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Bifunctional Ligand-Assisted Cu-Catalyzed Intermolecular Cyclo-hexenone γ -C(sp³)-H Amination: Controlled Synthesis of *p*-Aminophenols

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A 1,10-phenanthroline-type bifunctional ligand has been developed for Cu catalyzed direct γ -C(sp³)-H amination with intermolecular anilines. Stabilizing *N*-centered radicals via amide group installed on the bifunctional ligands, a new catalytic system for site-selective γ -C(sp³)-H amination to synthesize *p*-aminophenols was established. The economical and practical approach by using oxygen as the terminal oxidant was mild and environmental friendly.

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The C(sp³)-H amination reaction is a hot and challengeable topic, owing to the economic strategy to offer functionalized nitrogen-containing molecules.¹ The α and β -site C(sp³)-H aminations have been achieved by metal-catalysis,²⁻⁷ organo-catalysts,⁸⁻⁹ or the strategies of photoredox and electro oxidative.¹⁰⁻¹¹ However, the intermolecular γ -C(sp³)-H amination, owing to its low regional and site selectivity, is significantly more challenging.

In recent years, only few examples about the γ -C(sp³)-N cross-coupling reaction were reported,¹²⁻¹³ one of which was the use of directing groups. In 2012, Chen disclosed a palladium-catalyzed intramolecular γ -C(sp³)-N crosscoupling to azetidine, where the picolinamide (PA) protected amine as directing group was necessary (Figure 1a).⁴ The other strategy was using visible light to promote C-N radical cross coupling for the γ -C(sp³)-H amination. The *N*-centered radical was generated from secondary amide substrates, and migrated to γ -site C(sp³) via Hofmann-Löffler-Freytag (HLF) type 1,5-hydrogen atom transfer (1,5-HAT), then, coupled with another *N*-centered radical (Figure 1b).¹³ These reactions benefit from their innate site-selectivity, either the directing group or the strategy of intramolecular radical 1,5-HAT offered the γ -C(sp³)-H amination product. Meanwhile, the innate site-selectivity also led to the substrate limitations. As a highly active species, *N*-centered radicals have the advantages of simplicity and efficiency in building diverse C-N bonds.¹⁴⁻²² However, the γ -site selective of C-N bond cross coupling reaction remains a significant challenge, which might be ascribed to the harsh conditions, requiring the generation of *N*-centered radicals via hydrogen abstraction or degradation pathways.¹⁵

We envision that a bifunctional ligand assisted Cu-catalyzed cyclohexanone γ -C(sp³)-H amination to aminophenols, where the amide on the ligand stabilizes *N*-centered radicals to γ site C(sp³)-H of cyclohexanone and realizes internal C-N bond cross coupling, avoiding the homo-coupling of amine. If the reaction is realized, various *p*-aminophenols can be synthesized. Simultaneously, *p*-aminophenol motif displays the properties of anticancer and biofilm eradication (Figure 1c).²³⁻²⁵

Results

Ligand design. Nitrogen-containing bidentate ligands had shown high catalytic efficiency in copper-catalyzed reactions, such as metal-Salen, metal-Box and metal-Phen.²⁶⁻²⁷ 1, 10-phenanthroline, a cheap and easy-to-modify ligand, was selected as scaffolds to design a new type of bifunctional ligands by installing an amide group or phosnated group.²⁸ Several bifunctional ligands **L5-L9** were synthesized via a Pd-catalyzed Suzuki coupling reaction (Figure 2).

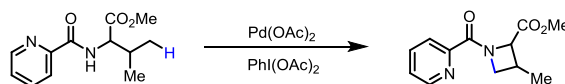
Reaction development. We began our studies by using *N*-methylaniline (**1a**) and cyclohex-2-en-1-one (**2**) as model substrates, a screen of conditions was investigated to identify the optimal conditions (Table 1).

Initially, Cu(OTf)₂ (5 mol%) was chosen as the catalyst, O₂ (1 atm) as the oxidant, and MgSO₄ (3.0 eq.) as the desiccant and the reaction was carried out in toluene at 80 °C for 8 h, no desired 4-(methyl(phenyl)amino)phenol **3a** was observed, along with less than 10% of *N*-methylaniline *para*-dimerization product **4a** (entry 1). A survey of additives were investigated, revealing that 2.5%

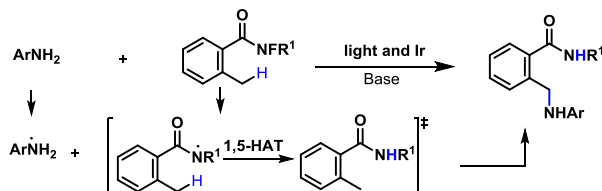
TFA is optimal to give 10% of desired product **3a** (entry 2). Various commercial available *N,N*-bidentate ligands (**L1-L4**, entries 3-6) were investigated, phenanthroline as the ligand improved the yields of **3a** to 29% (entry 4). While, more sterically hindered *N,N*-bidentate ligands **L3** and **L4** did not give a better results (entries 5-6). To our delight, **L5** as the ligand by installing an amide group on the *meta*-position of 2-phenyl-1,10-phenanthroline significantly improved the isolated yields to 73% (entry 7) and less than 2% yield of *para*-dimerization product **4a** was observed. Meanwhile, the easy aza-Michael addition product **5a** and C-1 site C-N condensation product **6a** were not observed.²⁹⁻³¹ Other ligands, like **L6-L9** by installing different amide and phosnated groups on different positions, were inferior to **L5** (entries 8-11).

Previous work:

a. Directing group assisted Pd-catalyzed intramolecular γ -C(sp³)-H amination



b. Visible-light promoted intramolecular 1,5-HAT and amination



This work:

c. New bifunctional ligand assisted catalytic γ -C(sp³)-H amination

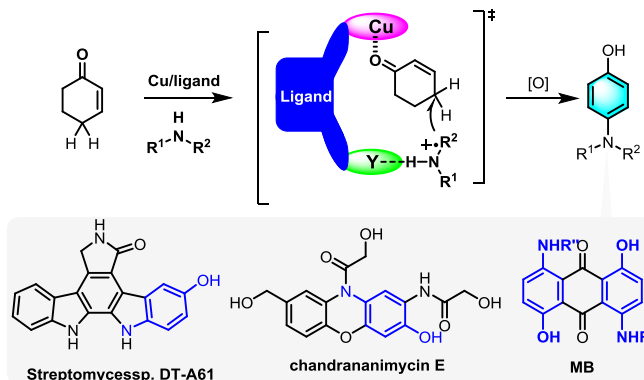


Figure 1. γ -C(sp³)-H amination

Catalyst and solvent effects were also investigated, but no superior results were obtained (entries 12-14, for more details, see SI). Further reducing the catalyst or ligand loading gave lower yields. Other oxidants, such as FeCl₃, MnO₂, DDQ and air gave lower yields (see SI) and molecular O₂ was found to be the best terminal oxidant.

Reaction scope investigation. Having optimized the reaction conditions for the γ selective C-N cross coupling reaction (Table 1, entry 7), we subsequently examined the reaction scope (Table 2).

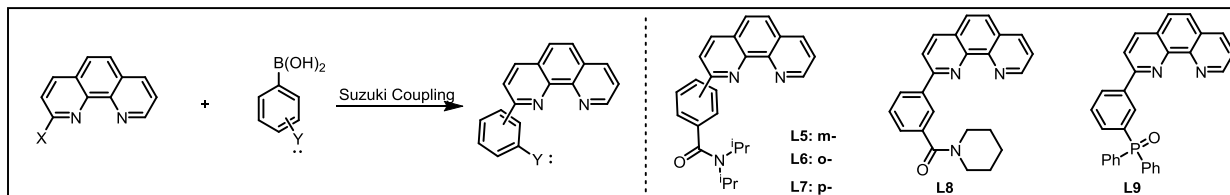


Figure 2. Design and synthesize new bifunctional ligands.

Table 1. Optimization of Reaction Conditions^a

Entry	Catalyst (mol%)	Ligand (mol%)	additive (equiv)	oxidant	solvent	yield(%) ^b	
						3a	4a
1	Cu(OTf) ₂ (5)	-	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	NR	< 10
2	Cu(OTf) ₂ (5)	-	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	10	< 10
3	Cu(OTf) ₂ (5)	L1(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	messy	< 5
4	Cu(OTf) ₂ (5)	L2(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	29	< 10
5	Cu(OTf) ₂ (5)	L3(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	32	< 10
6	Cu(OTf) ₂ (5)	L4(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	27	< 10
7	Cu(OTf)₂(5)	L5(10)	TFA(2.5%)/MgSO₄(3)	O₂	toluene	73	< 2
8	Cu(OTf) ₂ (5)	L6(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	44	< 2
9	Cu(OTf) ₂ (5)	L7(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	43	< 10
10	Cu(OTf) ₂ (5)	L8(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	68	< 10
11	Cu(OTf) ₂ (5)	L9(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	47	< 10
12	Cu(OTf) ₂ (5)	L5(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	toluene	35	< 2
13	Cu(OTf) ₂ (5)	L5(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	PhCl	66	< 2
14	Cu(OTf) ₂ (5)	L5(10)	TFA(2.5%)/MgSO ₄ (3)	O ₂	DCE	42	< 10

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [Cu] (5 mol %), L (10 mol %), solvent (3.0 mL), 1 atm O₂, 8 h. ^b Isolated yield.

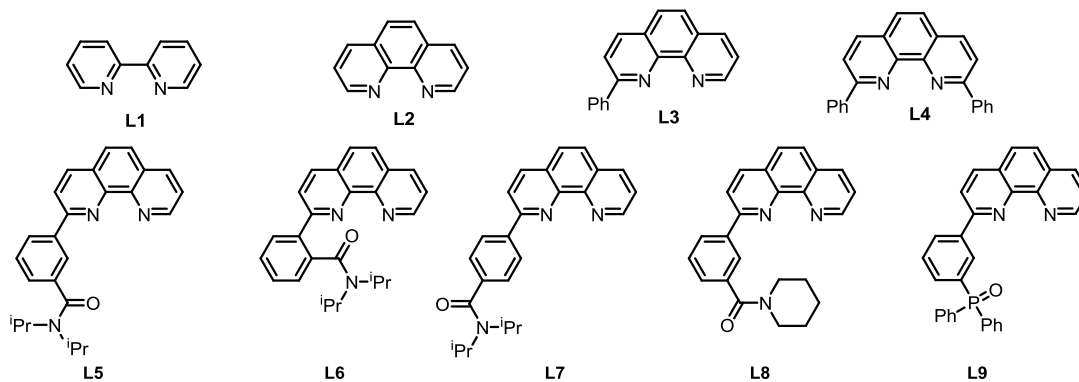
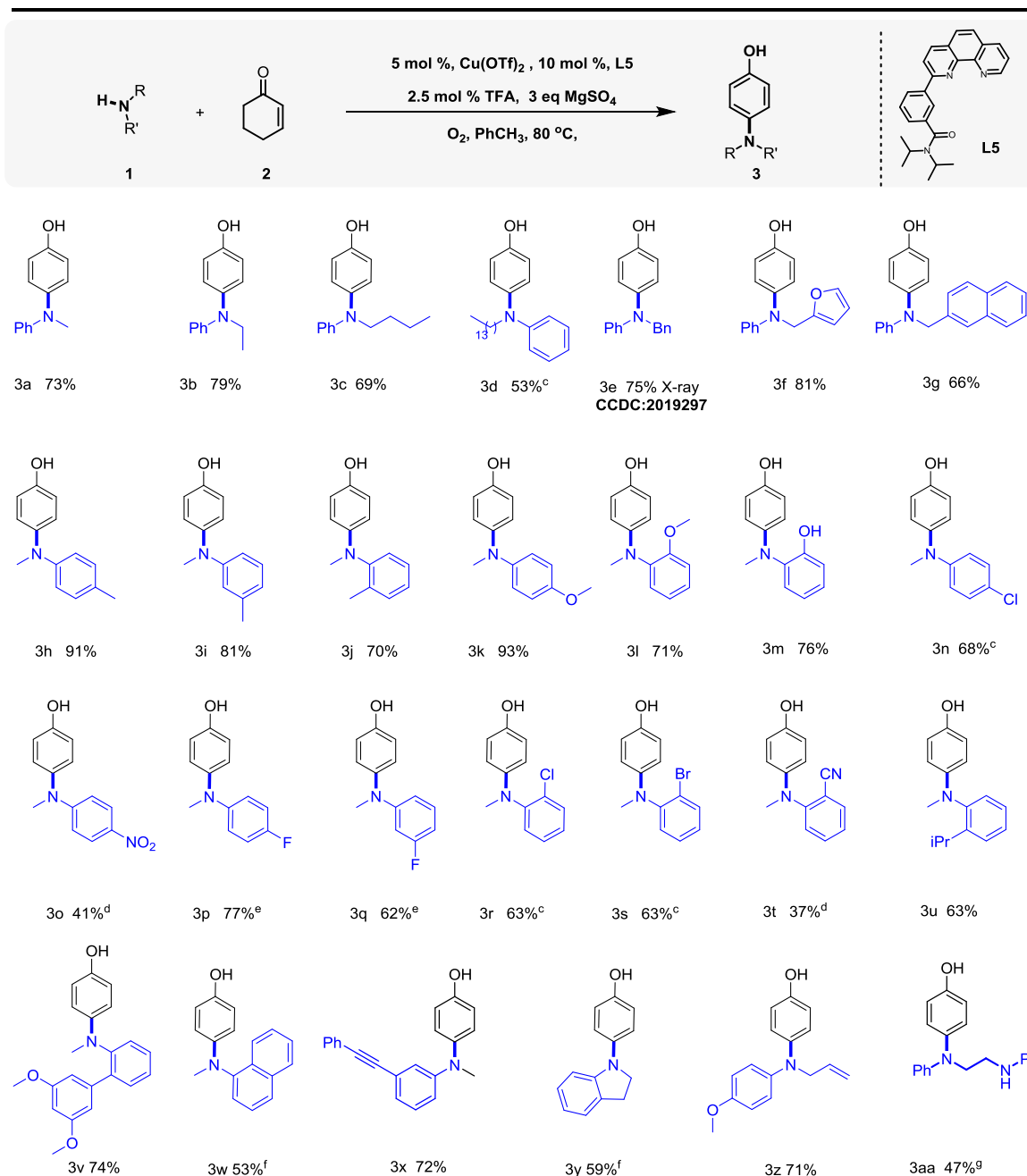


Table 2. Substrate Scope of Aromatic amine^{a,b}



^a Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), Cu(OTf)₂ (0.05 mmol), **L5** (0.1 mmol), toluene (3.0 mL), 80 °C, 1 atm O₂, 8 h. ^b Isolated yield. ^c 12 h. ^d 48 h. ^e 33 h. ^f 50 °C, 60 h. ^g Cu(OTf)₂ (0.03 mmol), **L5** (0.06 mmol), 24 h.

We found that various substituted aromatic anilines **1b-1g** possessing an aliphatic R group were tolerated. Specifically, a long alkyl chain group did not affect the reaction outcome significantly (**1d**). The relative configuration of the product **3e** was unambiguously assigned by X-ray crystallography. Various anilines with electron-donating and -withdrawing groups installed on benzene ring were also readily tolerated. The presence of electron donating groups on the aryl ring dramatically increased the yield, such as 4-Me, 3-Me and 4-OMe (products **3h-1**). Moreover, an interesting aniline with an *ortho*-OH substituted group was transferred to afford the desired **3m** in 76% yield,

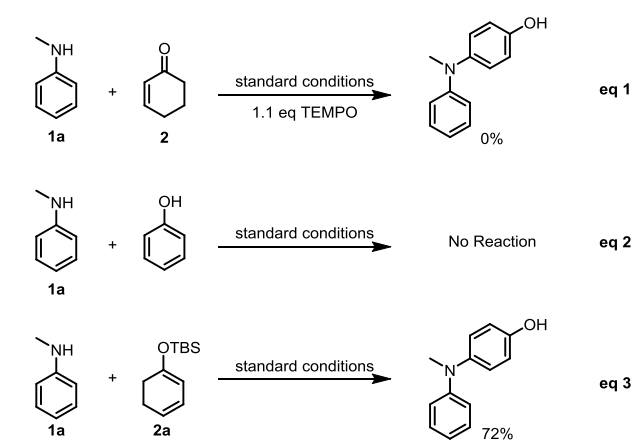
which indicated that the free hydroxy aniline was not the radical quencher to end the cross coupling. The presence of electron withdrawing groups, such as 4-Cl, 4-NO₂, 2-CN, resulted in decreased but serviceable yields (products **3n-3t**). The steric effect of the R' group was also considered, such as **1u** and **1v**; an isopropyl and steric benzene ring, were readily tolerated at the *ortho*-position of aniline

Moreover, considering synthetically useful transformations, anilines such as **1w-1aa** with different substitutions were also investigated and the desired products **3w-3aa** were obtained in

moderate to good yield. An alkynyl and an allyl group were tolerated, and their π bonds did not noticeably interfere with the desired C-N bond cross coupling. Somewhat to our surprise, the replacement of the methyl group in **1a** with a diamine substrate could offer a single aminated product **3aa** in 47% yield.

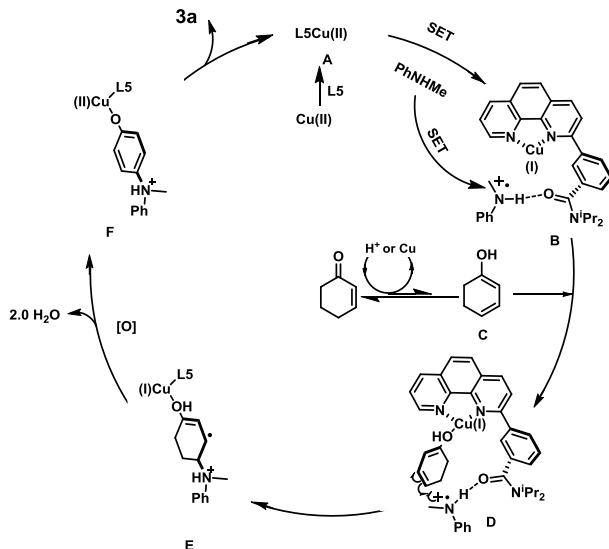
Mechanism study. In order to gather additional experimental evidence for the mechanism, we examined the reaction in the presence of 1.1 equivalent of TEMPO under the standard conditions and no **3a** was observed, which indicated that this reaction is a radical process (Scheme 1, eq 1). When cyclohexenone was replaced by phenol under the standard conditions, no **3a** was obtained (eq 2). However, when silyl enol ether (**2a**) worked with aniline (**1a**), resulted in 72% yield of **3a**, indicating that cyclohexa-1,3-dienol might be the real intermediate (eq 3).

Scheme 1. Control Experiments



On the basis of the above observations, we propose the following plausible mechanisms for this transformation as shown in Scheme 2. (i) $\text{Cu}(\text{OTf})_2$ first coordinates with **L5** to **L5Cu(II)** complex **A**, which is used to oxidize the aniline **1a** via single electron transfer process to give *N*-centered radical and **L5Cu(I)** complex **B**.³²⁻³³ (ii) The amide group of **L5** traps the *N*-centered radical via hydrogen bonding. Cyclohexenone is isomerized to cyclohexa-1,3-dienol and coordinates with **L5Cu(I)** complex **B** to afford copper-enol intermediate **D**. (iii) The *N*-centered radical, stabilized by amide group of **L5**, attacks on the γ -position of cyclohexenone to give intermediate **E**. (iv) Intermediate **E** is immediately oxidized to the aromatized complex **F** and released **3a**.³⁴ The **L5Cu(I)** complex is oxidized to **L5Cu(II)** and closes the catalytic cycle.

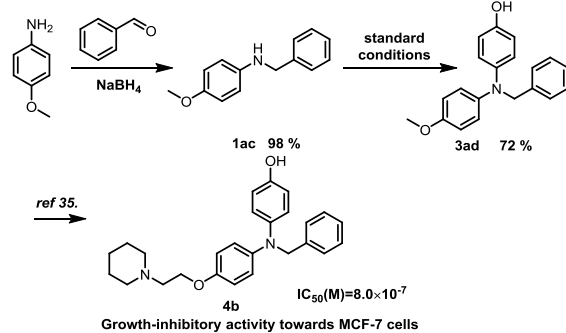
Scheme 2. Proposal Mechanism.



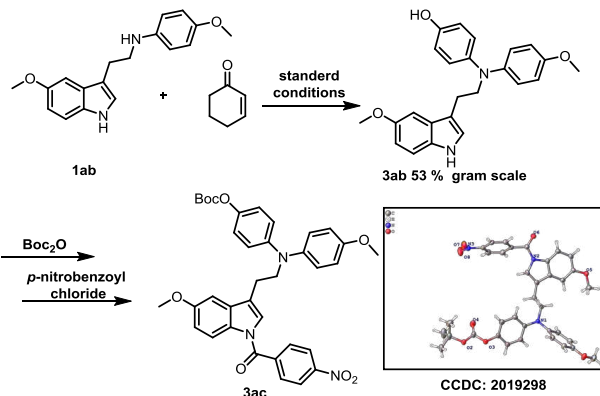
Synthetic utility. The synthetic utility of this approach was examined for the synthesis of biologically active molecules. Diphenylaminophenol derivatives are basic skeleton of novel estrogen receptor (ER) agonists.³⁵ With this protocol, the precursor **3ad** was synthesized with a total yield of 72% in two steps from readily available starting materials. (Scheme 3a) Indole substituted aniline **1ab** was also tolerated to afford the desired **3ab** in 53% yield at a gram scale. (Scheme 3b) The relative configuration of the structure of **3ac**, a derivative of **3ab**, was unambiguously assigned by X-ray crystallography.

Scheme 3. Convenient Synthesis of Bioactive Molecules

a. Application of biologically active compound



b. Gram scale and application



Discussion

In conclusion, we have realized a practical Cu(II)-catalyzed intermolecular γ -C(sp³)-H amination, in which a novel *N,N*-bidentate bifunctional ligand enables reactive *N*-centered radical intermediates, stabilized by amide group on the ligand, to undergo internal C-N bond cross coupling on the γ -site of cyclohexenone. The design of the bifunctional ligand relies on the amide group could stabilize *N*-centered radical via hydrogen bonding. The copper catalyzed reaction provides facile access to various *para*-*N*-substituted phenols with mostly good to excellent yield. This new class of ligands could usher in a new and synthetically highly valuable phase of exploiting the bifunctional roles in organic synthesis.

Data availability

The authors declare that the data supporting the findings of this study are available within this article and its Supplementary Information file, or from the corresponding author upon reasonable request. The experimental procedures and characterization of all new compounds are provided in Supplementary Information. The X-ray crystallographic for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2019297 (3e), and CCDC 2019298 (3ac). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

K.J. and F.Y. designed and directed the investigations and composed the manuscript with revisions provided by the other authors. Z.X. developed the catalytic method, and studied the substrate scope. Q. Z., and S. Z. analyzed and interpreted the experimental data. Z. C. were involved in the analysis of results and discussions of the project.

Competing interests

The authors declare no competing interests.

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