, 81%, 94:6 er; **6s**, 75%, 93:7 er; **6t**, 57%, 92:8 er

6u, 65%, 91:9 er; **6v**, 35%, 87:13 er; **6w**, 29%, 82:18 er; **6x**, 68%, 86:14 er; **6y**, 95%, 90:10 er

Fig. 3 | Substrate scope of the enantioselective C–H oxidation. PMP, *para*-$OMeC_6H_4$; Np, naphthyl.

To demonstrate the synthetic usefulness of the reaction, we transformed oxidation product **3a** to chiral alcohol **7** by removing the protecting group with $Mo(CO)_6$ and found that the enantiomeric purity of the product was unchanged (Fig. 4a). Additionally, deprotection of **3a** with hydrazine hydrate produced chiral *O*-(1-(naphthalen-1-yl)ethyl)hydroxylamine (**8**), also with no loss of enantiomeric purity (Fig. 4a). The resulting chiral hydroxylamine is a key intermediate in the manufacture of some pesticides.[46] The reaction of arylalkane **1y** with NHPI yielded the oxidation product **3y**, which is a crucial intermediate in the synthesis of encaleret, a potent, short-acting oral calcilytic (Fig. 4b).[47] Furthermore, the reaction of 5β-cholanic acid with 2-ethylnaphthalene under the conditions B produced corresponding derivative **6z** with high enantioselectivity. These studies showed that enantioselective benzylic C–H oxidation has a application potential in the synthesis of bioactive molecules and drug discovery.

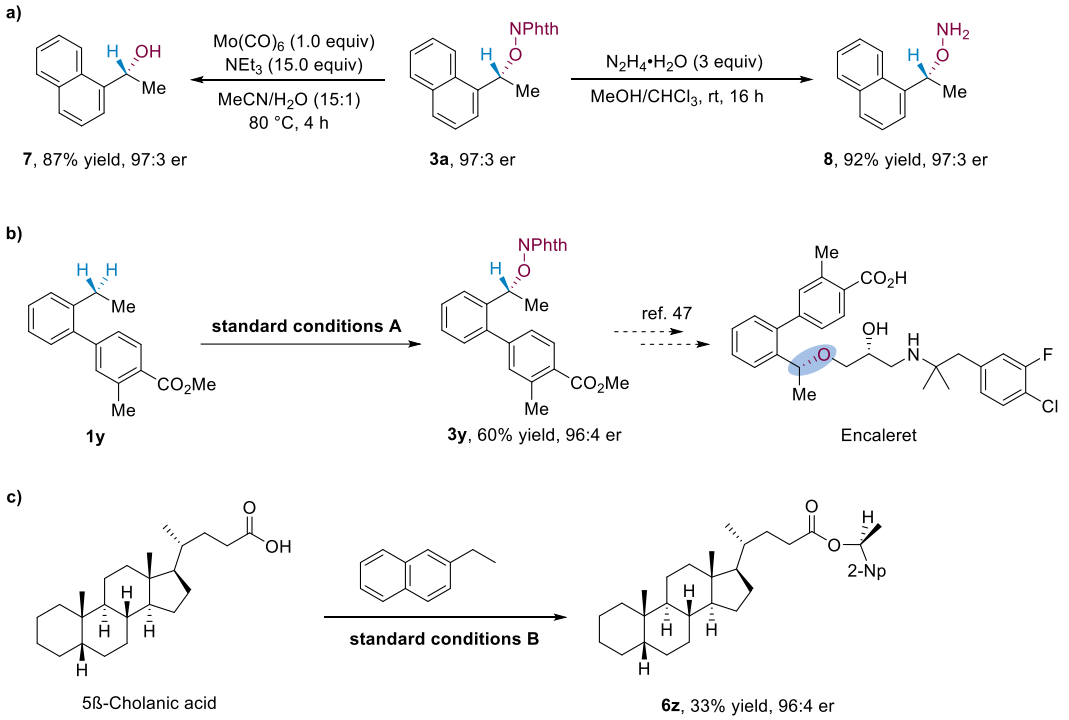


Fig. 4 | Applications of the enantioselective C–H oxidation. **a**, Transformations of oxidation product **3a**. **b**, Synthesis of the intermediate of encaleret by using enantioselective C–H oxidation.

To elucidate the reaction mechanism, we carried out a radical trapping experiment and found that the reaction was completely inhibited when TEMPO (2,2,6,6-tetramethyl-1-oxylpiperidine) was present in the reaction mixture, indicating that radicals are involved in the reaction (Fig. 5a). Kinetic isotope effect experiments indicated that k_H/k_D was 3.1, which shows that the abstraction of a benzylic hydrogen atom from the arylalkane substrate might be the rate-limiting step (Fig. 5b). We then synthesized Cu^{II}-O^{t}Bu and Cu^{II}-OBz complexes **Int-I** and **Int-II** and found that they catalyzed the reaction to afford the target products (Fig. 5c). These results confirm the involvement of Cu^{II} intermediates. UV–vis absorption spectroscopy showed that Cu^{I} is immediately oxidized to Cu^{II} in the presence of DTBP (Fig. 5d). Cu^{II} radical signals were detected by electron paramagnetic

resonance spectroscopy of a solution containing CuCl, $NaBAr_F$, **L1**, and DTBP (Fig. 5e), which confirms that Cu^{II} radicals are formed during the reaction. Light-on/light-off experiments showed that when irradiation was stopped, the reaction did not proceed (Fig. 5f), indicating that a free radical chain process is not involved.

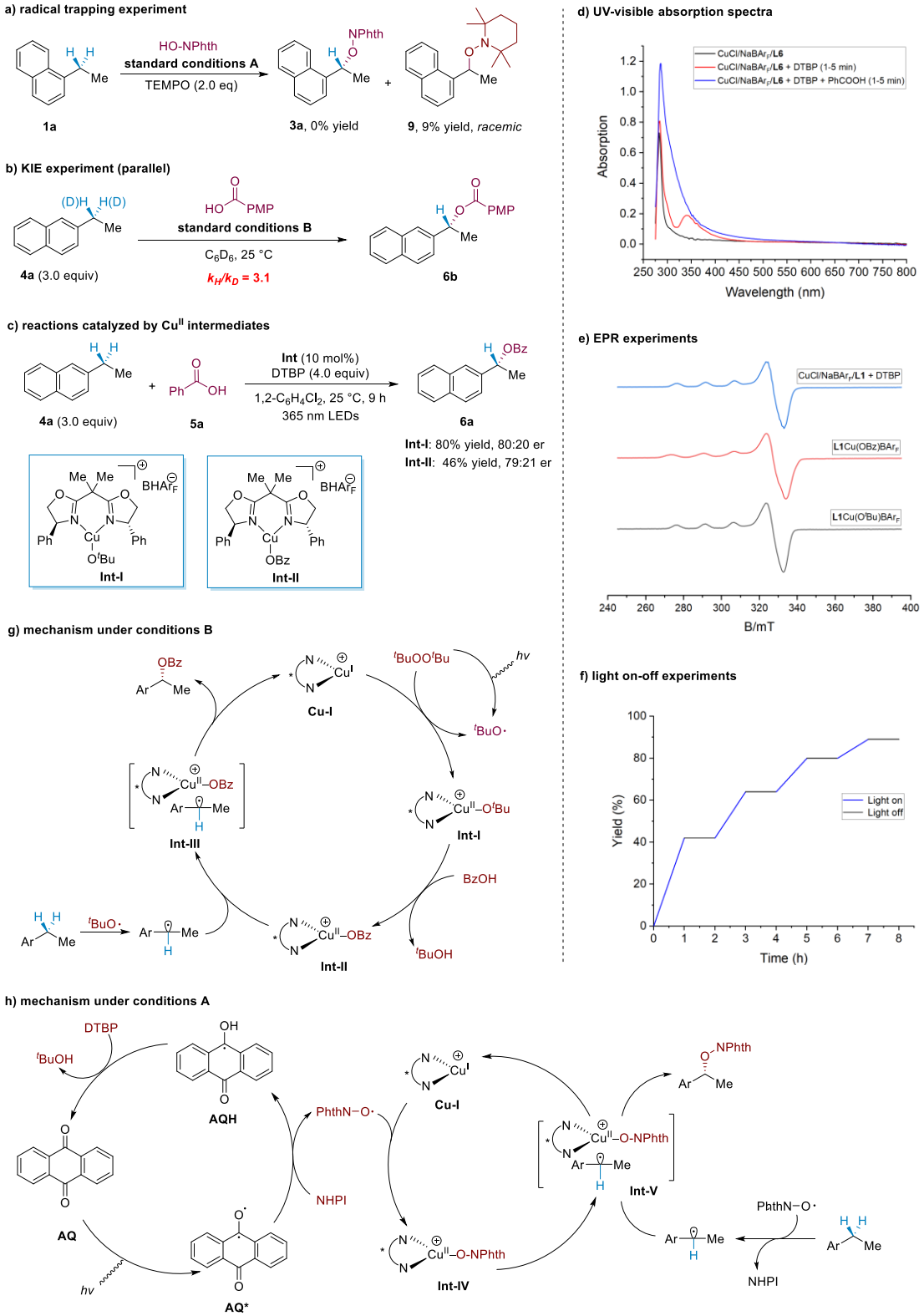


Fig. 5 | Mechanism study. a, Radical trapping experiment. **b**, Kinetic isotope effect (KIE) experiments. **c**, Oxidation reaction of **4a** catalyzed by **Int-I** and **Int-II**. **d**, UV–vis absorption

spectroscopy. **e**, EPR experiments. **f**, Light on-off experiments. **g**, Proposed mechanism for the reaction under conditions B. **h**, Proposed mechanism for the reaction under conditions A.

On the basis of our experimental findings and literature reports,[44,45,48,49,50,51,52,53] we propose that these enantioselective benzylic C(sp^3)–H oxidation reactions proceed by the mechanisms shown in Fig. 5. In reactions with a carboxylic acid as the oxygen nucleophile (Fig. 5g), irradiation decomposes DTBP to *tert*-butoxy radicals, which react with Cu^I complex **Cu-I** to form Cu^{II}-O^{t}Bu intermediate **Int-I** and also abstract a benzylic hydrogen atom from the arylalkane to form a benzylic radical. A ligand exchange reaction of **Int-I** with benzoic acid leads to Cu^{II}-OBz intermediate **Int-II**, which reacts with the benzylic radical to form the product via intermediate **Int-III** and regenerate catalyst **Cu-I**.

In reactions with NHPI as the oxygen nucleophile (Fig. 5h), photoexcitation of AQ generates diradical AQ*, which abstracts a hydrogen atom from NHPI to produce a phthalimide *N*-oxyl radical. This radical abstracts a hydrogen atom from the benzylic position of the arylalkane to form a benzylic radical and, simultaneously, oxidizes **Cu-I** to **Int-IV**. Subsequently, **Int-IV** captures the benzylic radical to yield final product via intermediate **Int-V**. AQ is regenerated by oxidation of AQH with DTBP.

In summary, we have developed a method for enantioselective oxidation of the benzylic C(sp^3)–H bonds of arylalkanes by combining photoredox and copper catalysis. The method not only extends the asymmetric Kharasch–Sosnovsky reaction to arylalkanes but also eliminates the requirement for using a peroxide as both the oxidant and the oxygen nucleophile. Using the developed method, we synthesized various chiral alcohols and esters directly from readily available arylalkanes with good to high enantioselectivities. Our findings offer a new approach to exploration of the asymmetric functionalization reactions of unactivated C–H bonds.

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