Organic & Biomolecular Chemistry

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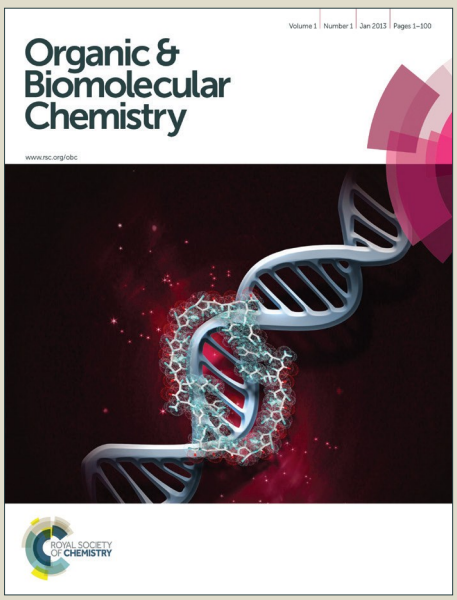

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DOI: 10.1039/C5OB02325D

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Iron-catalyzed direct α-arylation of α-amino carbonyl compounds with indoles†

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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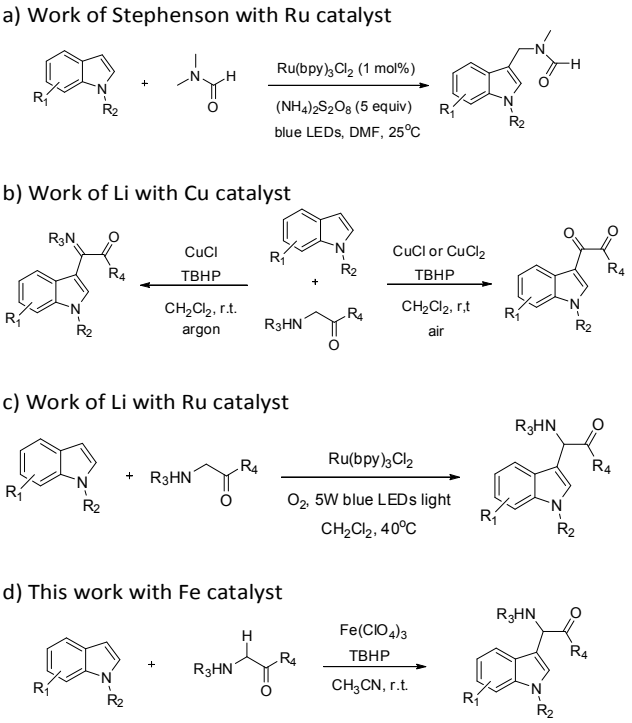
A mild and general α-arylation of α-amino carbonyls with indoles catalyzed by $Fe(ClO_4)_3$ has been developed. The C-H activation is smoothly fulfilled by using TBHP as the oxidant with good yields. Two hydrogen dissociations make this transformation more environmentally benign because of high atom efficiency.

Functionalization of α-C-H bonds of the carbonyl group in the α-amino carbonyl compounds is a hot topic in organic synthesis because the α-amino carbonyl motif is an important structure component of multitudinous natural products and biomolecules.[1-4] Many mild and general methods have been well-established for accessing this important motif. Among these efficient reactions for the functionalization of C-H bonds α to a carbonyl group, transition-metal-catalyzed α-arylation reactions are rare and are limited: the arylation reaction is realized through deprotonation (in situ generation of carbonyl enolate) with the aid of a base and requires the use of expensive aryl sources with the aid of transition metal catalysis.[5-9]

Recently, some transition-metal-catalyzed α-arylation of α-amino carbonyls leading to nonnaturally α-arylated aminocarbonyl compounds from cleavage of α-C-H bond without the aid of base have been researched. Stephenson[10] and co-workers reported the $Ru(bpy)_2Cl_2$-catalyzed Friedel-Crafts amidoalkylation (Scheme 1a). It was achieved by oxidation of dialkylamides using an oxidant persulfate under the visible light at room temperature via a reactive N-acyliminium intermediate. In light of the pharmaceutical activity of indole motif, almost at the same time, Li[11] and co-workers reported a base-free copper-catalyzed α-arylation of α-amino carbonyls with indoles in the presence of *tert*-butyl hydroperoxide (TBHP) through a C-H oxidation strategy. However, 2-(1*H*-indo-3-yl)-2-imino-carbonyls and 2-(1*H*-indo-3-yl)-2-oxo-carbonyls, not α-amino carbonyl products, were selectively obtained as the terminal products under argon or air atmosphere (Scheme 1b). Then, after a series trials, they found a visible-light photoredox catalysis strategy for 2-(1*H*-indo-3-yl)-2-amino-carbonyl compounds synthesis by direct α-arylation between α-amino carbonyl compounds and indoles with the aid of $Ru(bpy)_3Cl_2$, 5W LEDs light and O_2, avoiding both the uses of bases and the conversions of the amino groups into imino groups in the products (Scheme 1c).[12]



Scheme 1 Transition-metal-catalyzed α arylation of α-amino carbonyl compounds

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[1] These two authors contributed equally to this work and should be considered co-first authors.

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and spectra of new compounds. For ESI See DOI: 10.1039/x0xx00000x

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However, to our knowledge, iron-catalyzed α arylation of α-amino carbonyls using a C-H oxidation strategy has not been established. Based on our research, [13] herein we report a novel and mild route to the C-H oxidation/cross-coupling of α-amino carbonyl compounds with indoles catalyzed by iron catalysis in the presence of TBHP (Scheme 1d).

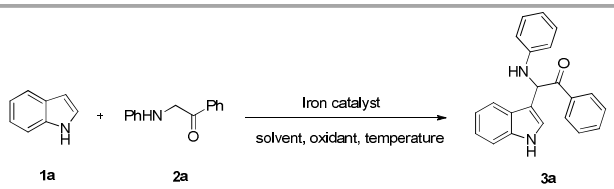
Our investigation began with the reaction of 1*H*-indole (**1a**) and 1-phenyl-2-(phenylamino)ethanone (**2a**) and 15 mol% $FeCl_2$ in CH_3CN at room temperature under air atmosphere (Table 1): a trace of desired 2-(1*H*-indo-3-yl)-1-phenyl-2-(phenylamino)ethanone (**3a**) was observed (entry 1). These results encouraged us to optimize the other reaction parameters. After a series of trials, we were pleased to find that the yield of **3a** could be enhanced in the presence of oxidants, including benzoyl peroxide (BPO), di-*tert*-butyl peroxide (DTBP) and *tert*-butyl hydroperoxide (TBHP) (entries 2-4). Subsequently, a series of other iron catalysts, including $FeCl_2$, $FeCl_3$, $Fe(ClO_4)_3$, $Fe_2(SO_4)_3$, $Fe(NO_3)_3$ were tested and $Fe(ClO_4)_3$ displayed higher catalytic efficiency for the reaction in the presence of TBHP (entries 5-8). It is noteworthy that the reaction cannot take place without an iron catalyst (entry 9). Gratifying, good yields were still achieved when using either 15 mol% or 10 mol% $Fe(ClO_4)_3$, but the latter required a prolonged reaction time (entry 10). Among the effect of solvents examined, it turned out that CH_3CN was the most effective solvents examined, while both toluene and CH_2Cl_2 displayed a lower effect, the reaction in EtOH still gave moderate yield (entries 11-13). Finally, the reactions at 40°C and 60°C were tested: they could take place, but low yields were isolated because of the synthesis of some unidentified products (entries 14-15).

With the optimal reaction conditions in hand, the scope of both indoles **1** and the α-amino ketones **2** was explored (Table 2). In the presence of 1*H*-indole (**1a**), $Fe(ClO_4)_3$ and TBHP, a number of other arylamino groups in α-amino carbonyls were initially investigated. For 1-phenyl-2-aminoethanones having Me-substituted phenylamino groups, the order of the reactivity is *meta*>*ortho*> H in terms of yields (compounds **3a**-**3c**). No product was found with *para*-Me phenylamino group. The results demonstrated that substituents, such as phenylamino, *o*-tolylamino groups, in 2-amino-1-*p*-tolylethanones were compatible with the optimal conditionds (compounds **3d**, **3e**). Interestingly, halo substituent such as Cl, on the aryl ring of the arylethanone moiety was consistent with the optimal conditions (compound **3f**).

The optimal conditions were found to be viable for a wide range of indloes with high substituents compatibility: several substituents, including Me, Br, Cl and aryl groups, on the aromatic ring of indoles were well-tolerated in the presence of 1-phenyl-2-phenylaminoethanone (**2a**), 1-phenyl-2-(*o*-tolylamino)ethanone (**2b**), 1-phenyl-2-(*m*-tolylamino)ethanone (**2c**), 1-*p*-tolyl-2-(*o*-tolylamino)ethanone (**2e**) and 1-(*p*-chlorophenyl)-2-(*o*-tolylamino)ethanone (**2f**). For example, treatment of 5-Me-substituted indole with **2a**, **2b**, **2c**, **2e**, **2f**, $Fe(ClO_4)_3$ and TBHP afforded the corresponding **3g**, **3j**, **3m**, **3p**, **3s** in 32%, 41%, 61%, 46% and 35% yields, respectively. Halo substituents, Cl and Br, on the indole ring were compatible with optimal conditions (compounds **3h**, **3i**, **3k**, **3l**, **3n**, **3o**, **3q**, **3r**). Gratifyingly, substituents, Me or aryl, at the 2- and 6-position of indoles were also compatible with the optimal conditions. In the presence of $Fe(ClO_4)_3$ and TBHP, 2-methyl-1*H*-indole and 6-methyl-1*H*-indole successfully underwent the arylation reaction with 1-phenyl-2-(*o*-tolylamino)ethanone (**2b**) leading to the desired product **3t** and **3u** in moderate yields (58% and 36%). Screening revealed that indoles with a phenyl displayed high reactivity under the same conditions, furnishing the target product in moderate yield (compounds **3v** and **3w**). Finally, substituents on the nitrogen atom of indole moiety were tested, 1-methyl indole and 1-benzyl indole were successfully reacted with 1-*p*-tolyl-2-(*o*-tolylamino)ethanone (**2e**) $Fe(ClO_4)_3$ and TBHP in good yields (compounds **3x** and **3y**).

The reactions of indoles **1** and α-amino esters **2** were also explored. α-Amino esters with methyl and ethyl substituted were all consistent with the optimal conditions (compounds **3z**-**3oo**).

Table 1 Optimization of the Iron-catalyzed direct α-arylation between α-amino carbonyl compound and indole[a]



Entry	[Fe] (mol%)	Oxidant	Solvent	Temperature	Yield (%)[b]
1	$FeCl_2$(15)	air	CH_3CN	r.t.	8
2	$FeCl_2$(15)	BPO	CH_3CN	r.t.	18
3	$FeCl_2$(15)	DTBP	CH_3CN	r.t.	22
4	$FeCl_2$(15)	TBHP[c]	CH_3CN	r.t.	30
5	$FeCl_3$(15)	TBHP	CH_3CN	r.t.	18
6	$Fe(ClO_4)_3$(15)	TBHP	CH_3CN	r.t.	63
7	$Fe_2(SO_4)_3$(15)	TBHP	CH_3CN	r.t.	31
8	$Fe(NO_3)_3$(15)	TBHP	CH_3CN	r.t.	16
9	—	TBHP	CH_3CN	r.t.	0
10	$Fe(ClO_4)_3$(10)	TBHP	CH_3CN	r.t.	62
11	$Fe(ClO_4)_3$(10)	TBHP	CH_2Cl_2	r.t.	25
12	$Fe(ClO_4)_3$(10)	TBHP	toluene	r.t.	33
13	$Fe(ClO_4)_3$(10)	TBHP	EtOH	r.t.	51
14	$Fe(ClO_4)_3$(10)	TBHP	CH_3CN	40°C	41
15	$Fe(ClO_4)_3$(10)	TBHP	CH_3CN	60°C	35

[a] Reaction conditions: 1*H*-indole (**1a**) (0.5 mmol), 1-phenyl-2-(phenylamino)ethanone (**2a**) (0.5 mmol), iron catalysis, solvent (3mL), oxidant (1 equiv) under air atmosphere for 10-12h. [b] Isolated yield. [c] TBHP (5.0-6.0 M in decane).

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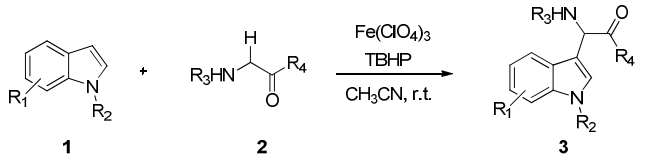
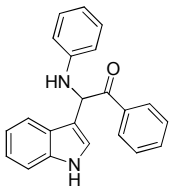
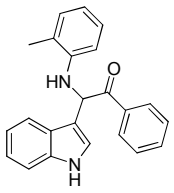
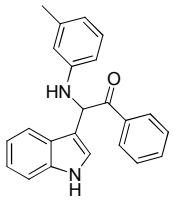
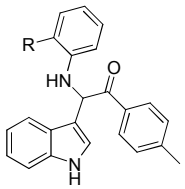
Table 2 Iron-catalyzed direct α-arylation between α-amino carbonyl compounds and indoles[a, b]

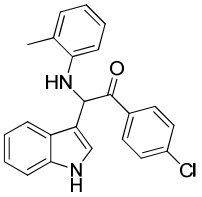


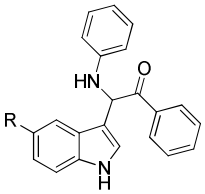

3a, 62%

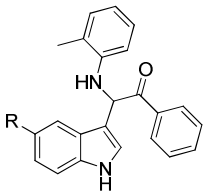

3b, 70%

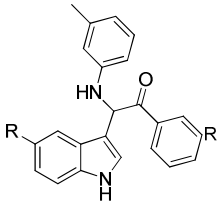

3c, 83%

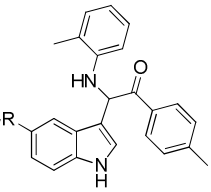

R = H, **3d**, 43%
R = CH_3, **3e**, 41%

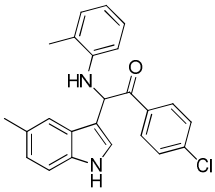

3f, 35%

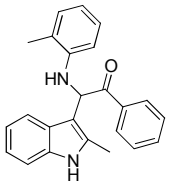

R = Me, **3g**, 32%
R = Cl, **3h**, 48%
R = Br, **3i**, 47%

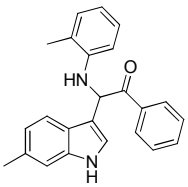

R = Me, **3j**, 41%
R = Cl, **3k**, 62%
R = Br, **3l**, 64%

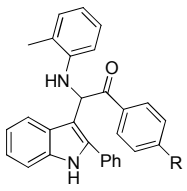

R = Me, **3m**, 58%
R = Cl, **3n**, 48%
R = Br, **3o**, 46%

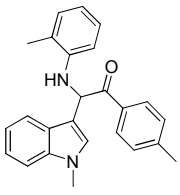

R = Me, **3p**, 32%
R = Cl, **3q**, 76%
R = Br, **3r**, 58%

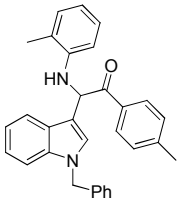

3s, 35%

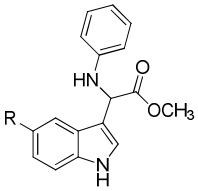

3t, 58%

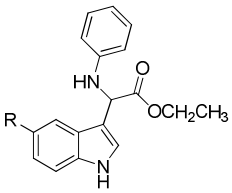

3u, 58%

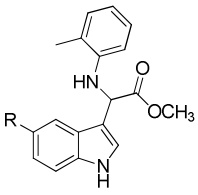

R = CH_3, **3v**, 39%
R = Cl, **3w**, 56%

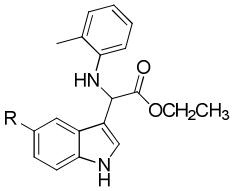

3x, 34%


3y, 3o%


R = H, **3z**, 71%
R = Me, **3aa**, 67%
R = Cl, **3bb**, 63%
R = Br, **3cc**, 59%


R = H, **3dd**, 68%
R = Me, **3ee**, 75%
R = Cl, **3ff**, 70%
R = Br, **3gg**, 65%


R = H, **3hh**, 58%
R = Me, **3ii**, 49%
R = Cl, **3jj**, 61%
R = Br, **3kk**, 60%


R = H, **3ll**, 61%
R = Me, **3mm**, 68%
R = Cl, **3nn**, 71%
R = Br, **3oo**, 69%

[a] Reaction conditions: indole (**1**) (0.5 mmol), α-amino carbonyl compound (**2**) (0.5 mmol), $Fe(ClO_4)_3$ (10 mmol%), CH_3CN (3mL), TBHP (1 equiv, 5.0-6.0 M in decane) under air atmosphere for 10-12h. [b] Isolated yield.

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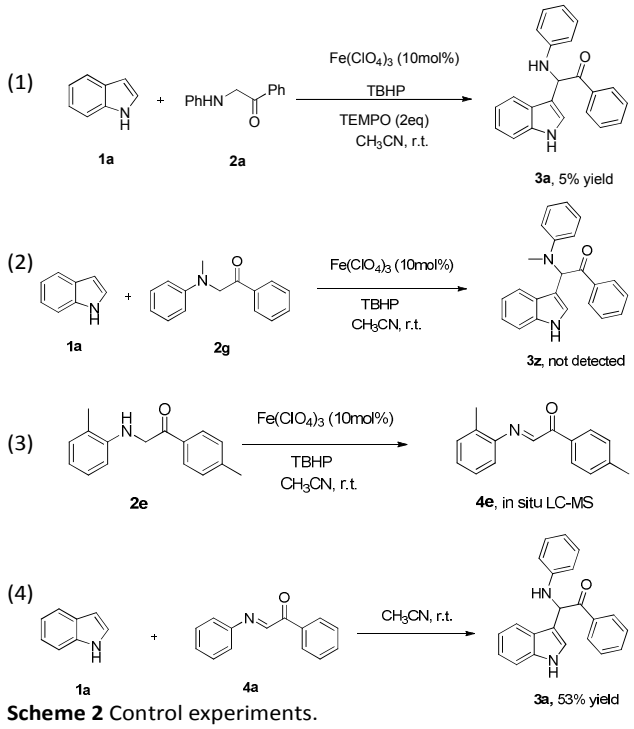
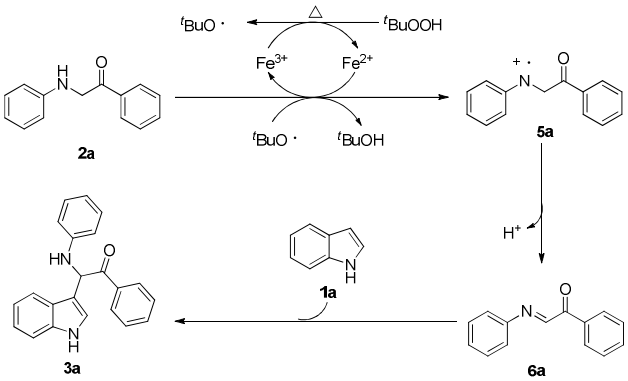


Scheme 2 Control experiments.



Scheme 3 Possible mechanism.

To gain insight into the Fe-catalyzed α-arylation of α-amino carbonyls, several control experiments were carried out to elucidate the mechanism. As shown in Scheme 2, a model reaction was performed again with an additional 2 equiv. of radical inhibitor 2,2,6,6-tetramethylpiperidinooxy (TEMPO), and the formation of **3a** was completely inhibited (eq 1), which implies that a radical species may be involved in this reaction. Substrate **2g** with a tertiary amine group was not viable for the reaction under the optimal conditions (eq 2). **2e** with 10 mol % of $Fe(ClO_4)_3$ was reacted in the presence of oxidant (TBHP) but in the absence of indole **1a**. The in situ LC-MS analysis of the resulting mixture did not show any signals corresponding to amino peroxide. The only new species identifiable was the iminium[14] (eq 3). As expected, treatment of indole **1a** with 1-(*p*-tolyl)-2-(*o*-tolylimino)ethanone **4a**[15] offered the desired product **3a** in the absence of both iron catalyst and TBHP.

Based on the present results and relevant literature,[16-20] a possible mechanism outlined in Scheme 3 was proposed. TBHP decomposes into *tert*-butoxyl radical and hydroxyl anion in the presence of the ferrous catalyst. Subsequently, a single electron transfer (SET) from *tert*-butoxyl radical to 1-phenyl-2-(phenylamino)ethanone **2a** takes place to offer the radical intermediate **5a**. The radical intermediate **5a** readily undergoes the deprotonation reaction leading to imine intermediate **6a**. Finally, the reaction of indole **1a** with intermediate **6a** affords the desired product. Overall, the Fe^{2+}-Fe^{3+} redox processes play key roles in the present α-arylation of amino carbonyl compound, which are the reductive heterolytic cleavage of O-O bond in the peroxide, the SET reaction of 1-phenyl-2-(phenylamino)ethanone and the oxidation of the intermediate **5a** to imine intermediate **6a**.

In summary, we have demonstrated a novel and efficient protocol for the α-arylation of α-amino carbonyl compounds via cross dehydrogenative couplings catalyzed by $Fe(ClO_4)_3$. The reaction proceeds with high functional group tolerance and broad substrate scope to give the nonnatural α-amino carbonyl compounds which are extremely useful synthetic intermediates in the construction of biologically important compounds.

We thank for the National Natural Science Foundation of China (No. 21302067), the National Natural Science Foundation of Jiangsu Province (No. BK20130120) and National Undergraduate Training Programs for Innovation and Entrepreneurship (201510295049) for financial support.

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