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Copper-catalyzed aerobic asymmetric cross-dehydrogenative coupling of C(sp³)–H bonds driven by visible light

Kexu Zhou, Ying Yu, Yu-Mei Lin, Yanjun Li and Lei Gong*

Asymmetric cross-dehydrogenative coupling (CDC) of C(sp³)–H bonds exhibits great potential for rapid and stereoselective construction of C–C bonds and use of molecular oxygen as the oxidant for such transformations is appealing in the context of green synthetic methodologies. However, the poor reactivity of oxygen at the ground state and the challenges in controlling the stereochemistry make it extremely difficult to access highly enantioselective aerobic CDC reactions of C(sp³)–H precursors. Herein we report our effort towards this goal *via* copper-based asymmetric photocatalysis. A chiral-copper catalyst initiates the visible-light-driven oxidative CDC reaction by molecular oxygen, and governs the stereochemistry. In this way, a diastereo- and enantioselective cross-dehydrogenative coupling between carbonyl compounds and xanthene derivatives has been achieved. This work provides an economic and manageable approach to stereoselective C–C bond formation, and demonstrates a potential application of chiral copper catalysts in difficult asymmetric photochemical reactions.

Introduction

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Direct cross-dehydrogenative coupling of two C-H bonds has attracted great attention since it avoids prior functionalization of the substrates, thereby providing atom and step economy for C-C bond formation.^{1,2} CDC reactions of C(sp³)-H bonds are extremely desirable in view of the abundance of these bonds in organic compounds.³ In this field, Li et al. and others have made significant contributions and developed a number of valuable transformations,⁴ but there are still several challenges associated with this strategy. One of the critical holdback is the typical requirement of harsh conditions including the use of strong chemical oxidants such as 2,3dicyano-5,6-dichlorobenzoquinone (DDQ), tert-butyl hydroperoxide (TBHP) or ammonium persulfate to activate the inert C(sp³)–H bonds. This leads to side reactions including homocoupling, and to waste byproducts, limitations in compatible functional groups and difficulties in large-scale applications, and as a result, very few methods for their catalytic asymmetric variants have been reported.5,6

Molecular oxygen is an environmentally benign, abundant and mild oxidant. It is also not hampered by toxic byproducts, since it is either reduced to water or incorporated into the target structure.⁷ Combining aerobic oxidation with asymmetric crossdehydrogenative coupling is appealing for the development of green synthetic approaches to stereoselective construction of C–C bonds but has been very rarely investigated, probably due to the poor reactivity of oxygen or air at the ground state.⁸ Pioneering work has demonstrated that synergistic enamine and acid catalysis or heavy metal catalysis can provide promising access to aerobic asymmetric CDC of C(sp³)–H precursors.⁹ Use of first-row transition metal catalysts, which potentially offers economic and low-toxic strategies, has not been developed to date.

Copper-based photocatalysis has emerged as a powerful tool in the discovery of new synthetic methodologies.¹⁰ For instance, Reiser et al. reported that copper phenanthroline complexes exhibited unique features in a range of visible-light-mediated synthetic transformations including selective chlorosulfonylation, oxoazidation and atom transfer radical addition.^{11a-11c} Hwang et al. developed visible-light-driven coupling of terminal alkynes with other substrates through the copper-alkyne complexes generated in situ as the photosensitizers.^{11d, 11e} Collins et al. reported bifunctional copper photocatalysis for reductive pinacol-type couplings, ^{11f} and Fu et al. disclosed that a chiral phosphine copper complex was capable of catalyzing light-induced enantioselective C-N cross-couplings as the asymmetric catalyst and the precursor of the photocatalyst.^{11g} Very recently, we found that one class of chiral bisoxazoline copper(II) catalysts could effectively induce both photoactivation and asymmetric catalysis.¹² We questioned whether employing asymmetric photocatalysis by copper for activation of molecular oxygen to reactive oxygen species (ROS),13,14 initiation of the CDC reactions and government of the stereochemistry would be feasible (Scheme 1). Here, we report our discovery of asymmetric cross-

Key Laboratory of Chemical Biology of Fujian Province, iChEM, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China. Email: gongl@xmu.edu.cn

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dehydrogenative coupling between carbonyl compounds and xanthene derivatives, enabled by a single chiral copper catalyst under visible light and aerobic conditions.



Scheme 1 Overview of this work: copper-catalyzed aerobic enantioselective cross-dehydrogenative coupling driven by visible light.

Results and discussion

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Investigation of reaction conditions. To examine whether copper-based photocatalysis is applicable to the aerobic cross-dehydrogenative couplings of C(sp³)–H bonds, we chose acetone (1a) and xanthene (2a) as the model substrates and the in-situ generated [Cu^{II}-L1] (a premixed copper salt $Cu(OTf)_2$ with a ligand (L1) in acetone) as the catalyst. Stirring in the dark at 25 °C (Table 1, entry 1) or 50 °C (entry 2), the reaction of 1a and 2a failed to provide any desired product (3a) in air. However, 3a was produced under irradiation of a 24 W blue LEDs lamp, although at a modest rate (53% within 72 h) and with formation of a side-product (3a') (entry 3). Removal of the ligand (L1) or Cu(OTf)₂ led to a significantly decreased yield (entry 4) or no product (entry 5). Upon replacement of the copper salt with Mg(OTf)₂ (entry 6) or $Zn(OTf)_2$ (entry 7), addition of a radical quencher such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (entry 8), the reaction did not provide any desired product. These results indicate that the reaction $1a+2a \rightarrow 3a$ is driven by visible light probably through a radical pathway, and the copper salt and the ligand are both crucial for the transformation.

Next, we attempted to improve the catalytic efficiency of the copper-catalyzed photochemical reaction and access its asymmetric variants. By choosing appropriate bidentate chelating substrates, effective transition-metal activation and asymmetric induction could be achieved in photocatalytic reactions.¹² Accordingly, a range of carbonyl compounds (1b-**1f**) with different heteroatom-containing α -substituents (Z) were screened in the photocatalytic aerobic crossdehydrogenative coupling with xanthene (2a) (Table 2, entries 1-5). 2-Acyl imidazole (1f) was found to give the best enantioselectivity (38% ee, entry 5)¹⁵ and ligand screening experiments revealed that the chiral bisoxazoline ligand (L7) provided the best results with regards to conversion and enantioselectivity (71% conv. and 70% ee within 48 h, entries 7–13). The reaction could be significantly improved by use of acetone as the solvent and $Cu(BF_4)_2$ H₂O as the metal salt (76%) conv. and 92% ee, entries 14-17). Reduking the Geaction temperature decreased the reaction rate remarkably while improving the enantioselectivity only slightly (entries 18, 19).

Table 1 Initial experiments.^a

0 1a	+ ()		Ph L1 Ph metal salts (15 mol%) L1 (17 mol%) air, 72 h 24 W blue LEDs		3a	+ + 3a'		
Entry	Metal salt I	Ligand	Light source	Temp [°C]	Additive	3a [%] ^b	3a' [%] ^b	
1	Cu(OTf) ₂	L1	none	25	none	0	0	
2	Cu(OTf) ₂	L1	none	50	none	0	trace	
3	Cu(OTf) ₂	L1	24 W blue LEDs	25	none	53	30	
4	Cu(OTf) ₂	none	24 W blue LEDs	25	none	26	19	
5	none	L1	24 W blue LEDs	25	none	0	0	
6	$Mg(OTf)_2$	L1	24 W blue LEDs	25	none	trace	trace	
7	Zn(OTf) ₂	L1	24 W blue LEDs	25	none	trace	trace	
8	Cu(OTf) ₂	L1	24 W blue LEDs	25	TEMPO ^c	0	0	

^a Reaction conditions: acetone (1a, 1.0 mL), xanthene (2a, 0.20 mmol), metal salt (15 mol%), ligand (17 mol%), indicated temperature and light source, in air. ^b Yield determined by ¹H NMR. ^c 3 equiv.

 Table 2 Optimization of conditions for the photocatalytic
 aerobic enantioselective cross-dehydrogenative coupling reaction.^a



Entry	Metal salt	Ligand	Substrate	Solvent	Т	t	Product	Yield	ee
					[°C]	[h]		[%] ^b	[%] ^c
1	Cu(OTf) ₂	L1	1b	CH_2CI_2	25	24	3b	68	11
2	Cu(OTf) ₂	L1	1c	CH_2CI_2	25	24	3c	47	5
3	Cu(OTf) ₂	L1	1d	CH_2CI_2	25	24	3d	34	0
4	Cu(OTf) ₂	L1	1e	$\rm CH_2\rm Cl_2$	25	24	3e	49	3
5	Cu(OTf) ₂	L1	1f	CH_2CI_2	25	24	3f	40	38
6	Cu(OTf) ₂	L1	1f	CH_2CI_2	25	48	3f	71	38
7	$Cu(OTf)_2$	L2	1f	CH_2CI_2	25	48	3f	68	32

8	Cu(OTf) ₂	L3	1f	CH_2CI_2	25	48	3f	69	41
9	Cu(OTf) ₂	L4	1f	CH_2CI_2	25	48	3f	55	7
10	Cu(OTf) ₂	L5	1f	CH_2CI_2	25	48	3f	68	33
11	Cu(OTf) ₂	L6	1f	CH_2CI_2	25	48	3f	59	23
12	Cu(OTf) ₂	L7	1f	CH_2CI_2	25	48	3f	71	70
13	Cu(OTf) ₂	L8	1f	CH_2CI_2	25	48	3f	69	41
14	Cu(OTf) ₂	L7	1f	acetone	25	48	3f	74	89
15	Cu(OTf) ₂	L7	1f	CH_3CN	25	48	3f	77	84
16	$Cu(MeCN)_4BF_4$	L7	1f	acetone	25	48	3f	57	91
17	$Cu(BF_4)_2H_2O$	L7	1f	acetone	25	48	3f	76	92
18	$Cu(BF_4)_2H_2O$	L7	1f	acetone	0	48	3f	32	93
19	$Cu(BF_4)_2 H_2O$	L7	1f	acetone	-20	48	3f	6	92

^{*a*} Reaction conditions: **1b–1f** (0.10 mmol), **2a** (0.20 mmol), metal salt (15 mol%), ligand (17 mol%), indicated solvents (1.0 mL), indicated temperature, indicated light source, in air, see more details for the screening of solvent and light source in Supplementary Information. ^{*b*} Yield determined by ¹H NMR. ^{*c*} ee value determined by chiral HPLC.

Reaction scope. With the optimal reaction conditions in hand, we evaluated the generality of the method. First, 2-acyl imidazoles bearing different alkyl or aryl substituents (R²) on the α -carbon neighboring the carbonyl group as well as Nprotecting groups (R¹) were examined (Scheme 2). A range of 2-acyl imidazoles containing a primary alkyl or cyclopropyl substituent (R²) were found to be tolerated well in this reaction. The products (3f-3i) were afforded in 62-74% yields with 87-92% ee. However, a phenyl substituent led to significantly decreased enantioselectivity, giving 3j with 58% ee. N-protecting groups (R¹) including methyl (product **3k**), ethyl (product **3I**), *n*-propyl (product **3m**), *n*-butyl (product 3n), benzyl (product 3o) and *i*-propyl (product 3p) were all regarding the yields of 58–73% compatible and enantioselectivities of 85-94%. In all but one case, an N-tbutyl protected imidazole failed to provide the desired product (3q), probably because the sterically more demanding group causes insuperable hindrance to the intermolecular reaction.

Scheme 3 reveals that different substituted xanthenes are well tolerated in the copper-catalyzed aerobic enantioselective cross-dehydrogenative coupling reaction. For example, the symmetrical xanthenes with a 2-, 3-, 4methyl group or a benzo-fused substitution provided 3v-3z in 61-70% yields and with 77-91% ee. The non-symmetrical substituted xanthenes (products 3za-3zk) also gave reasonable yields (31-66%), and good to excellent enantioselectivity (81-97%) ee), but only modest diastereoselectivity (1.2:1-2.3:1 dr). Notably, the strong electron-deficient substitution on the xanthene moiety such as CF₃ (target product **3zi**) was not compatible in the reaction. Some other diaryl methane derivatives were tested in the system. For example, the reaction of N-phenyl-9,10dihydroacridine afforded a product (3zm) in 74% yield, but as a racemate. Reactions of diphenylmethane or 3-benzyl-1methyl-1H-indole failed to generate the desired products (3zn, 3zo respectively).



Scheme 2 Substrate scope of 2-acyl imidazoles.

Mechanistic studies. To verify the photoactive species in the copper-catalyzed photochemical reaction, the UV-Vis spectra of the reaction components were measured (Scheme 4a). The individual substrates (**1f**, **2a**), the chiral ligand (**L7**), copper salts $Cu(BF_4)_2 \cdot H_2O$ and $Cu(MeCN)_4BF_4$ showed no obvious absorption in the visible light region, but bisoxazoline copper complexes [**Cu^{II}-L7**], [**Cu^I-L7**], [**Cu^{II}-L7-1f**] and [**Cu^I-L7-1f**], which potentially existed in the catalytic system, exhibited significant absorption enhancement in the range of 400–550 nm. It is assumed that one or all of these complexes serve as photosensitizers in the reaction.

Cyclic voltammetry of substrate (1f, 2a) and copper complex [Cu¹-L7] was measured under argon to estimate their redox abilities (Scheme 4b–4d). 2-Acyl imidazole (1f) did not show any obvious reduction/oxidation signals between -2.0 V and +2.0 V. Xanthene (2a) exhibited an irreversible oxidation peak at +1.78 V ($E_{ox}(2a^{-+}/2a)$). Reversible reduction/oxidation signals were observed at $E_{1/2} = +0.30$ V for the copper complex [Cu¹-L7] (E_{red} ([Cu^{II}-L7]/[Cu¹-L7])), revealing that direct electron transfer between catalyst [Cu^{II}-L7] and 2a is thermodynamically unfavorable at the ground state.^{12a}



Scheme 4 UV-Vis and electrochemical analysis. **a)** UV-Vis spectra of the reaction components in acetone (0.030 M). **b)** Cyclic voltammograms of substrate **1f. c)** Cyclic voltammograms of substrate **2a. d)** Cyclic voltammograms of complex [Cu^L-L7] generated *in situ* by stirring a 1:1 mixture of Cu(MeCN)₄BF₄ and chiral ligand (L7). Conditions for cyclic voltammograms

-25

0.4 0.6 0.8

Potential vs. Hg₂Cl₂/KCI / V

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analysis: a solution in acetone (0.030 M) containing 0.1 M nBu NPF, scan view Article Online DOI: 10.1039/D0GC00262C

Several control experiments were conducted to probe the reaction pathway. For example, the reaction of an electronrich xanthene (2n) failed to give the desired product (3zh), affording instead a self-coupling product (4) in 14% yield (Scheme 5a). This observation indicates the involvement of benzyl radicals in the photochemical reaction. The reaction of xanthene (2a) and the copper catalyst revealed that 2a could only be oxidized to the dimeric compound (5) and 9Hxanthen-9-one in air and under visible light irradiation (Scheme 5b). Interference of the reaction $1g+2a \rightarrow 3g$ with a strong nucleophile such as a silyl enol ether led to the formation of product 6 in 31% yield instead of 3g, suggesting a possible pathway via nucleophilic attack (Scheme 5c). The cyclopropyl-substituted 2-acylimidazole (1i) as a substrate for the radical clock experiment provided product 3i without any ring-opened product (7), thus excluding mechanisms involving the α -carbon radicals of enolate complexes (Scheme 5d).^{4h}

a) Evidence for engagement of the benzylic radical



b) Evidence for light-driven oxidation of the xanthene substrate by copper(II)



c) Evidence for possible involvement of the benzylic cation



conditions 1i 2a

Scheme 5 Mechanistic studies.

Mechanism proposal. Based on our initial experiments, reaction scope evaluation and mechanistic studies, a plausible mechanism for the photocatalytic aerobic crossdehydrogenative coupling between 2-acylimidazoles and xanthene derivatives is proposed in Scheme 6. On one hand, xanthene substrate (2) is oxidized by Cu^{II} to the radical cation (A) and concurrently generates a Cu^I species, probably through ligand exchange/light-induced homolysis.^{11a,12a} It is known that the Cu^I species is sufficient for the reduction of molecular oxygen to its superoxide radical anion (O_2/O_2^{-}) with the reduction potential residing at -0.56 V at SCE,¹⁶ at the same time closing the photocatalytic cycle. The superoxide

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1.5

Potential vs. Hg,Cl,/KCl / V

-100-

3i

62% vield

7

0% vield

1.0

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radical anion O_2^{--} reacts with intermediate **A** to generate benzyl radical (**B**) and HOO[•] followed by radical-radical coupling, or directly produced the peroxide C^{17} which has been detected by HRMS analysis of the reaction mixture. Protonation of **C** leads to the formation of the benzyl cation (**C**) and H_2O_2 .¹⁸ On the other hand, 2-acylimidazole (**1**) undergoes fast ligand exchange with the copper(II) catalyst to form enolate complex (**E**), which proceeds *via* a nucleophilic attack on the electrophilic intermediate (**D**). The further ligand exchange between neutral complex (**F**) and substrate **1** leads to the formation of **3** in an enantioselective fashion and regeneration of intermediate **E**.



Scheme 6 Plausible mechanism.

Conclusions

We have developed an effective and green strategy for aerobic cross-dehydrogenative coupling reaction between two $C(sp^3)$ -H bonds *via* copper-based asymmetric photocatalysis. Good to excellent yields, enantioselectivity and modest diastereoselectivity have been achieved. Mechanistic studies reveal that the copper catalyst provides both photoactivation to initiate the CDC reaction between carbonyl compounds and xanthene derivatives, as well as powerful asymmetric induction. This work demonstrates potential applications of chiral copper catalysts in challenging asymmetric photochemical transformations, and offers an economic and easily-handled approach to stereoselective C-C bond formation.

Conflicts of interest

There are no conflicts to declare.

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