Cross-Coupling

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Iron-Catalyzed Direct Oxidative Alkylation and Hydroxylation of Indolin-2-ones with Alkyl-Substituted N-Heteroarenes

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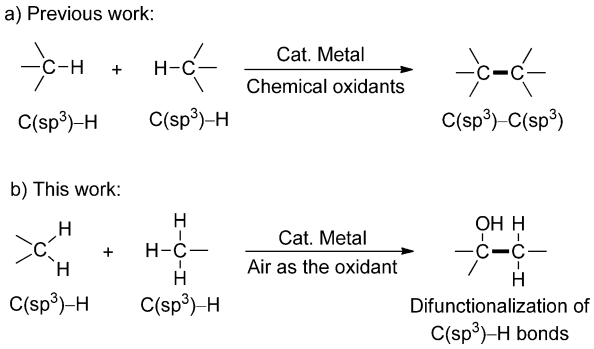
Abstract: *Presented herein is the first direct alkylation and hydroxylation reaction between two different C(sp³)–H bonds, indolin-2-ones and alkyl-substituted N-heteroarenes, through an oxidative cross-coupling reaction. The reaction is catalyzed by a simple iron salt under mild ligand-free and base-free conditions. The reaction is environmentally benign, employs air (molecular oxygen) as the terminal oxidant and oxygen source for the synthesis of O-containing compounds, and produces only water as the byproduct.*

The construction of C–C bonds is a fundamental transformation in organic synthesis. In the past few years, the transition-metal-catalyzed oxidative C(sp³)–H functionalization for construction of new C–C bonds has attracted great interest.[1] Among these reactions, the coupling reactions of two different C(sp³)–H bonds is the most attractive as it avoids the prefunctionalization steps for both substrates, and therefore saves times and reduces the waste (Scheme 1 a).[2]



Scheme 1. Transition-metal-catalyzed oxidative C(sp³)–H/C(sp³)–H cross-dehydrogenative coupling.

Despite tremendous progress being made, the rapid and efficient construction of C(sp³)–C(sp³) bonds by transition-metal catalysis remains a challenging issue.

The use of inexpensive and environmentally friendly catalysts instead of rare and expensive noble-transition-metal catalysts is highly desirable. Iron is the one of the most abundant metals in the Earth's crust. Iron salts are cheap, safe, stable, and have low toxicity, making them the ideal metal catalyst or reagent for chemical transformations.[3] Also, the use of molecular oxygen instead of traditional oxidation reagents is greatly desired. Molecular oxygen, especially air, is an ideal green oxidant because of it is inexpensive, has high atom economy, and is environmentally benign.[1a,4] More importantly, the use of molecular oxygen as the terminal oxidant and oxygen source for the construction of a C–O bond is one of the most ideal transformations in organic synthesis.[5] Therefore, combining the above two concepts, the use of iron catalyst systems with air (molecular oxygen) as the terminal oxidant and oxygen source for the construction of a C(sp³)–C(sp³) bond and C–O bond between two different C(sp³)–H bonds is highly desired (Scheme 1 b).

C3-difunctionalized indolin-2-ones are privileged structures found in a vast majority of natural molecules, pharmaceutical targets, and agrochemicals.[6] They exhibit a wide spectrum of biological activities such as antimicrobial, anticonvulsant, antitumor, antidepressant, and anti-HIV.[6,7] Particularly, C3-alkylated 3-hydroxyindolin-2-ones constitute a key structural feature in many alkaloid natural products and important compounds with pharmaceutical and biological activities (Figure 1).[6b,8] Here, we describe an unprecedented iron-catalyzed direct alkylation and hydroxylation reaction between two different C(sp³)–H bonds for the synthesis of C3-alkylated 3-hydroxyindolin-2-one derivatives. This work has achieved the following: 1) a novel iron-catalyzed C(sp³)–H difunctionalization, 2) formation of a C-(sp³)–C(sp³) bond between methyl and methylene groups, 3) use of air (molecular oxygen) as the terminal oxidant and

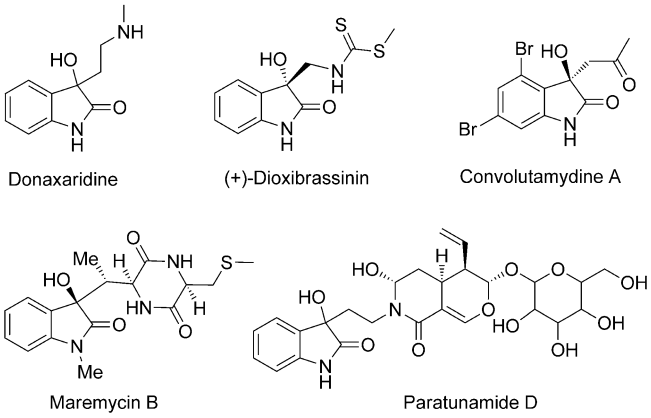


Figure 1. Selected biologically active and natural molecules containing C3-alkylated 3-hydroxyindolin-2-ones.

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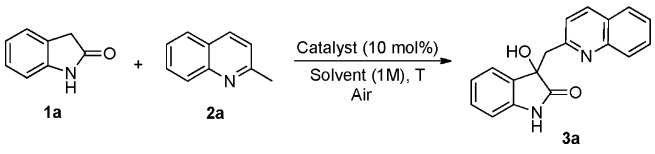
oxygen source for the synthesis of O-containing compounds, 4) use of mild, ligand-free, and base-free conditions (Scheme 1 b).

At the outset of our investigations, indolin-2-one (**1a**) and 2-methylquinoline (**2a**) were selected as the model substrates for the iron-catalyzed alkylation and hydroxylation reaction by using air as the sole oxidant (Table 1). Among the tested

Table 1: Optimization of the reaction conditions.[a]

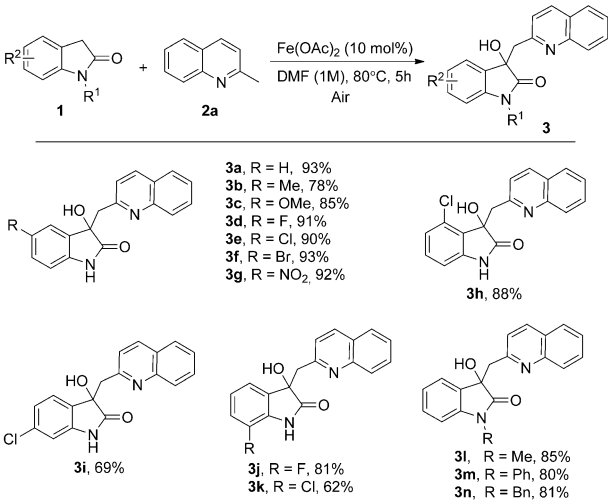


Entry	Cat (10 mol%)	Solvent [mL]	*T* [°C]	*t* [h]	Yield [%][b]
1	$FeCl_3$	EtOH	80	5	trace
2	$FeCl_3$	CH_3CN	80	5	trace
3	$FeCl_3$	1,4-dioxane	80	5	42
4	$FeCl_3$	PhCl	80	5	21
5	$FeCl_3$	DMF	80	5	45
6	$FeCl_3$	DMF	100	5	26
7	$FeCl_3$	DMF	120	5	23
8	$FeCl_3{\cdot}6H_2O$	DMF	80	5	47
9	$FeBr_3$	DMF	80	6	57
10	$Fe(NO_3)_3{\cdot}9H_2O$	DMF	80	6	62
11	$Fe(OTf)_3$	DMF	80	5	21
12	$Fe_2(SO_4)_3{\cdot}xH_2O$	DMF	80	7	65
13	$FeCl_2{\cdot}4H_2O$	DMF	80	5	54
14	$Fe(OAc)_2$	DMF	80	5	93
15	PhCOOH	DMF	80	6	–
16	*p*-TSA	DMF	80	6	–
17[c]	$Fe(OAc)_2$	DMF	80	7.5	93
18[d]	$Fe(OAc)_2$	DMF	80	7.5	90
19[e]	$Fe(OAc)_2$	DMF	80	7.5	84
20	–	DMF	80	6	–

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (10 mol%), solvent (1 mL), 80 °C, under open air, 5 h. [b] Yields of isolated products. [c] With 5 mol% catalyst. [d] With 1 mol% catalyst. [e] With 0.5 mol% catalyst. DMF = *N*,*N*′-dimethylformamide, Tf = trifluoromethanesulfonyl, TSA = toluene sulfonic acid.

solvents, DMF afforded the alkylation and hydroxylation product **3a** in a better yield of 45% (entry 5). However, raising the reaction temperature led to lower yields (entries 6 and 7). Next, various iron salts were evaluated in DMF, and the results were very encouraging (entries 8–14). All iron salts could facilitate the reaction, with $Fe(OAc)_2$ giving an excellent yield of up to 93% (entry 14). Other catalysts such as PhCOOH and *p*-TSA did not give any product (entries 15 and 16). Subsequently, we tried to reduce the amount of the catalyst. To our surprise, $Fe(OAc)_2$ was very efficient for this transformation. The same yield was obtained when the catalyst loading was decreased to 5 mol% (entry 17). Even when the amount of the catalyst was reduced to either 1 or 0.5 mol%, the reaction still proceeded smoothly to provide **3a** in good yields (entries 18 and 19). However, the $Fe(OAc)_2$ is very cheap, so we chose to use a higher catalyst loading to save time in the following reactions.

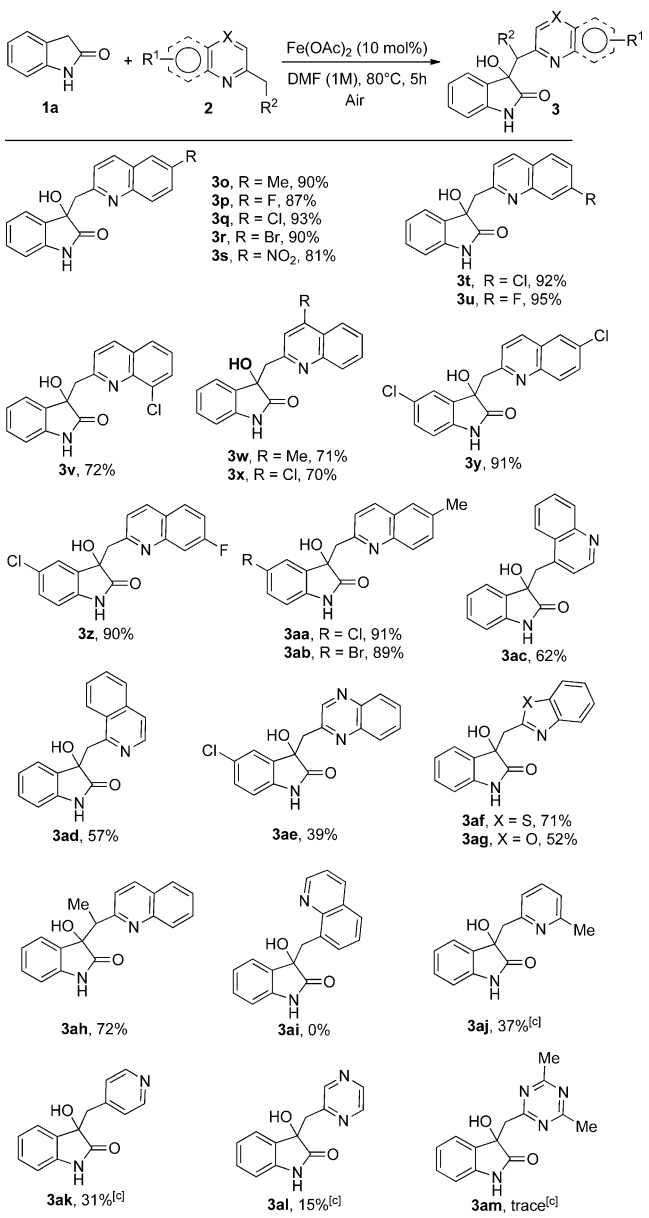
With the optimized reaction conditions in hand (Table 1, entry 14), we then carried out the alkylation and hydroxylation reaction between **2a** with various indolin-2-ones (Scheme 2). The 5-substituted indolin-2-ones with both electron-donating and electron-withdrawing substituents were all competent in the reaction, giving the desired products in good to excellent yields (**3b–g**, 78–93%).



Scheme 2. Scope with respect to the indolin-2-ones. [a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv), **2a** (1.2 mmol, 1.2 equiv), $Fe(OAc)_2$ (10 mol%), DMF (1 mL), 80 °C, under open air. [b] Yields of isolated products.

Especially, the indolin-2-one with a strong electron-withdrawing nitro group is well tolerated under standard reaction conditions (**3g**). It is worth highlighting that the indolin-2-ones with halogen substituents (fluoro, chloro, and bromo) at different positions all afforded the corresponding products in high yields (**3h–k**, 62–88%), including the sterically hindered 4-chloro-indolin-2-one, which could be further functionalized. In addition, N-substituted indolin-2-ones were also compatible with this reaction, delivering the desired products in satisfactory yields (**3l–n**, 81–85%).

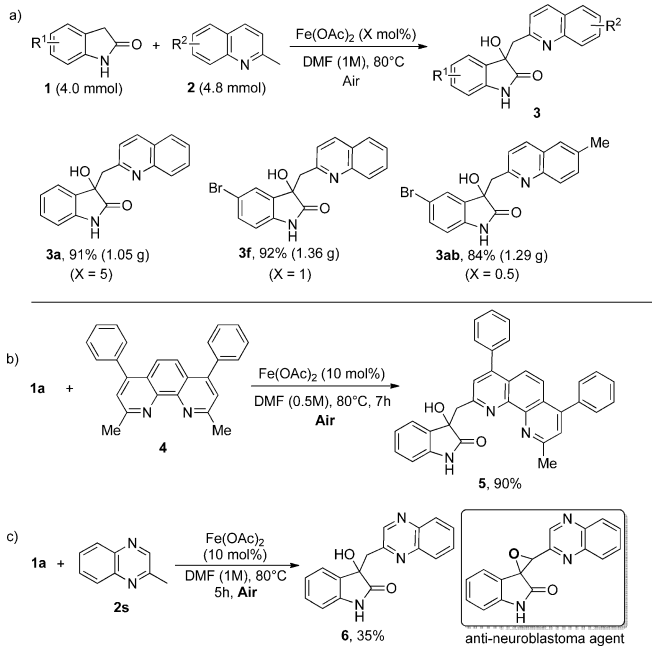
Next, we investigated the scope with various alkyl-substituted heteroarenes (Scheme 3). We were pleased to see that this iron-catalyzed alkylation and hydroxylation transformation was effectively translated to a wide range of alkyl-substituted heteroarenes. The 6-substituted 2-methylquinolines with either electron-withdrawing or electron-donating groups were well tolerated, providing the alkylation and hydroxylation products **3o–s** in 81–93% yields. The 2-methylquinoline with substituents at other position such as 7-Cl, 7-F, 8-Cl, 4-Cl, and 4-Me, all proceeded smoothly, delivering the corresponding products **3t–x** in 70–95% yields. Both the substituted indolin-2-ones and 2-methylquinolines went well in the reaction, giving the products **3y–ab** in excellent yields (89–91%). Other kinds of alkyl-substituted heteroarenes were also investigated. The substrates of 4-methylquinoline and 1-methylisoquinoline were compatible with the present catalytic system, providing the desired products **3ac** and **3ad** in moderate yields. However, 2-methylquinoxaline was less reactive, and the reaction of which with indolin-2-one afforded **3ae** in 39% yield. Strik-



Scheme 3. Scope with respect to the methyl-substituted N-heteroarenes. [a] Reaction conditions: **1a** (1.0 mmol, 1.0 equiv), **2** (1.2 mmol, 1.2 equiv), $Fe(OAc)_2$ (10 mol%), DMF (1 mL), 80°C, under open air. [b] Yields of isolated products. [c] Reaction time 8 h.

ingly, 2-methylbenzothiazole and 2-methylbenzoxazole could also be employed in this transformation, and corresponding products **3af** and **3ag** were isolated in 71 and 52% yield, respectively. In addition, secondary carbon atoms could be subjected to this procedure, delivering the alkylation and hydroxylation product **3ah** in a good yield of 72%. However, 8-methylquinoline could not be employed successfully. These results indicated that the nitrogen atom and alkyl substituent in the same heteroarene is essential in this transformation. The nitrogen atom has the following two functions: a) the participation in tautomerism, b) the lone pair of electrons on the nitrogen atom could stabilize the intermediate **E** (see Scheme 6). Furthermore, alkyl-substituted heteroarenes containing one aromatic ring unit, such as 2,6-dimethylpyridine, 4-methylpyridine, 2-methylpyrazine, and 2,4,6-trimethyl-1,3,5-triazine, were also evaluated in the reaction, but the products were often isolated in low yields (**3aj**–**am**).

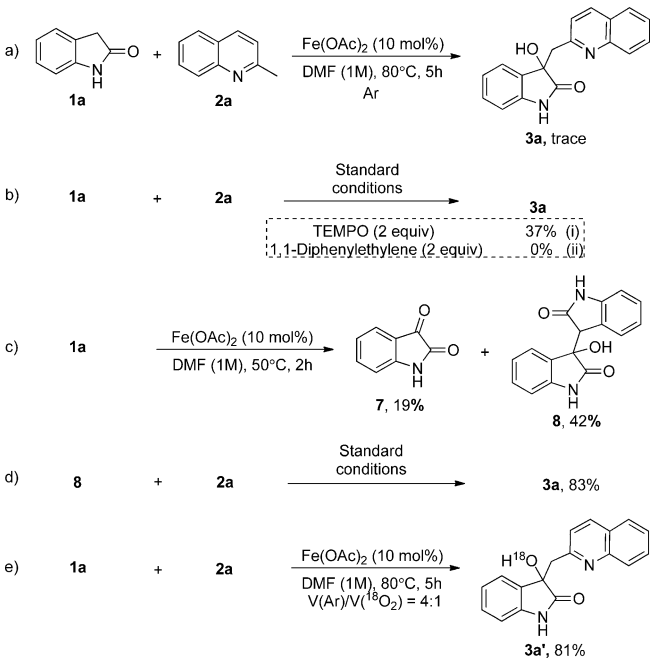
Encouraged by this unique alkylation and hydroxylation reaction between two different $C(sp^3)$–H bonds, we next show the practicality of this method. First, we conducted the gram-scale synthesis for **3a**, **3f**, and **3ab** (Scheme 4a). The product



Scheme 4. Gram-scale synthesis and synthetic manipulations.

3a was obtained in 91% (1.05 g) yield under the optimized reaction conditions in the presence of 5 mol% $Fe(OAc)_2$. To our delight, when we decreased the catalyst loading to either 1 or 0.5 mol%, the reactions smoothly proceeded to provide **3f** and **3ab** in 92% (1.36 g) yield and 84% (1.29 g) yield, respectively. Then, we turned our attention to the direct derivatization of bathocuproine, which has been reported as is a ligand in many important transformations (Scheme 4b).[9] Moreover, this reaction was also applied to the synthesis of the core structure of an anti-neuroblastoma agent (Scheme 4c).[7e]

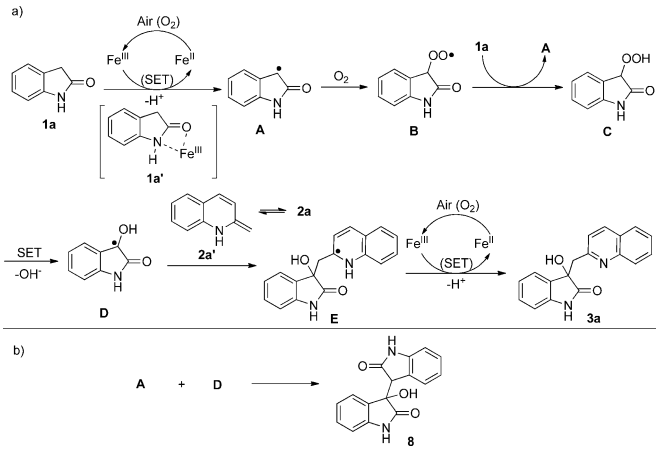
To gain insights into the reaction mechanism, several control experiments were conducted. Firstly, the reaction of **1a** with **2a** was run under an argon atmosphere, and only a trace amount of **3a** was obtained (Scheme 5a). It implies the importance of air (molecular oxygen) in this transformation. Next, radical scavengers were added in the reaction mixture under the standard reaction conditions. The product yield was sharply decreased in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy; Scheme 5b). The reaction was completely inhibited when DPE (1,1-diphenylethylene) was added into the reaction (Scheme 5b). These results indicate that a radical process may be involved in this transformation. In another control experiment, **1a** was transformed into the oxidation product isatin (**7**) and oxidative homocoupling product **8** under milder reaction conditions (Scheme 5c). The



Scheme 5. Control experiments.

formation of **8** suggests that two intermediates (**A** and **D**; see Scheme 6) may be generated in the reaction. Furthermore, **8** could react with **2a** under the standard reaction conditions, affording **3a** in 83% yield (Scheme 5d). In addition, an ^{18}O-labelling experiment clearly showed that the O in OH group originates from molecular oxygen (Scheme 5e).

On the basis of the preliminary experimental results and previous reports,[10] a possible mechanism for this transformation is proposed in Scheme 6a. Initially, **1a** is oxidized to the corresponding radical **A** through a single-electron-transfer (SET).[11] In this step, **1a** may play the role as an auxiliary ligand, and react with Fe^{III}, leading to the chelate Fe complex **1a′**, which plays the key role in the oxidation step of **1a** to **A**. Next, **A** reacts with O_2 to give the radical **B**, which abstracts a hydrogen atom from **1a** to afford **A** and **C**. Then **C** loses a hydroxy group to give the radical **D**. After that, the attack of **D** onto **2a′** followed by SET to form the desired alkylation and hydroxylation product **3a**. The lone pair of electrons on the nitrogen atom of **2a** could stabilize the intermediate **E**, and may be the reason for the lower yields obtained with **2l** and **2m**. The formation of **A** and **D** is supported by the isolation of the oxidative homocoupling product **8**, which could be formed by a cross-coupling reaction from **A** and **D** (Scheme 6b).



Scheme 6. Proposed reaction mechanism.

In summary, we have reported the first iron-catalyzed $C(sp^3)$–H difunctionalization for the direct alkylation and hydroxylation between two different $C(sp^3)$–H bonds. This oxidative cross-coupling reaction, performed under mild ligand-free and base-free conditions by using air (molecular oxygen) as the terminal oxidant and oxygen source for the synthesis of O-containing compounds, provides a simple and green approach toward C3-alkylated 3-hydroxyindolin-2-one derivatives. Moreover, iron is the one of the most abundant metals in the Earth's crust. Catalysis with iron salts serves to preserve our rare-noble-metal resources. Further investigations into more interesting reactivity of iron salts in novel transformations are currently in progress in our laboratory. The results will be reported soon.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · iron · molecular oxygen · N-heteroarenes · oxidation

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