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Electrochemically Oxidative α-C-H Functionalization of Ketones: A Cascade Synthesis of α-Amino Ketones Mediated by NH_4I

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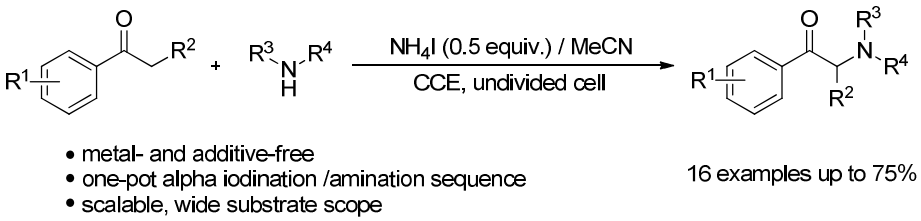
Keywords: C-H oxidative functionalization, indirect electrolysis, α-amino ketone, halide ion as redox catalyst

Abstract:

An efficient electrochemical protocol for the synthesis of α-amino ketones via the oxidative cross dehydrogenative coupling of ketones and secondary amines has been developed. The electrochemistry performs in a simple undivided cell using NH_4I as a redox catalyst and cheap graphite plate as electrodes under constant current conditions. Gram scale reaction demonstrates the practicality of the protocol. The reaction is proposed to procced through an initial α-iodination of ketone, followed by a nucleophilic substitution of amines.

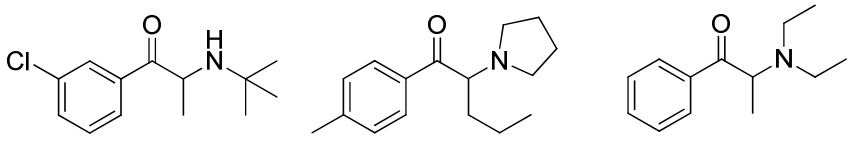
Graphical Abstract:



1. Introduction

Direct oxidative cross dehydrogenative coupling of C−H and N−H bond to form a new C−N bond has emerged as an important method in organic synthesis. It represents a high step- and atom-economical process since prefunctionalization of the substrates is avoided and hydrogen is the

only formal byproduct.[1] Along this line, significant advances have been made, especially in the oxidative C(sp^2)–H couplings to form various C–N bonds.[2] Extensive efforts have also been devoted to the oxidative amination of C(sp^3)–H bond, such as relatively active benzylic-,[3] allylic-C–H,[4] as well as α-C-H of alkyl ethers [5].



Bupropin Pyrovalerone Amfepramone

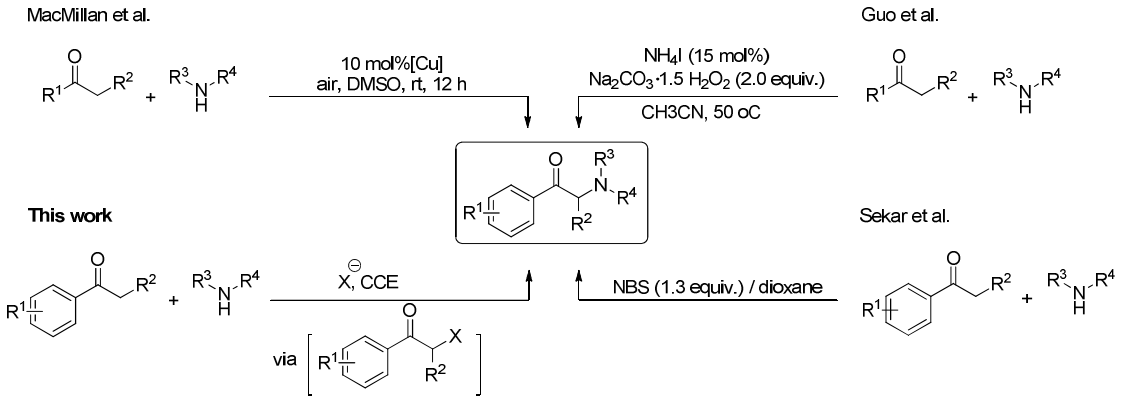
Figure 1. Some examples of biologically significant α-amino ketones

α-C(sp^3)–H functionalization and amination of ketones are also significant chemical conversions since α-amino ketones constitute the core structural scaffold of various natural products and pharmaceuticals. For example, bupropion, pyrovalerone and amfepramone are proved to be potential pharmacotherapies for antidepressant and psychoactive diseases (Figure 1).[6] Moreover, α-amino ketones are important intermediates and precursors for the synthesis of heterocycles and 1,2-amino alcohols.[7] Consequently, atom-economical and efficient approaches for the synthesis of α-amino ketones are in demand.

Typically, α-amino ketones are prepared by the substitution reaction of α-halo/hydroxy ketones with nucleophilic nitrogen sources[8] or α-amination of carbonyl compounds with electrophilic nitrogen sources.[9] These procedures require prefunctionalization of starting substrates. The direct oxidative amination of α-C(sp^3)−H bonds of carbonyl compounds provides an alternative approach for the construction of highly functionalized α-amino ketones.[10] For instance, MacMillan and co-workers developed a procedure for the α-amination of ketones, esters, and aldehydes via a combination of copper catalysts and bidentate nitrogen ligands.[10e] Transition metal-free oxidative α-C−H amination of ketones was also described by Guo and co-workers using ammonium iodide as a catalyst and sodium percarbonate as a co-oxidant.[10f] Very recently, an one-pot strategy to synthesize α-amino ketones has also been developed by Sekar and co-workers starting from benzylic secondary alcohol using N-bromosuccinimide (NBS) as an oxidant via sequential alcohol oxidation, α-bromination of ketone and C-N bond formation.[6b] Although much progress has been made in the processes described above, the need to use toxic and stoichiometric or excess of

external oxidant does not meet the guiding principles of green and sustainable chemistry (Scheme 1).[11]

Electrochemistry has proved to be an environmentally benign method to achieve the formation of a new chemical bond and a functional group conversion by using electron as oxidant rather than additional chemicals.[12] In this context, we have explored novel redox catalysts based upon the triarylimidazole scaffold for the oxidative functionalization of C-H bonds.[13a-b] Recently, we have also applied simple halide ions as redox catalysts to achieve electrochemical C-H bond functionalization, leading to the formation of new C-C, C-N, C-O and C-S bonds.[13c-f] Based on our experience in halide ions-mediated indirect electrolysis, we hypothesized that a constant current electrolysis (CCE) of ketone in the presence of halide ion might initially generate α-halocarbonyl ketone that would further undergo a substitution reaction in the presence of a nucleophilic amine source to fulfill the desired α-amino ketones (Scheme 1).



Scheme 1. Methods for the synthesis of α-amino ketones

Herein, we reported an electrochemical protocol for the one pot synthesis of α-amino ketones using NH_4I as a redox catalyst. The protocol features the following advantages: (1) the chemistry is performed via an α-iodination and amination sequence, which avoids the pre-preparation and isolation of the key intermediate, α-iodo ketone, thus minimizing the production of waste; (2) the anode serves as a co-oxidant that is physically separated from the organic layer containing the substrate and is thus easily removed; therefore, no terminal chemical co-oxidant is needed; and (3) the process is conveniently carried out at a constant current in a simple beaker-type cell. To the best

of our knowledge, this work represents the first example of the electrochemically oxidative α-C-H amination of ketones and further demonstrates that halide ions are versatile mediators capable of promoting a variety of different transformations.

2. Results and discussion

To demonstrate the feasibility of the one pot electrochemical α-amination of ketones via the α-iodination and amination sequence, we commenced on the optimization studies using propiophenone (**1a**) and piperidine (**2a**) as model substrates. Based on our previous successful use of a graphite working electrode in halide ion-induced C-H bond functionalization,[13] we chose to use it rather than to explore other options. The initial constant current electrolysis of a mixture of **1a** (1 mmol) and **2a** (3 mmol) was carried out in $LiClO_4$ / CH_3CN at room temperature in the presence of 0.5 equiv of NaI as a redox catalyst. To our delight, the desired product **3a** was obtained in 61% yield (entry 1, Table 1). When NaI was replaced by other halide salt, such as NaCl, NaBr, NH_4Br or *n*-Bu_4NBr, product **3a** was not detected (entries 2-5), indicating that chloride and bromide are inefficient for the cross dehydrogenative coupling reaction. Further catalysts screening disclosed that NH_4I provided the best yields of **3a**, although KI and Bu_4NI also led to acceptable results (entries 6-8). Notably, in the absence of NH_4I, **3a** was not produced (entry 9), thereby revealing that iodide ion plays an essential role for the cross dehydrogenative coupling reaction. The assay of the amount of NH_4I disclosed that 0.5 equiv of NH_4I was necessary in order to obtain acceptable yield. Lowering the loading to 0.2, 0.3 or 0.4 equiv. or increasing to 0.7 equiv. resulted in an decrease of the yield of **3a** to 0%, 56%, 69%, 73% respectively (entries 10-13). We observed that the yield of **3a** improved from 43% to 59% when the ratio of **1a** to **2a** was increased from 1:1.5 to 1:2 (entries 14-15). A further increase in the ratio to 3 equiv of **2a** afforded the highest yield of **3a** (entry 8). Additional increases did not improve the efficiency (entry 16).

The effect of current density on the reaction was also examined. The reaction did not proceed without electrolysis (entry 17), indicating the necessity of electrolysis. It was found that almost identical yield of **3a** was produced when a current density of 6 mA/cm^2 (entry 18) or 10 mA/cm^2 (entry 19) was employed instead of an optimal 8 mA/cm^2.

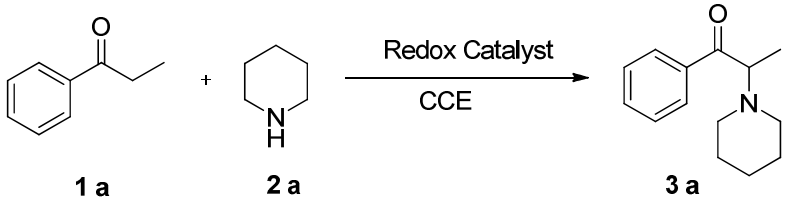
We further investigated the possibility to produce α-amino ketones electrochemically, but in the absence of the supporting electrolyte, $LiClO_4$. It was observed that the voltage of the cell was in

the range of 2.0 – 3.0 volts in the presence of 0.1 M $LiClO_4$, whereas it increased to 4.0 – 5.0 volts when conductive salt was not added as a result of the diminished conductivity. Nevertheless, the reaction proceeded smoothly without sacrificing efficiency, and nearly the same yield of adduct **3a** was obtained (entry 20). In addition, rising temperature has no significant impact on the yield of product **3a** (entry 21).

In order to investigate the possible effects of solvent, several solvents were examined. As shown in Table 1, when the reaction was performed in CH_3OH, the well-known ketalization reaction occurred and 2-hydroxyl-1,1-dimethoxypropylbenzene was obtained (entry 22).[14] When DMF and DMSO were used as solvents (entries 23-24), the voltage increased sharply and resulted in a dramatic corrosion of the working electrode. Moreover, the desired product **3a** was not detected at all. Based upon these observations, we suggested that MeCN was the best solvent for the reaction.

From the results described above, we concluded that the optimal reaction conditions call for constant current electrolysis using 0.5 equiv of NH_4I as the redox catalyst and CH_3CN as the solvent in an undivided cell equipped with a graphite plate anode and a graphite cathode.

Table 1. Optimization of the reaction conditions [a]



1 a **2 a** **3 a**

Entry	**2a** (equiv)	Redox cat. (equiv)	J/(mA/cm^2)	Solvent	Yield [b]
1	3	NaI (0.5)	8	MeCN	61
2	3	NaCl (0.5)	8	MeCN	0
3	3	NaBr (0.5)	8	MeCN	0
4	3	NH_4Br (0.5)	8	MeCN	0
5	3	n-Bu_4NBr (0.5)	8	MeCN	0

6	3	KI (0.5)	8	MeCN	70
7	3	n-Bu_4NI (0.5)	8	MeCN	65
8	3	NH_4I (0.5)	8	MeCN	72
9	3	NH_4I (0)	8	MeCN	0
10	3	NH_4I (0.2)	8	MeCN	0
11	3	NH_4I (0.3)	8	MeCN	56
12	3	NH_4I (0.4)	8	MeCN	69
13	3	NH_4I (0.7)	8	MeCN	73
14	1.5	NH_4I (0.5)	8	MeCN	43
15	2	NH_4I (0.5)	8	MeCN	59
16	4	NH_4I (0.5)	8	MeCN	70
17	3	NH_4I (0.5)	-	MeCN	0
18	3	NH_4I (0.5)	6	MeCN	73
19	3	NH_4I (0.5)	10	MeCN	66
20[c]	3	NH_4I (0.5)	8	MeCN	62
21[d]	3	NH_4I (0.5)	8	MeCN	60
22[e]	3	NH_4I (0.5)	8	MeOH	0
23	3	NH_4I (0.5)	8	DMF	0
24	3	NH_4I (0.5)	8	DMSO	0

[a] Reaction conditions: propiophenone **1a** (1 mmol), piperidine **2a** and 0.1 M $LiClO_4$ as supporting electrolyte in 20 mL of solvent, undivided cell, graphite plate anode and cathode, room temperature, CCE.

[b] ^1H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

[c] Additional supporting electrolyte $LiClO_4$ was not employed.

[d] T = 50 ^oC

[e] NaOH (1 equiv.) was added.

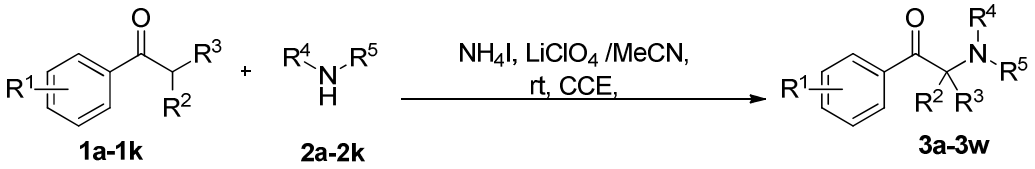
With the optimized conditions in hand, we turned toward exploration of the scope and limitation of the α-amination reaction of ketones under the standard conditions (Table 2). First, the

reactions of propiophenone **1a** with various secondary amines were investigated. It was observed that the reaction of **1a** and cyclic secondary amines, such as 4-methylpiperidine (**2b**), 3-methylpiperidine (**2c**), morpholine (**2e**), and 1,2,3,4-tetrahydroisoquinoline (**2f**) proceeded smoothly and afforded the corresponding α-amination products **3b, 3c, 3e** and **3f** in 30−65% isolated yield. However, 2-methylpiperidine (**2d**) was not a suitable coupling partner owing to the steric hindrance, its reaction with propiophenone **1a** did not give the corresponding adduct **3d.** Acyclic secondary amines also reacted with propiophenone **1a**, albeit in a bit lower yield. For example, N-methylbenzylamine (**2g**) and N-ethylbenzylamine (**2h**) afforded the corresponding α-amination products **3g** and **3h** in 28% and 32% yield. Notably, aliphatic and aryl primary amine did not work. For example, when butylamine (**2i**), cyclohexanamine (**2j**) and *p*-methylbenzeneamine (**2k**) were used as the amine sources, the corresponding adducts **3i-3k** were not obtained.

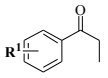
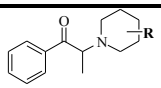
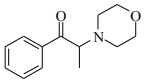
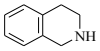
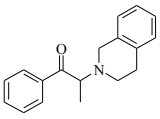
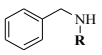
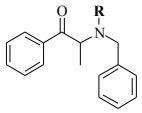
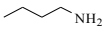
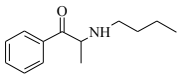
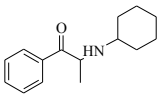
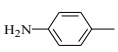
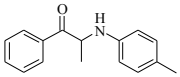
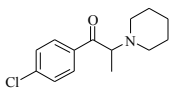
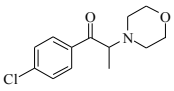
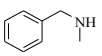
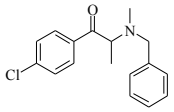
The oxidative cross dehydrogenative coupling of various propiophenones with piperidine were also examined. It was observed that electron-poor and –rich propiophenone proceeded smoothly with piperidine. More specifically, the direct amination reaction was most efficient when an electron-withdrawing substituent was appended on the benzene ring of propiophenone. For example, the chloro- and fluoro-substituted propiophenones, **1b** and **1d,** afforded the corresponding adducts **3l** and **3p** in 70% and 75% yields, respectively, higher than that of **3a** (65% yield). On the contrary, when electron-donating group, such as methyl- and methoxyl was installed in the phenyl ring, the corresponding **3q** and **3s** was isolated in a slightly lower yield. This observation indicates that the electrochemical α-amination of ketone prefers a substrate that is prone to enolate formation. Indeed, when aliphatic ketone, such as **1h**, was subjected to reaction with piperidine under the standard electrochemical conditions, the corresponding dehydrogenative coupling product **3t** did not generate, due to the less prone to enol/enolate formation of aliphatic ketone. Moreover, α-substituted propiophenones were also not suitable partners. For example, when α-methyl propiophenone (**1i**) and cyclopropylphenylmethanone (**1j**) were subjected to electrochemical coupling with piperidine, the starting ketones remained intact and the corresponding adduct **3u** and **3v** were not obtained due to the steric hindrance. Notably, it was observed that the α-amination of 2-cyclopropyl-1-phenylethanone, **1k**, proceeded smoothly and the corresponding **3w** was obtained in 45% yield. The observation implies that radical intermediate **5k** might not be generated and

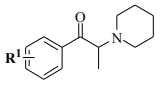
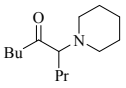
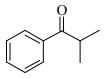
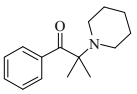
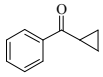
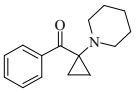
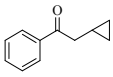
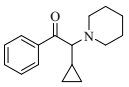
therefore rule out the possibility of being a radical pathway for the electrochemical α-amination of ketones (Detailed discussion see mechanism section and Scheme 5). In addition, the electron-rich aromatic system do not undergo Friedel-Crafts iodination under these electrochemical conditions.

Table 2. Substrate scopes of α-amino ketones synthesis [a]



1a-1k **2a-2k** **3a-3w**

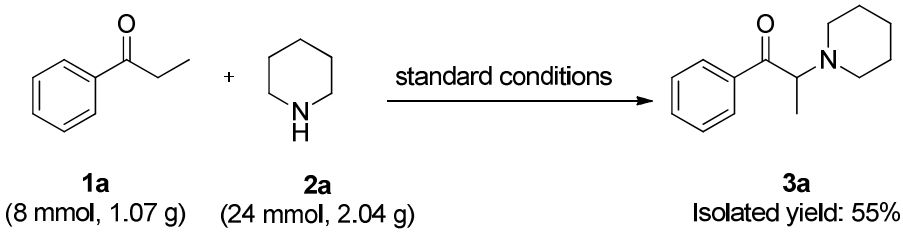
Entry	Ketone 1	Amine 2	Product 3	Yield (%) [b]
1	 **1a,** R^1=H	 **2a,** R=H	 **3a**	65
2		**2b,** R=4-Me	**3b**	60
3		**2c,** R=3-Me	**3c**	65
4		**2d,** R=2-Me	**3d**	trace
5		 **2e**	 **3e**	30
6		 **2f**	 **3f**	50
7		 **2g,** R=Me	 **3g**	28
8		**2h,** R=Et	**3h**	32
11		 **2i**	 **3i**	0
12		 **2j**	 **3j**	trace
13		 **2k**	 **3k**	0
14	**1b,** R^1=4-Cl	 **2a**	 **3l**	70
15		 **2d**	 **3m**	48
16		 **2g**	 **3n**	44

17		**1c,** R^1=3-Cl		**2a**		**3o**	60
18		**1d,** R^1=4-F				**3p**	75
19		**1e,** R^1=4-Me				**3q**	52
20		**1f,** R^1=3-Me				**3r**	55
21		**1g,** R^1=4-MeO				**3s**	50
22		**1h**				**3t**	0
23		**1i**				**3u**	0
24		**1j**				**3v**	0
25		**1k**				**3w**	45

[a] Reaction conditions: ketone (1 mmol), amine (3 mmol), NH_4I (0.5 mmol) and 0.1 M $LiClO_4$ as supporting electrolyte in 20 mL of MeCN, undivided cell, graphite plate anode, graphite plate cathode, room temperature, CCE, 14 F/mol.

[b] The isolated yield after column chromatography.

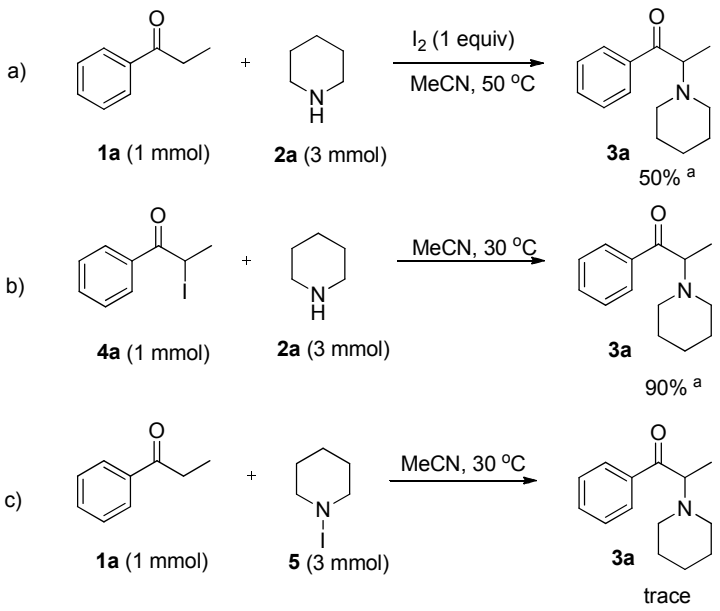
To further demonstrate the practicability of this one-pot protocol, a gram-scale reaction was also explored using 8 mmol of **1a** (1.07 g) under the standard reaction conditions. This transformation proceeded smoothly and **3a** was isolated in a 55% yield without significant loss of reaction efficiency (Scheme 2).



Scheme 2. Gram-scale electrochemically oxidative α-C-H amination of propiophenone (**1a**) with piperidine (**2a**).

In order to better understand the reaction mechanism and to determine the possible active intermediates involved, several control experiments were conducted. As shown in Scheme 3, when molecular iodine was employed as oxidant, the desired product was obtained in a 50% yield (Scheme 3, a). Therefore, the in situ generated molecular iodine (I_2) was suggested to be one of the active species. Moreover, the reaction of 2-iodo-1-phenylpropan-1-one, **4a**,[10e] and piperidine gave excellent yield of **3a** (Scheme 3, b), which suggests that **4a** is a possible intermediate in this transformation and that a nucleophilic substitution might be involved in the reaction process.

In principle, the reaction of **1a** with electrophilic nitrogen source, such as N-iodopiperidine may also lead to product **3a**. To verify this, N-iodopiperidine **5** was synthesized separately and subjected to reaction with **1a**. The results prove that the desired product **3a** was not detected, therefore the pathway involving the participation of an electrophilic nitrogen source was ruled out (Scheme 3, c).



[a] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard

Scheme 3. Control experiments

To further gain insight into the mechanism of the electrochemically oxidative α-C-H amination of ketones with amines, the electrochemical reaction of **1a** and **2a** was repeated while monitoring in real time by GC and GC-MS. As shown in Figure 2, with the proceeding of electrolysis, two new peaks with retention times at 17.27 min and 19.67 min appeared while the intensity of piperidine

(the peak at 6.64 min) and propiophenone (the peak at 12.79 min) decreased (spectra 1-3, Figure 2). By GC-MS (EI) analysis and comparison with authentic samples of **4a** and **3a**, we can assign that the peaks at 17.27 min and 19.67 are 2-iodopropiophenone, **4a**, and product **3a**, respectively. Moreover, it was observed that 2-iodopropiophenone disappear quickly, if the current power supply was turn off while stirring at room temperature. Based on these results, it is safe to believe that **4a** is an intermediate and, once it forms, soon undergoes nucleophilic substitution with amine **2a** to give the final product **3a**.

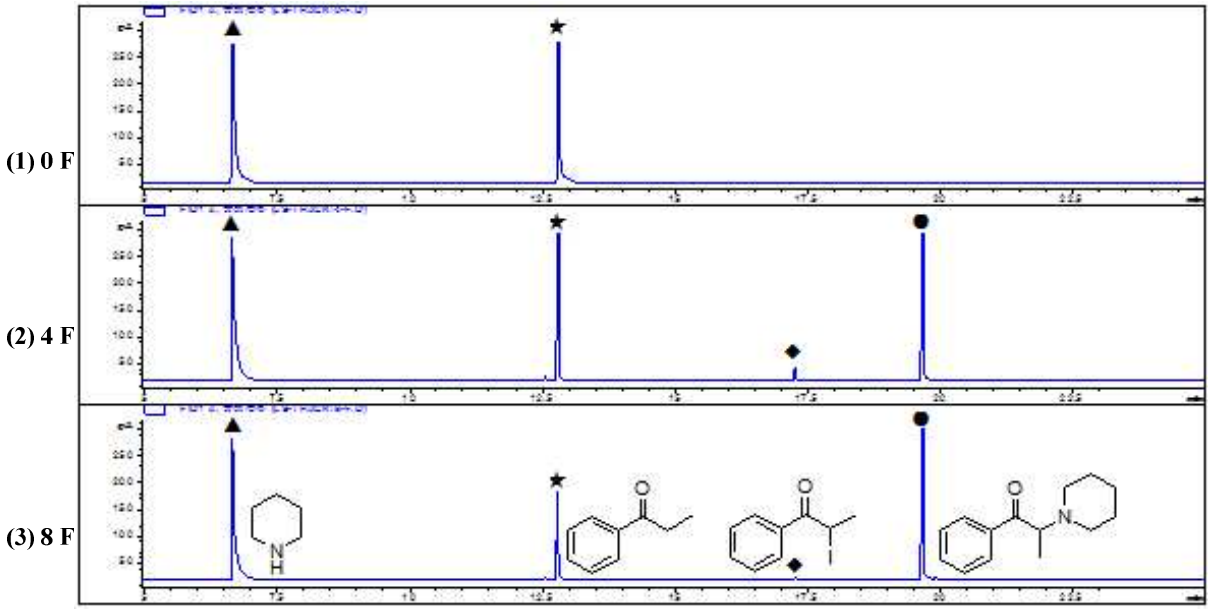
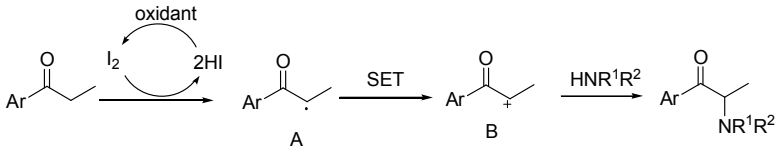


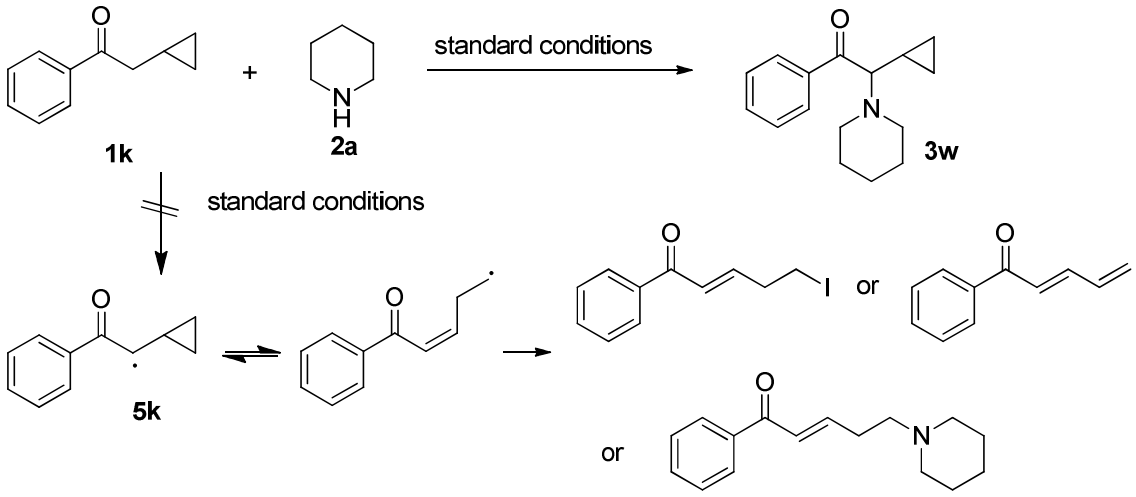
Figure 2. Propiophenone **1a** (1 mmol), Piperidine **2a** (3 mmol) and 0.1 M $LiClO_4$ as supporting electrolyte in 20 mL of solvent, undivided cell, graphite plate anode and cathode, 30 ^oC, CCE.

It is worth noting that oxidative α-amination of aryl ketone may also involve a radical pathway. For example, Guo and coworkers reported α-C−H amination of ketones using ammonium iodide as the catalyst and sodium percarbonate as the co-oxidant.[10e] The authors proposed that the in situ generated molecular iodine decompose into iodine radical, which abstracts the α-H of propiophenone to form a carbon-centered radical intermediate A. Followed by a single electron transfer (oxidation), the radical intermediate A converts to cation B. Finally, the nucleophilic substitution of amine to B gives the desired α-amination products (Scheme 4). Similar radical mechanism was also proposed by Batra et al for the α-nitrotion of ketones using I_2 as catalyst and H_2O_2 as co-oxidant in DMSO.[15]



Scheme 4. A radical pathway for the α-amination of aryl ketone proposed by Guo et al

To clarify whether our electrochemical α-amination of ketone involves the formation of radical intermediate A, a radical clock experiment was performed. As mentioned in Table 2, when substrate **1k** was subjected to electrolysis in the presence of **2a** under the standard electrochemical conditions, adduct **3w** was obtained in acceptable yield. Since we did not find the presence of 5-iodo-1-phenyl-2-penten-1-one, 1-phenylpenta-2,4-dienone or 5-piperidin-1-phenyl-2-penten-1-one from the crude reaction mixture using ^{1}H NMR methode, and therefore the radical pathway, similar to that reported by Guo,[10e] is ruled out.

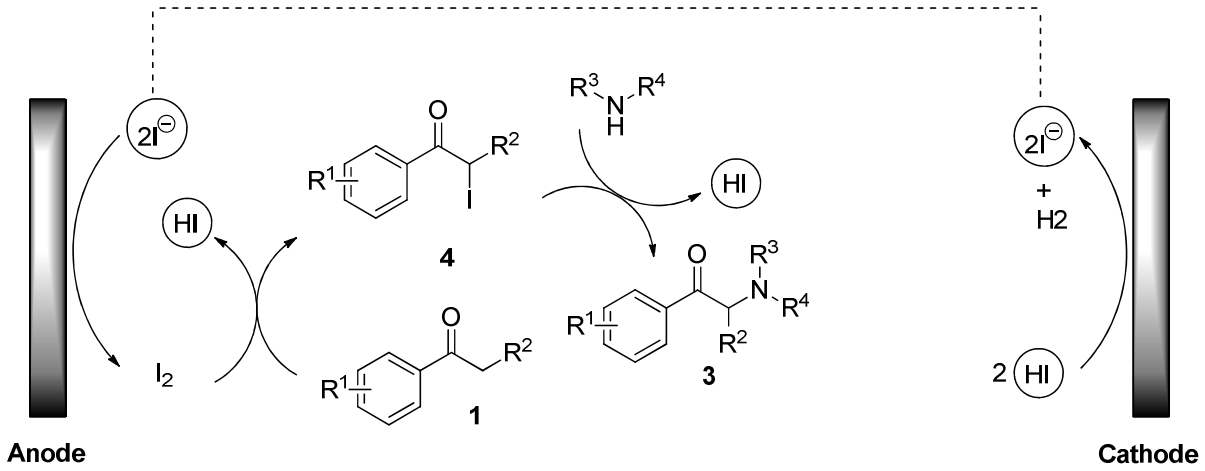


Scheme 5. Radical clock experiment.

It is necessary to mention that, when TEMPO and BHT were added as a radical scavenger, the α-amination reaction of ketone did not work. This was observed for both the electrochemical reaction as well as the control experiment with molecular iodine. However, the outcomes do not represent a proof of a radical process since it is reported that molecular iodine could oxidize TEMPO,[16] with high possibility through an inner-sphere electron transfer.[17]

On the basis of the observations described above, we propose a mechanism for the electrochemical α-amination of ketone with secondary amine. As illustrated in Scheme 6, the

reaction begins with the anodic oxidation of iodide to generate molecular iodine, which undergoes reaction with ketone **1** to form α-iodo ketone **4**, along with one molecule of HI. Once the key intermediate **4** is formed, it soon undergoes a nucleophilic substitution reaction with amine, leading to the final α-amination product **3**, accompanying the second molecular HI. Simultaneously, the in situ generated HI is reduced to evolve H_2 on the surface of cathode. In the course of the reaction, iodide ion is regenerated from steps of the α-iodination of ketone **1** to **4** and nucleophilic substitution of **4** to **3**, and re-enters the redox catalyst cycle, thereby only sub-stoichiometric or catalytic amount of NH_4I is required.



Scheme 6. The proposed reaction mechanism for the formation of α-amino ketones.

3. Conclusion

In conclusion, we have developed an efficient electrochemical protocol for the synthesis of α-amino ketones via the oxidative cross dehydrogenative coupling of ketones and secondary amines at ambient temperature. The electrochemistry was performed under constant current conditions in a simple undivided cell using NH_4I as the redox catalyst and cheap graphite plate as working electrode. A wide range of functional groups are proved to be compatible with the standard conditions. Gram scale reaction of **1a** and **2a** demonstrates the practicality of the protocol. In addition, it is possible to carry out the chemistry without having to employ additional supporting electrolyte. Mechanistic studies reveal that the electrochemical α-C-H amination of ketones likely undergoes initial α-iodination of ketone, followed by a nucleophilic substitution of amines. In this way, the iodide ion can be used catalytically, thereby avoiding the utilization of stoichiometrical

amount of molecular iodine or a combination of iodide and co-oxidant and therefore represents an environmentally benign means by which to achieve the transformation. Application of these ideas and results to other types of reactions is underway in our laboratory.

4. Experimental

4.1. Instruments and reagents

All melting points were measured with an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded with a 300 MHz spectrometer (300 MHz ^{1}H frequency, 75 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS). Coupling constants are reported in Hz. Starting materials and solvents were obtained from commercial sources and used without further purification. Products were purified by chromatography on silica gel (Petroleum ether/EtOAc). GC analysis was performed using gas chromatograph and gas chromatograph–mass spectrometer. The column used was a HP-5 and HP-5MS capillary column (30 m, 0.25 mm i.d., and 0.25 mm film) and the gas carrier was N_2 and He at a rate of 1 ml/min. The injector, detector and MS transfer line temperature were maintained at 250 ^{o}C, 250 ^{o}C and 230 ^{o}C. For the HP-5 and HP-5MS column, the oven temperature was held at 50 ^{o}C for 1 min, raised to 250 ^{o}C at 10 ^{o}C/min and held for 4 min. An electron ionization system was used with ionization energy of 70 eV.

4.2 Procedure for the synthesis of 2-cyclopropyl-1-phenyl-1-ethanone **(1k)**

4.2.1 Procedure for the synthesis of 1-phenylbut-3-en-1-ol [18]

To a 250 mL three-necked flask was equipped with a magnetic stirrer, a pressure equalizing dropping funnel, and reflux condenser mounted with a nitrogen source. To the flask were added magnesium (1.2 g, 50 mmol), a small amount of iodine, and 10 mL of ether. To this was added a small amount allyl chloride. The reaction mixture was stirred until the purple iodine color disappeared at room temperature. To this was added 20 mL of a solution of allyl chloride (3.8 g, 50 mmol) slowly at −10 °C. After 30 min, a solution of benzaldehyde (5.3 g, 50 mmol) in 30 mL of ether was added dropwise at such a rate to maintain the internal temperature below −10 °C. After 2

h, the reaction was quenched with a 0.1 M aqueous solution of HCl, followed by the addition of 40 mL ether. The organic phase was washed with brine, dried with anhydrous magnesium sulfate, and removed under reduced pressure. The crude product was purified by silica-gel column chromatography. 1-phenylbut-3-en-1-ol was obtained as a colorless oil (5.9 g, 80% yield).

1-Phenylbut-3-en-1-ol: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (br, 1H), 2.50 (m, 2H), 4.69 (m, 1H), 5.10-5.17 (m, 2H), 5.72-5.85 (m, 1H), 7.23-7.34 (m, 5H). ^{13}CNMR (75 MHz, $CDCl_3$): δ 43.7, 73.2, 118.3, 125.8, 127.5, 128.3, 134.4, 143.8.

4.2.2 Procedure for the synthesis of 1-phenylbut-3-en-1-one [19, 20]

To a 200 mL round bottom flask containing a stirbar was added the above obtained 1-Phenylbut-3-en-1-ol (5.9 g, 40 mmol). To the flask were added 10 mL of acetone. To this was added a solution of Jones' reagent (25 mL) and H_2O (25 mL) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 2 h, H_2O (50 mL) was added, and extracted with Et_2O. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate and removed under reduced pressure. The crude product was purified by silica-gel column chromatography. 1-phenylbut-3-en-1-one was obtained as a colorless oil (4.9 g, 85% yield).

1-Phenylbut-3-en-1-one: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (dt, J = 6.6 Hz, J = 1.2 Hz, 2H), 5.19-5.25 (m, 2H), 6.03-6.16 (m, 1H), 7.44-7.59 (m, 3H), 7.95-7.96 (m, 2H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 43.4, 118.7, 128.3, 128.6, 131.0, 133.2, 136.5, 198.0.

4.2.3 Procedure for the synthesis of 2-Cyclopropyl-1-phenyl-1-ethanone [21, 22]

To a 250 mL round bottom flask containing a stirbar was added Et_2Zn (30 mmol, 1.5 M in hexanes) and dry CH_2Cl_2 (20 mL) under N_2. The solution was cooled to 0 ^{o}C, and a solution of trifluoroacetic acid (3.42 g, 30 mmol) in CH_2Cl_2 (10 mL) was added dropwise into the reaction mixture by syringe. After stirring for 20 min, a solution of CH_2I_2 (8.0 g, 30 mmol) in CH_2Cl_2 (10 mL) was added. After an additional 20 minutes of stirring, a solution of the 1-Phenylbut-3-en-1-one (4.4 g, 30 mmol) in CH_2C1_2 (10 mL) was added, and the reaction mixture was slowly warmed to room temperature. After an additional 1 h of stirring, the reaction mixture was quenched with a 0.1 M aqueous solution of HCl and extracted with Et_2O. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate and removed under reduced pressure. The crude product was purified by silica-gel column chromatography. 2-Cyclopropyl-1-phenyl-1-ethanone was obtained as a colorless oil (3.8 g, 80% yield).

2-Cyclopropyl-1-phenyl-1-ethanone: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.17-0.21 (m, 2 H), 0.43-0.63 (m, 2 H), 1.12-1.21 (m, 1 H), 2.88 (d, J = 6.6 Hz, 2 H), 7.43-7.48 (m, 2 H), 7.53-7.58 (m, 1 H), 7.91-7.99 (m, 2 H). ^{13}C NMR (75MHz, $CDCl_3$): δ 4.5, 6.6, 43.8, 128.1, 128.5, 132.9, 136.9, 200.0

4.3 General procedure for the electrochemically oxidative α-C-H amination of ketones

A 50 mL undivided cell was equipped with a graphite plate cathode and a graphite plate anode (each about 2 × 3 cm^2 and the distance is about 0.5 cm) which were connected to a DC regulated power supply. To the cell was added ketone **1** (1 mmol), amine **2** (3 mmol), NH_4I (0.5 mmol) and $LiClO_4$ (0.1 M) dissolved in 20 mL of CH_3CN. The mixture was electrolyzed under constant current conditions at 8 mA/cm^2 at room temperature while stirring. The electrolysis was terminated when 14 F/mol of charge had been consumed. After the electrolysis, the solvent was removed under reduced pressure. The residue was poured into a saturated aqueous $Na_2S_2O_3$ and the product was then extracted with DCM (3×10 mL), dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel using a mixture of petroleum ether/EtOAc as eluent.

2-Piperidin-1-phenylpropan-1-one (3a)[10e] Yield: 141 mg, 65 %; Brown oil; Flash chromatography (petroleum ether/ethyl acetate, 1/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (d, *J* = 6.9 Hz, 3H), 1.37-1.42 (m, 2H), 1.51-1.56 (m, 4H), 2.48-2.58 (m, 4H), 4.06 (q, *J* = 6.6 Hz, 1H), 7.40-7.45 (m, 2H), 7.50-7.56 (m, 1H), 8.09-8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.1, 24.3, 26.3, 50.7, 65.0, 128.2, 128.8, 132.7, 136.4, 201.1.

2-(4-Methyl)piperidin-1-phenyl-propan-1-one (3b)[10e] Yield: 139 mg, 60 %; Brown oil; Flash chromatography (petroleum ether/ethyl acetate, 5/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81 (d, *J* = 6.0 Hz, 3H), 1.04-1.26 (m, 6H), 1.52-1.62 (m, 2H), 2.11 (td, *J* = 11.4 Hz, 2.4 Hz, 1H), 2.37 (td, *J* = 11.4 Hz, 2.4 Hz, 1H), 2.73 (d, *J* = 11.1 Hz, 1H), 2.89 (d, *J* = 11.1 Hz, 1H), 4.07 (q, *J* = 6.6 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.3, 21.9, 30.8, 34.4, 34.8, 48.5, 51.7, 64.9, 128.2, 128.9, 132.7, 136.5, 201.1.

2-(3-Methyl)piperidin-1-yl)-1-phenylpropan-1-one (3c) Yield: 150 mg, 65 %; Brown oil; Flash chromatography (petroleum ether/ethyl acetate, 5/1); ^{1}H NMR($CDCl_3$, 300 MHz): δ 0.81 (q, *J* = 6.0 Hz, 3 H), 1.04-1.26(m, 6 H), 1.52-1.62(m, 2 H), 2.11(td, *J* = 11.4、2.4 Hz, 1 H), 2.37(td, *J* = 11.4、2.4 Hz, 1 H), 2.73(d, *J* = 11.1 Hz, 1 H), 2.89(d, *J* = 11.1 Hz, 1H), 4.07(q, *J* = 6.6 Hz, 1 H), 7.43(t, *J* = 7.5 Hz, 2 H), 7.53(t, *J* = 7.5 Hz, 1 H), 8.09(d, *J* = 7.5 Hz, 2 H); ^{13}C NMR($CDCl_3$, 75 MHz): δ 10.6, 10.8, 19.6, 25.6, 25.9, 31.2, 31.6, 32.9, 48.7, 51.7, 56.4, 59.4, 64.9, 128.2, 128.9, 128.9, 132.7, 136.5, 136.5, 200.9, 201.0. HRMS (ESI) m/z calcd for $C_{15}H_{22}NO$(M+H) 232.1696, found 232.1691.

2-Morpholino-1-phenylpropan-1-one (3e)[10e] Yield: 66 mg, 30 %; Brown oil; Flash chromatography (petroleum ether/ethyl acetate, 3/1); ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.28 (d, *J* = 6.9 Hz, 3H), 2.51-2.65 (m, 4H), 3.63-3.75 (m, 4H), 4.06 (q, J = 6.9 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.7, 50.0, 64.7, 67.1, 128.4, 128.7, 133.0, 136.0, 200.2;

2-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-phenylpropan-1-one (3f)[10e] Yield: 133 mg, 50 %; Brown oil; Flash chromatography (petroleum ether/ethylacetate, 10/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (d, *J* = 6.9 Hz, 3H), 2.80-2.87 (m, 4H), 3.80 (d, *J* = 14.7 Hz, 1H), 3.92 (d, *J* = 14.7 Hz, 1H), 4.31 (q, *J* = 6.6 Hz, 1H), 7.00-7.13 (m, 4 H), 7.42-7.46 (t, *J* = 7.5 Hz, 2H), 7.52-7.56 (t, *J* = 7.2 Hz, 1H), 8.14−8.16 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR($CDCl_3$, 75 MHz): δ 11.2, 29.5, 47.1, 52.0, 64.1, 125.5, 125.9, 126.5, 128.3, 128.6, 128.9, 132.9, 134.4, 134.7, 136.1, 200.5.

2-(N-Benzyl-N-methylamino)-1-phenylpropan-1-one (3g)[10e] Yield: 71 mg, 28 %; Brown oil; Flash chromatography (petroleum ether/ethylacetate, 10/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (d, *J* = 6.6 Hz, 3H), 2.21 (s, 3H), 3.63 (s, 2 H), 4.31 (q, *J* = 6.6 Hz, 1H), 7.19-7.29 (m, 5 H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.8, 37.6, 58.3, 62.1, 127.0, 128.2, 128.2, 128.9, 128.9, 132.7, 136.4, 139.0, 200.8.

2-(N-Benzyl-N-ethylamino)-1-phenylpropan-1-one (3h)[10e] Yield: 85 mg, 32 %; Brown oil; Flash chromatography (petroleum ether/ethyl acetate, 10/1); ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 2.56 (q, *J* = 7.2 Hz, 2 H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.70 (d, *J*

= 13.8 Hz, 1H), 4.40 (q, *J* = 6.6 Hz, 1H), 7.15-7.17 (m, 5H), 7.38-7.42 (t, *J* = 7.5 Hz, 2H), 7.50-7.54 (t, *J* = 7.5 Hz, 1H), 7.90-7.92 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR($CDCl_3$, 75 MHz): δ 8.8, 13.7, 44.3, 54.6, 58.8, 126.9, 128.1, 128.1, 128.9, 128.9, 132.5, 136.8, 139.8, 201.9.

2-Piperidin-1-(4-chlorophenyl)propan-1-one (**3l**)[6b] Yield: 203 mg, 70 %; Brown oil; Flash chromatography (petroleum ether/ethylacetate, 8/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (d, *J* = 6.6 Hz, 3H), 1.36-1.42 (m, 2H), 1.47-1.55 (m, 4H), 2.42-2.53 (m, 4H), 3.96 (q, *J* = 6.6 Hz 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.2, 24.3, 26.3, 50.6, 65.5, 128.4, 130.5, 134.6, 138.9, 199.7.

2-Morpholino-1-(4-chlorophenyl)propan-1-one (**3m**)[10e] Yield: 122 mg, 48 %; Brown solid; mp: 83-87℃; Flash chromatography(petroleum ether/ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (d, *J* = 6.6 Hz, 3H), 2.47-2.61 (m, 4 H), 3.59-3.70 (m, 4H), 3.97 (q, *J* = 6.6 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR($CDCl_3$, 75 MHz): δ 10.9, 49.8, 65.1, 67.0, 128.6, 130.3, 134.2,139.3 198.8.

2-(N-Methyl-N-phenylmethyl-amino]-1-(4-chlorophenyl)propan-1-one (**3n**) Yield: 126 mg, 44 %; Brown oil; Flash chromatography (petroleum ether/ethylacetate, 10/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (d, *J* = 6.6 Hz, 3H), 2.20 (s, 3H), 3.62 (s, 2H), 4.22 (q, *J* = 6.6 Hz, 1H), 7.19-7.30 (m, 5H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR($CDCl_3$, 75 MHz): δ 8.05, 37.5, 58.4, 62.1, 127.2, 128.3, 128.5, 128.9 130.5, 134.6, 138.8, 139.0, 199.4. HRMS (ESI) m/z calcd for $C_{17}H_{19}ClNO(M+H)^+$ 288.1150, found 288.1153.

2-Piperidin-1-[(3-(chlorophenyl)]propan-1-one (**3o**)[23] Yield: 151 mg, 50 %; Brown oil; Flash chromatography(petroleum ether/ethyl acetate, 8/1);^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.9 Hz, 3H), 1.37-1.44 (m, 2H), 1.47-1.56 (m, 4H), 2.43-2.52 (m, 4H), 3.97 (q, *J* = 6.6 Hz, 1H), 7.3 (t, *J* = 7.8 Hz, 1H), 7.47-7.51 (m, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 8.13 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.2, 24.3, 26.3, 50.6, 65.6, 127.1, 129.1, 129.5, 132.5, 134.3, 137.9, 199.6.

2-Piperidin-1-(4-fluorophenyl)propan-1-one (**3p**) Yield: 176 mg, 75 %; Brown oil; Flash

chromatography (petroleum ether/ethyl acetate, 2/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (d, *J* = 6.9 Hz, 3H), 1.37-1.43 (m, 2H), 1.49-1.56 (m, 4H), 2.43-2.55 (m, 4H), 3.97 (q, *J* = 6.6 Hz, 1H), 7.06-7.12 (m, 2H), 8.16-8.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.5, 24.3, 26.3, 50.7, 65.7, 115.0 (d, *J*(C,F) = 21.4 Hz), 131.6 (d, *J*(C,F) = 9.0 Hz), 132.7 (d, *J*(C,F) = 3.1 Hz), 163.8 (d, *J*(C,F) = 252.6 Hz), 199.4. HRMS (ESI) m/z calcd for $C_{14}H_{19}FNO(M+H)^+$ 236.1445, found 236.1443.

2-Piperidin-1-(4-methylphenyl)propan-1-one (**3q**)[10b] Yield: 120 mg, 52 %; Brown oil; Flash chromatography(petroleum ether/ethyl acetate, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.9 Hz, 3H), 1.37-1.42 (m, 2H), 1.45-1.52 (m, 4H), 2.40 (s, 3H), 2.48-2.55 (m, 4H), 4.04 (q, *J* = 6.9 Hz, 1H), 7.23(d, *J* = 8.1 Hz, 2H), 8.01 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 21.6, 24.4, 26.3, 50.8, 65.0, 128.9, 129.0, 134.0, 143.5, 200.7.

2-Piperidin-1-(3-methylphenyl)propan-1-one (**3r**)[6b] Yield: 127 mg, 55 %; Brown oil; Flash chromatography(petroleum ether/ethyl acetate, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.6 Hz, 3H), 1.37-1.45 (m, 2H), 1.47-1.53 (m, 4H), 2.40 (s, 3H), 2.45-2.59 (m, 4H), 4.05 (q, *J* = 6.8 Hz, 1H), 7.31-7.34 (m, 2H), 7.88-7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 21.4, 24.4, 26.3, 50.8, 64.9, 126.0, 128.1, 129.2, 133.5, 136.6, 138.0, 201.3.

2-Piperidin-1-(4-methoxyphenyl)propan-1-one (**3s**)[10f] Yield: 124 mg, 50 %; Brown oil; Flash chromatography(petroleum ether/ethyl acetate, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.6 Hz, 3H), 1.37-1.42 (m, 2H), 1.50-1.54 (m, 4H), 2.43-2.57 (m, 4H), 3.86 (s, 3H), 3.98 (q, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 8.12 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 24.4, 26.3, 50.8, 55.4, 65.2, 113.3, 129.4, 131.2, 163.1, 199.7.

2-Piperidin-2-Cyclopropyl-1-phenyl-1-ethanone (3w) Yield: 109 mg, 45 %; Brown oil; Flash chromatography(petroleum ether/ethyl acetate, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04-0.11 (m, 1 H), 0.37-0.40 (m, 1 H), 0.70-0.74 (m, 1 H), 1.09-1.12 (m, 1 H), 1.44-1.46 (m, 2 H), 1.44-1.57 (m, 4 H), 2.38-2.41 (m, 2 H), 2.66-2.69 (d, J = 9.6 Hz, 1 H), 2.79-2.80 (m, 2 H), 7.41-7.46 (m, 2 H), 7.52-7.56(m, 1 H), 8.29-8.31 (m, 2 H). ^{13}C NMR (75MHz, $CDCl_3$): δ 1.6, 7.3, 10.9, 24.5, 26.1, 52.6,

79.5, 128.2, 129.2, 132.8, 136.5, 200.1. HRMS (ESI) m/z calcd for $C_{16}H_{22}NO$ $(M+H)^+$ 244.1696, found 244.1694.

2-Iodo-1-phenylpropan-1-one (4a). ^{1}H NMR($CDCl_3$, 300 MHz): δ 2.07(d, *J* = 6.6 Hz, 3H), 5.50(q, *J* = 6.6 Hz, 1H), 7.51(t, *J* = 8.0 Hz, 2H), 7.63(t, *J* = 8.0 Hz, 1H), 7.99(d, *J* = 6.8, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.1, 22.0, 128.6, 128.7, 133.4, 133.5, 194.7. HRMS (ESI) m/z calcd for $C_9H_{10}IO$ $(M+H)^+$ 260.9771, found 260.9779.

2-hydroxyl-1,1-dimethoxypropylbenzene: ^{1}H NMR ($CDCl_3$): δ 0.96 (d, *J* = 6.3 Hz 3H), 2.41 (dr, 1H), 3.22 (s, 3H), 3.37 (s, 3H), 4.11 (q, *J* = 6.3 Hz, 1H), 7.26-7.48 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.4, 49.3, 50.0, 70.7, 103.5, 127.7, 128.0, 128.0, 137.3.

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The authors declare no competing financial interest.

Supporting Information Available: Copies of ^{1}H, ^{13}C NMR spectral of related starting material and products, cyclic voltammetry of redox catalyst and GC-MS monitored control reactions between **1a** and **2a** and cyclic voltammetry of redox catalyst. This material is available free of charge via the Internet at http://pubs.acs.org

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(17) We have performed cyclic voltammetry measurement (see Supporting Information for detail) and found that the oxidation potential of TEMPO (0.73 V vs Ag/AgCl) is higher than I^- (0.31 V vs Ag/AgCl) in CH_3CN. Therefore, it seems not possible that molecular iodine oxidize TEMPO to $TEMPO^+$. In addition, it is well-known that it is $TEMPO^+$, instead of TEMPO radical, oxidize alcohol to C=O. Consequently, we conclude that it ought to be an inner-sphere process for the oxidation of benzylic alcohol using I_2/TEMPO as oxidant.

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