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Copper-catalyzed aerobic oxygenative cross dehydrogenative coupling of methyl ketones with *para*-C-H of primary anilines

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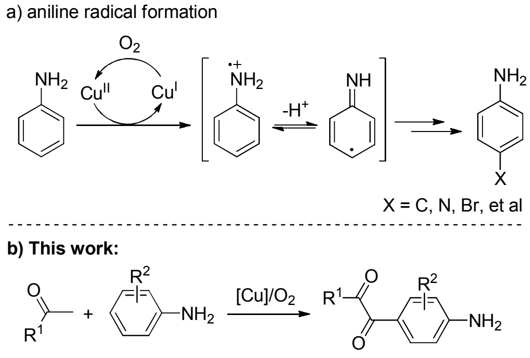
A novel oxygenative cross dehydrogenative coupling of methyl ketones with *para*-C-H of primary anilines under copper/oxygen catalytic system is discribed. This methodology features advantages including readily available starting materials, green oxidant, and broad functional group tolerance.

Oxidative cross dehydrogenative coupling (CDC) has gained intensive attention in synthetic chemistry over the past decade.[1] Copper/oxygen catalytic system is found to be powerful and versatile in this field, which enables CDC to efficiently construct C-C and C-heteroatom bonds under facile conditions.[2,3] And more importantly, the employment of oxygen as the oxidant in those oxidative transformations really features incomparable among those with other oxidants with respect to the development of sustainable chemical process.[4]

In particular, the oxidative coupling of the C-H bond at the *para*-position of anilines by copper/oxygen catalytic system has been well known for the polymerizations[5] and *para*-halogenation[6] of anilines. Generally, anilines undergo single electron oxidation and loss of a proton, affording the key highly active aniline radical. While nitrogen-centred radical enables the formation of various N-X (X=C, N, et al.) bonds,[7] *para*-carbon-centred radical provides desirable opportunities for the *para*-C-H functionalization (Scheme 1a). However, few examples of aniline *para*-C-H derivation were realized due to the highly sensitive free amino group to acid and metal catalysts.[8] Herein, as our continuing effort on copper/oxygen catalytic transformations,[9] we disclose a novel oxygenative CDC reaction of methyl ketones with the *para*-position of anilines to provide unique access to the motif of anilin-1,2-diketones (Scheme 1b). The compatibility of the free amino group in the procedure highlights this charming copper/oxygen system to be highly feasible to prepare some active molecules with aromatic amine moiety.



Scheme 1 *Para*-selective reactions of primary anilines under copper/O_2 catalytic system.

Our initial investigations began with the coupling of acetophenone (**1a**) and aniline (**2a**) in the presence of copper catalyst under molecular oxygen (Table 1). Trace of 1-(4-aminophenyl)-2-phenylethane-1,2-dione (**3aa**) was obtained with $Cu(OTf)_2$ as the catalyst (entry 1). The use of $BF_3 \cdot Et_2O$ as additive with $Cu(OAc)_2$ catalyst afforded the desired coupled product **3aa** in 23% yield (entry 2). It was discovered that the identity of the copper catalyst was crucial for obtaining high yield of the coupled product **3aa**. After examining various catalysts, we were delighted to find that the reaction proceeded smoothly with CuI as catalyst along with $BF_3 \cdot Et_2O$ as additive, delivering the desired product **3aa** in 81% yield (72% isolated yield; entries 2-8). Replacing the additive $BF_3 \cdot Et_2O$ with other Lewis Acid ($FeCl_3$ and $Sc(OTf)_2$) resulted in less efficiency (entries 9 and 10). Moreover, the employment of Brønsted acid (PivOH and CF_3CO_2H) as additive led to a significant decrease in the yield (entries 11 and 12). The reaction did not afford the coupling product in the absence of $BF_3 \cdot Et_2O$ or copper catalyst (entries 13 and 14). Then the screening of solvent and reaction temperature indicated that DMSO was irreplaceable for the coupling and the reaction at 105 °C gave the best result (entries 15 and 19).

Having identified the optimized reaction conditions, we next investigated the scope of methyl ketone derivatives with

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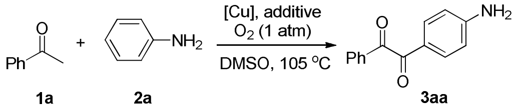
aniline **2a** as coupling partner. As shown in Table 2, a broad range of electron-withdrawing and electron-donating substituents at the aryl *para* position of acetophenone were well tolerated, delivering the corresponding products (**3aa**-**3la**) in moderate to good yields. It was worth noting that the functional groups typically sensitive to low-valent transition metals or strong oxidative conditions, such as iodide, hydroxyl, benzyl ether, thioether, nitrile, and nitro on the benzene ring, were compatible, enabling the products for further transformations. Acetophenone bearing methoxy and amide groups at the *meta* position of the aryl ring reacted smoothly with **2a** to provide the desired product **3ma** and **3na** in 80% and 51% yield, respectively. 1-(2-Methoxyphenyl)ethanone furnished the corresponding product **3oa** in a slightly attenuated yield, presumably due to the steric hindrance of the *ortho* substituent. In addition, 1-(naphthalen-1-yl)ethanone and 1-(naphthalen-2-yl)ethanone gave products **3qa** and **3ra** in moderate yields. Satisfyingly, heteroaromatic methyl ketone **1s** performed well to afford the coupled product **3sa** in 57% yield. Notably, alkyl substituted methyl ketone **1t** (1-cyclopropylethanone) was identified to be a suitable substrate, although only 35% yield was obtained.

Table 1 Optimization of the reaction conditions[a]

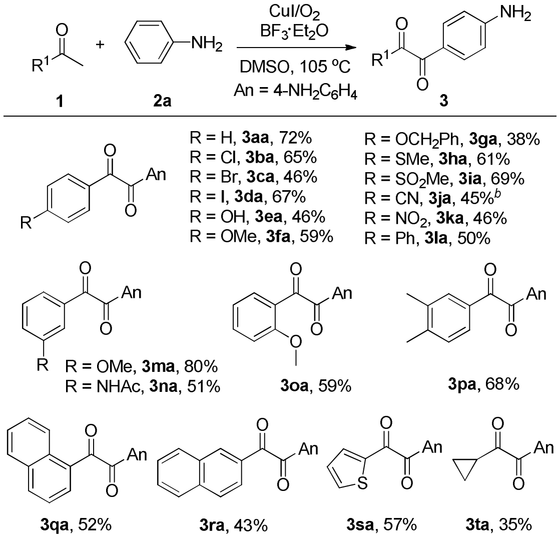


entry	[Cu] catalyst	additive	yield[b]
1	$Cu(OTf)_2$	-	trace
2	$Cu(OAc)_2$	$BF_3{\cdot}Et_2O$	23
3	$Cu(TFA)_2$	$BF_3{\cdot}Et_2O$	58
4	$CuBr_2$	$BF_3{\cdot}Et_2O$	42
5	$CuCl_2$	$BF_3{\cdot}Et_2O$	53
6	CuCl	$BF_3{\cdot}Et_2O$	51
7	CuBr	$BF_3{\cdot}Et_2O$	70
8	CuI	$BF_3{\cdot}Et_2O$	81(72[c])
9	CuI	$FeCl_3$	40
10	CuI	$Sc(OTf)_2$	58
11	CuI	PivOH	22
12	CuI	CF_3CO_2H	trace
13	CuI	-	trace
14	-	$BF_3{\cdot}Et_2O$	ND
15[d]	CuI	$BF_3{\cdot}Et_2O$	15
16[e]	CuI	$BF_3{\cdot}Et_2O$	trace
17[f]	CuI	$BF_3{\cdot}Et_2O$	ND
18[g]	CuI	$BF_3{\cdot}Et_2O$	75
19[h]	CuI	$BF_3{\cdot}Et_2O$	80

[a] Reaction conditions: acetophenone **1a** (0.3 mmol, 1.0 equiv), aniline **2a** (0.33 mmol, 1.1 equiv), copper catalyst (5 mol%), and additive (20 mol%) in 0.5 mL of DMSO at 105 °C for 14 h. [b] GC yield based on **1a** is given. [c] Isolated yield. [d] DMF as the solvent. [e] DMA as the solvent. [f] Toluene as the solvent. [g] At 100 °C. [h] At 110 °C. ND = not detected.

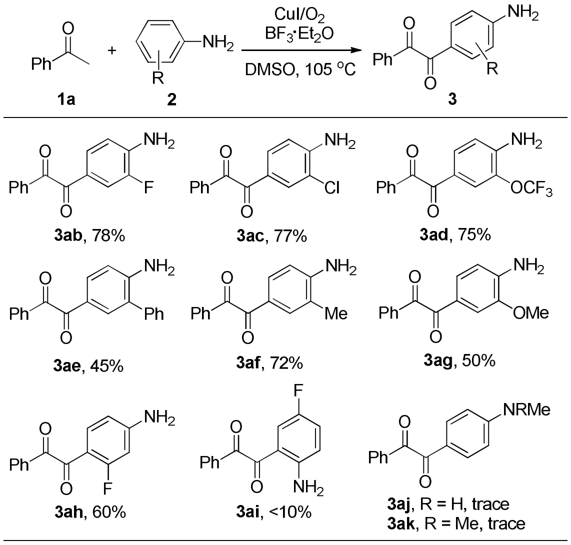
With the methyl ketones scope established, we then turned our attention to the generality and the limitation of aniline derivatives (Table 3). A variety of *ortho* substituted anilines smoothly underwent the cross dehydrogenative coupling with acetophenone, generating the desired products (**3ab**-**3ag**) in moderate to good yields. 3-Fluoroaniline was also productive in the reaction, yielding the coupled product **3ah** in 60% yield. Then, 4-fluoroaniline was tested to examine whether the coupling reaction could proceed in the *ortho* position of anilines, however, <10% yield was observed. Unfortunately, N-substituted anilines (**2j** and **2k**) were unsuccessful in the coupling reaction with acetophenone in this protocol, only trace of the desired product was detected.

Table 2 The coupling of anilineyu with methyl ketones[a]



[a] Reaction conditions: methyl ketone **1** (0.3 mmol, 1.0 equiv), aniline **2a** (0.33 mmol, 1.1 equiv), CuI (5 mol %), and $BF_3{\cdot}Et_2O$ (20 mol%) in 0.5 mL of DMSO at 105 °C for 14 h. Isolated yields. [b] The reaction was performed for 4 h.

Table 3 The coupling of acetophenone with anilines[a]



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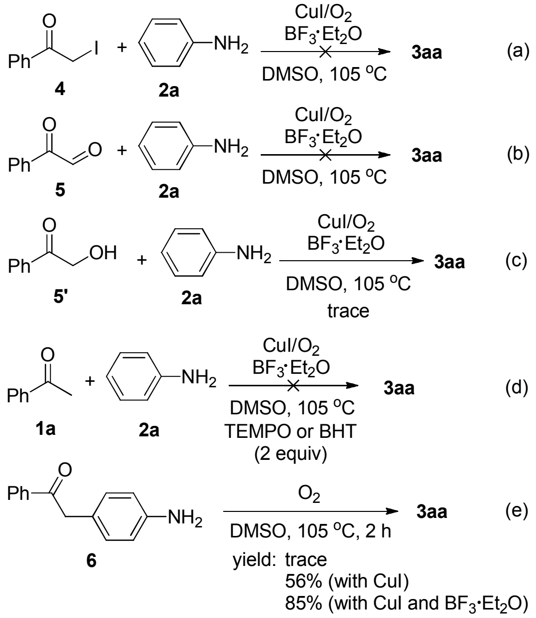
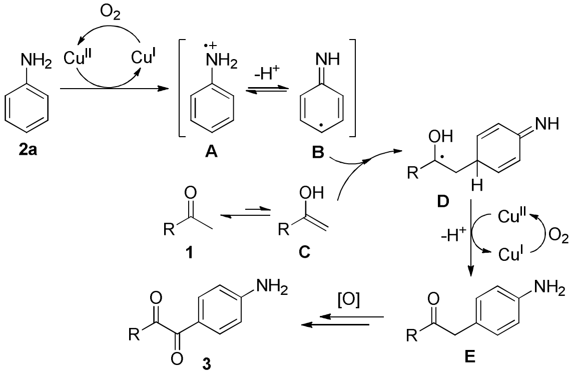
[a] Reaction conditions: acetophenone **1a** (0.3 mmol, 1.0 equiv), aniline derivatives **2** (0.33 mmol, 1.1 equiv), CuI (5 mol%), and $BF_3 \cdot Et_2O$ (20 mol%) in 0.5 mL of DMSO at 105 °C for 14 h. Isolated yields.

With respect to the reaction mechanism of *para*-functionaliztion of anilines, a Friedel-Crafts-type pathway is generally involved. In the present system, however, nitrogen-alkyl-substituted anilines featured very low reactivity, which goes against the Friedel–Crafts-type mechanism. Then 2-iodo-1-phenylethanone (**4**), phenylglyoxal (**5**) and 2-hydroxy-1-phenylethanone (**5'**) were proposed to be the key intermediates. However, neither **4** nor **5** furnished the target **3aa** in the present copper catalytic system (Scheme 2a-b), and trace amount of product was detected with 2-hydroxy-1-phenylethanone (Scheme 2c). Furthermore, the addition of radical trapping reagent TEMPO or BHT completely quenched the transformation (Scheme 2d), which revealed that this reaction probably involved a radical pathway. Finally, amino-1,2-diphenylethanone **6**, prepared by known method,[10] was found highly active to transform into **3aa** under the standard catalytic system within 2 h, while much lower yield was obtained in the absence of trifluoroborane and trace amount of **3aa** was given in the case of no any catalyst (Scheme 2e), indicating compound **6** might be a crucial intermediate in this copper/O_2 catalytic system.



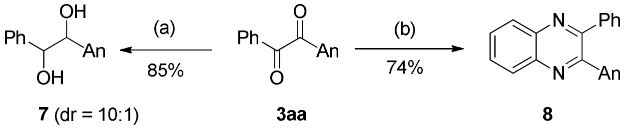
Scheme 2 Mechanistic investigations.

Based on the mechanistic investigations described above, a plausible mechanism for the reaction is given in Scheme 3. The reaction is initiated by the single electron transfer of aniline **2a** to Cu^{II} species, which is generated by the oxidation of Cu^{I} catalyst with molecular oxygen. The radical cation **A** tends to lose H^+ and tautomerize into cyclohexadienyl radical **B**, which is captured by methyl ketone **1** in its enol form **C** to deliver intermediated **D**. The single electron oxidation of **D** by Cu^{II} species and subsequent loss of H^+ results in intermediate **E**, which is further oxidized to the final product **3**. We speculate the reasion for the unsuccessful N-methylanilines is the much better stability of N-centred radical (**A**) than cyclohexadienyl radical (**B**). Actually, couplings of N-methylanilines at the methyl group have been widely investigated.[1]



Scheme 3 Proposed mechanism.

The resultant 1,2-diketones are versatile building blocks as handle for further manipulations. For example, the reduction of **3aa** with $NaBH_4$ afforded 4-aminophenyl 1,2-diol **7** in excellent yield. And the annulation of **3aa** through condensation with benzene-1,2-diamine under Lewis acid treatment gave 4-aminophenyl quinoxaline **8** in 74% yield.



Scheme 4 Transformation of the resultant diketone **3aa**. Reaction conditions: (a) **3aa** (0.2 mmol), $NaBH_4$ (2 equiv), H_2O (2 equiv), THF (0.2 M), reflux, 0.5 h; (b) **3aa** (0.2 mmol), benzene-1,2-diamine (1.2 equiv), $FeCl_3$ (2 equiv), EtOH (0.2 M), 65 °C, 12 h. An = 4-$NH_2C_6H_4$.

In conclusion, we have developed a copper-catalyzed oxidative cross dehydrogenative coupling reaction of methyl ketones with free anilines under molecular oxygen. This reaction is highly regioselective to proceed at the *para* position of anilines, providing an easy access to a series of *p*-aminophenyl diketone derivatives. Moreover, the extraordinarily broad functional-group tolerance, as well as the employment of green oxidant (O_2), makes this protocol an attractive strategy in synthetic chemistry. Further research on diverse *para*-position functionalizations of anilines for the construction of C-C and C-heteroatom bonds is currently under investigation in our laboratory.

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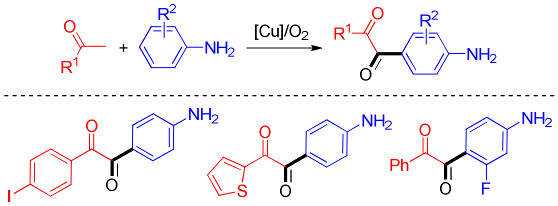

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