Preparation of indoles *via* iron catalyzed direct oxidative coupling⁺

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Iron-catalyzed aryl C-H and vinyl C-H bonds activation to give valuable substituted indole products was reported. The reaction shows high functional group tolerance.

Iron salts have been extensively investigated as alternative and promising catalysts for many organic transformations because of their ready availability, low price and environmentally friendly characters.¹ Recently, iron catalyzed carbon-carbon² and carbon-heteroatom³ cross-coupling reactions have been successfully developed. Iron catalyzed C-H bond activation⁴ and functionalization for C-C bond formation reactions have also been reported by several groups. Nakamura et al. described an efficient iron catalyzed ortho arylation of aryl C-H bonds under mild conditions.⁵ Li *et al.* developed an iron catalyzed carbon-carbon bond formation via activation of benzylic C-H bonds or C-H bonds adjacent to heteroatoms.⁶ Yu and co-workers reported an iron mediated arylation of aryl C-H bond using arylboronic acid.⁷ However, in comparison with other transition metals, such as Pd,⁸ Rh,⁹ Ru,¹⁰ iron catalyzed C-H bond activation and functionalization has remained largely undeveloped.11

The indole unit is probably the most abundant and ubiquitous heterocycle in natural products and pharmaceuticals.^{12,13} Although there are numerous methods for the preparation of indole and its derivatives,¹⁴ it is highly desirable to synthesize this type of molecule via direct C-H bond functionalization.¹⁵ It is required to explore a new catalyst system that involves cheap and environmentally friendly catalysts, albeit some important progress has been made by Glorius et al. using palladium as the catalyst.¹⁶ Herein, we report an efficient iron catalyzed intramolecular oxidative coupling of aryl C-H and vinyl C-H bonds for preparation valuable substituted indole products.

We initiated our investigation by cyclization of methyl 3-(phenylamino)but-2-enoate 1a to form the corresponding indole 2a (Table 1). We were pleased to find that treating 1a with FeCl₃ (10 mol%), CuCl₂ (3 equiv.), K₂CO₃ (3 equiv.) in DMF resulted in a moderate but promising yield of the cyclization product 2a (Table 1, entry 1). Screening of other Cu salts, such as Cu(OAc)₂, CuBr₂ and CuO as the oxidant showed that only moderate yields of 2a were obtained

Table 1 Optimization of Fe-catalyzed direct C-H activation reaction^a

	MeO ₂ C	solvent, base	→ 2a	CO ₂ Me	
Entry	Catalyst	Oxidant	Base	Solvent	Yield ^b (%)
1	FeCl ₃	CuCl ₂	K ₂ CO ₃	DMF	44
2	FeCl ₃	Cu(OAc) ₂	K ₂ CO ₃	DMF	15
3	FeCl ₃	CuBr ₂	K ₂ CO ₃	DMF	43
4	FeCl ₃	CuO	K ₂ CO ₃	DMF	18
5	FeCl ₃	Cu(OTf) ₂	K ₂ CO ₃	DMF	d
6	FeCl ₃	Tempo	K ₂ CO ₃	DMF	<10
7	FeCl ₃	Oxone	K ₂ CO ₃	DMF	30
8	FeCl ₃	$K_2S_2O_8$	K ₂ CO ₃	DMF	<10
9	FeCl ₃	PhI(OAc) ₂	K ₂ CO ₃	DMF	<10
10	FeCl ₃	$Cu(OAc)_2 \cdot CuCl_2^c$	K ₂ CO ₃	DMF	72
11	FeCl ₃	Cu(OAc) ₂ /CuCl ₂	K ₂ CO ₃	DMF	36
12	FeCl ₃	$Cu(OAc)_2 CuCl_2^c$	K ₂ CO ₃	Dioxane	<10
13	FeCl ₃	$Cu(OAc)_2 \cdot CuCl_2^c$	K ₂ CO ₃	Toluene	<10
14	FeCl ₃	$Cu(OAc)_2 \cdot CuCl_2^c$	Cs_2CO_3	DMF	31
15	FeCl ₃	$Cu(OAc)_2 \cdot CuCl_2^c$	Na ₂ CO ₃	DMF	50
16	FeCl ₂	$Cu(OAc)_2 \cdot CuCl_2^c$	K ₂ CO ₃	DMF	70
17	Fe(acac) ₃	$Cu(OAc)_2 \cdot CuCl_2^c$	K ₂ CO ₃	DMF	68
18	Fe(acac) ₂	$Cu(OAc)_2 \cdot CuCl_2^c$	K ₂ CO ₃	DMF	65
19	FeSO ₄	$Cu(OAc)_2 \cdot CuCl_2^c$	K_2CO_3	DMF	55
20		$Cu(OAc)_2 \cdot CuCl_2^c$	$\tilde{K_2CO_3}$	DMF	15
21	CuI/phen		Cs_2CO_3	DMF	n.r.
22	>99.99% FeCl ₃ ^f	$Cu(OAc)_2 \cdot CuCl_2^c$	K ₂ CO ₃	DMF	70
23	FeCl ₂	$Cu(OAc)_2 \cdot CuCl_2^c$	K_2CO_3	DMF	22^e
a Read	tion conditio	ns: 1a (0.2 mmol) E	Fe catalyst (10 mol%	oxidant

Reaction conditions: 1a (0.2 mmol), Fe catalyst (10 mol%), oxidant (0.6 mmol), base (0.6 mmol), in solvent (2 mL) at 120 °C for 2 h. Isolated yield. ^c See ESI for details. ^d 1a was decomposed. ^e The reaction under Ar atmosphere. ^f Aldrich.

(Table 1, entries 2–4). The use of $Cu(OTf)_2$ as the oxidant resulted in the rapid decomposition of the substrate 1a and therefore aniline was obtained in 60% yield (Table 1, entry 5). Other oxidants such as TEMPO, Oxone, K₂S₂O₈, PhI(OAc)₂ were employed, but did not improve the yield of 2a as well (Table 1, entries 6-9). To our delight, when the complex of Cu(OAc)₂·CuCl₂ was used as the oxidant, the reaction proceeded smoothly to give the indole product 2a in 72% yield (Table 1, entry 10). However, a physical mixture of $Cu(OAc)_2$ and $CuCl_2$ shows no special characteristics in the transformation (Table 1, entry 11). Further experiments indicated that DMF was the best solvent and K₂CO₃ was the most suitable base for this transformation (Table 1, entries 12-15). No significant improvement of the yield of the desired product 2a was observed when other iron salts were used as the catalyst, such as FeCl₂, Fe(acac)₃, Fe(acac)₂ and FeSO₄ (Table 1, entries 16–19).¹⁷ Control experiments

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confirmed that only low conversion was obtained in the absence of the iron catalyst (Table 1, entry 20). Very recently, a similar transformation of *N*-aryl enaminone to the indole skeleton using CuI as the catalyst has been reported.¹⁸ However, the reaction of methyl 3-(phenylamino)but-2-enoate **1a** did not proceed under the reported conditions (Table 1, entry 21).¹⁸ This experiment indicated that the reaction of 3-phenylamino)but-2-enoate derivatives possibly proceed from a different pathway than the reaction of *N*-aryl enaminones.¹⁹

Under the optimized conditions, for this direct C-H activation process, we have explored the substrate scope. The results are summarized in Table 2. This transformation displayed high functional group tolerance. Arenes with methyl, methoxyl, acetyl and chloro groups all gave moderate to good yields of corresponding indoles (Table 2). In general, better yields were obtained with arenes possessing an electron-donating group at the para position compared to those with same substituent at the *ortho* position (Table 2, entries 2-3, ²⁰ and 6-7). Similarly, higher yields were obtained with arenes possessing an electronwithdrawing grope at the ortho position rather than at the para position (Table 2, entries 9-10).²¹ Furthermore, the reaction was insensitive to the steric hindrance of the substitutent on the arenes. Arenes possessing a methyl group at the meta position gave a 2:1 ratio of the 4- and 6-substituted indole regioisomers (Table 2, entries 4-5), contrary to palladium catalyzed reaction of this type, while an arene with chloro substituent at the meta position resulted in a ratio of 1:1 of the two regioisomers (Table 2, entry 11). In addition, the substrate derived from naphthylamine also underwent the desired reaction to give the corresponding product 2j in good yield (Table 2, entry 12).

Notably, cyclization of arenes bearing a Br or I substitutent were achieved by this iron catalyzed C-H activation reaction (Table 3). Methyl 7-bromo-2,5-dimethyl-1H-indole-3-carboxylate 20 was formed exclusively in 70% yield (Table 3, entry 2) while the 5-bromoindole derivative 2n was obtained with slightly lower yield (Table 3, entry 1). An arene possessing an iodo group at the ortho position resulted in 37% of the product 2q along with 30% yield of the C-I cross coupling product 2b (Table 2, entry 4). These results were superior to those obtained by using palladium or copper as the catalyst.^{16,18} Evidently, the iron catalyst exhibits different properties from the palladium in this C-H activation reaction.²² In this manner, the resulting Br or I substituted indole products, which are versatile building blocks for subsequent synthetic modification, could be further expanded to a wider variety of functionalized indoles by undergoing cross-coupling reactions.²³ That is a distinct advantage of this indole synthesis.

In light of the foregoing experiments, a proposed mechanism for the present oxidative coupling reaction is shown in Scheme 1. As previously mentioned, the copper(II) promoted coupling reaction of methyl 3-(phenylamino)but-2-enoate **1a** in the absence of iron catalyst did not proceed to an appreciable extent. Furthermore, the identical result was observed when >99.99% FeCl₃ was used as the catalyst (Table 1, entry 22).²⁴ However, control experiment shows that only low yield was obtained when FeCl₂ was employed under argon atmosphere (Table 1, entry 23). These results indicate that Fe(III) species probably act as the catalyst. Based on above





^{*a*} Reaction conditions: **1** (0.3 mmol), FeCl₃ (4.8 mg, 10 mol%), Cu(OAc)₂·CuCl₂ (142 mg, 0.45 mmol), K₂CO₃ (124 mg, 0.9 mmol), in DMF (3 mL) at 120 °C for 2 h. ^{*b*} Isolated yields (average of two runs). ^{*c*} K₂CO₃ (248 mg, 1.8 mmol) was used as the base and Na₂SO₄ (85 mg, 0.6 mmol) was used as the additive. ^{*d*} Bu₄NCl (166 mg, 0.6 mmol) was used as the additive.

results and previously reported,²⁵ we assumed that the copper and iron bimetallic chelate complex **B** would be formed by the coordination of the nitrogen and the double bond of **1a**, which would significantly enhance the reaction activity of the enoates. The key intermediate **C** is formed by electrocyclic ring closure. Finally, the subsequent proton elimination and tautomerization gives the indole product **2a**.

In summary, we have developed an efficient and general method for the iron catalyzed C–H activation reaction for preparation of functionalized indoles. This iron catalyzed C–H

Table 3 Exploration of the scope of the Fe-catalyzed direct C–Hactivation reaction a



^{*a*} Reaction conditions: **1** (0.3 mmol), FeCl₃ (4.8 mg, 10 mol%), Cu(OAc)₂·CuCl₂ (142 mg, 0.45 mmol), K₂CO₃ (124 mg, 0.9 mmol), in DMF (3 mL) at 120 °C for 2 h. ^{*b*} Isolated yields (average of two runs). ^{*c*} K₂CO₃ (248 mg, 1.8 mmol) was used as the base and Na₂SO₄ (85 mg, 0.6 mmol) was used as the additive. ^{*d*} Bu₄NCl (166 mg, 0.6 mmol) was used as the additive.



Scheme 1 Proposed mechanism.

activation reaction shows high functional group tolerance and exhibits different properties from the palladium catalyzed reactions of this type. The cheap and environmentally benign iron catalyst combined with the highly active Cu(OAc)₂·CuCl₂ makes this C–H activation reaction practical and attractive in organic synthesis.

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