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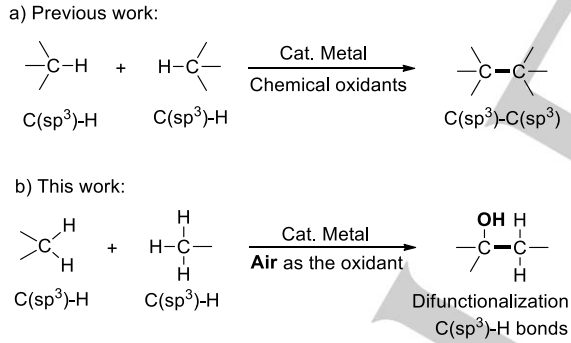
Iron-Catalyzed Oxidative Direct Alkylation and Hydroxylation of Indolin-2-ones with Alkyl-Substituted N-Heteroarenes

Ren-Ming Hu,†[a] Dong-Yang Han,†[a] Ning Li,[a] Jie Huang,[a] Yu Feng,[a] and Da-Zhen Xu*[a]

Dedication ((optional))

Abstract: Herein, we present the first direct alkylation and hydroxylation reaction between two different C(sp^3)-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, employing air (molecular oxygen) as the terminal oxidant and oxygen source for the synthesis of O-containing compounds, and producing 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(sp^3)-H functionalization for construction of new C-C bonds has attracted great interest.[1] Among these reactions, the coupling reactions of two different C(sp^3)-H bonds is the most attractive topic, which avoids the prefunctionalization steps for both substrates and therefore saves times and reduces the waste (Scheme 1a).[2] Despite tremendous progress being made, the rapid and efficient construction of C(sp^3)-C(sp^3) bonds by transition-metal catalysis remains a challenging issue.



Scheme 1. Transition-metal-catalyzed oxidative C(sp^3)-H/C(sp^3)-H cross-dehydrogenative coupling.

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 metal in the Earth's crust. The characteristics of cheap, safe, stable and low toxic make iron salts as the ideal metal catalyst or reagent in chemical transformations.[3] On another hand, the use of molecular oxygen instead of traditional oxidation reagents is greatly desired. Molecular oxygen, especially air, is an ideal green oxidant because of its inexpensive, high atom economy and environmentally benign characteristics.[4, 1a] More importantly, the use of molecular oxygen as the terminal oxidant and oxygen source for the construction of C-O bond is one of the most ideal transformation in organic synthesis.[5] Therefore, combining the above two concepts, the use of iron catalyst systems, which employ air (molecular oxygen) as the terminal oxidant and oxygen source for the construction of C(sp^3)-C(sp^3) bond and C-O bond between two different C(sp^3)-H bonds is highly desired (Scheme 1b).

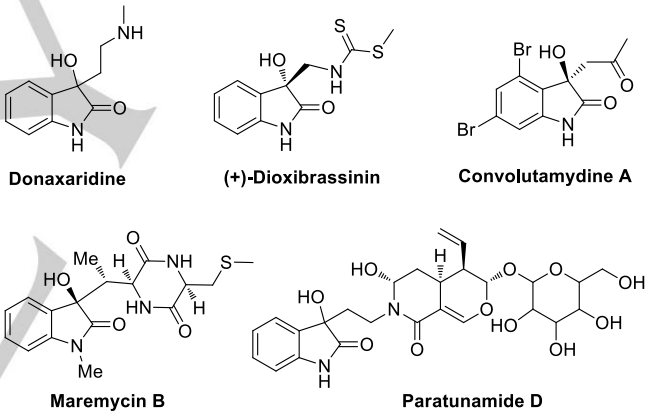


Figure 1. Selected biologically active and natural molecules containing C3-alkylated 3-hydroxyindolin-2-ones.

The 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, anti-tumor, 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 activity (**Figure** 1).[8,6b] Here, we describe an unprecedented iron-catalyzed direct alkylation and hydroxylation reaction between two different C(sp^3)-H bonds for the synthesis of C3-alkylated 3-hydroxyindolin-2-one derivatives. This work have achieved the following remarkable achievements: 1) a novel iron-catalyzed C(sp^3)-H difunctionalization, 2) C(sp^3)-C(sp^3) bond formation between methyl and methylene groups, 3) air (molecular oxygen) as the terminal oxidant and oxygen source for the synthesis of O-containing compounds, 4) mild, ligand-free and base-free conditions (Scheme 1b).

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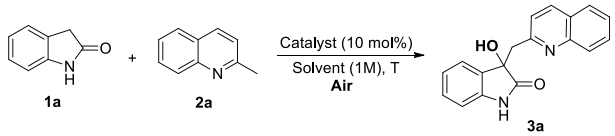
At the outset of our investigations, indolin-2-one (**1a**) and 2-methylquinoline (**2a**) were selected as the model substrates for the iron-catalyzed alkylation and hydroxylation reaction by using air as the sole oxidant (Table 1). Among the tested solvents, DMF afforded the alkylation and hydroxylation 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 the iron salts could drive the reaction, and $Fe(OAc)_2$ gave an excellent yield 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 efferent for this transformation. The same yield was obtained when the catalyst loading was decreased to 5 mol% (entry 17). Even the amount of the catalyst was reduced to 1 mol% or 0.5 mol%, the reaction still proceeded smoothly to provide **3a** in good yields (entries 18 and 19). However, the iron salt of $Fe(OAc)_2$ is very cheap. So we chose using more amount of catalyst to save time in the following reactions.

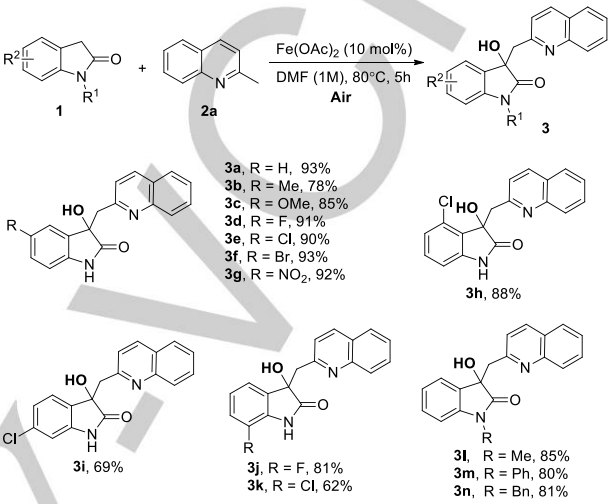
Table 1. Optimization of the reaction conditions.[a]



Entry	Cat (10 mol%)	Solvent (mL)	T (°C)	Time (h)	Yield (%)[b]
1	$FeCl_3$	EtOH	80	5	trace
2	$FeCl_3$	CH_3CN	80	5	trace
3	$FeCl_3$	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	$FeCl_3$•$6H_2O$	DMF	80	5	47
9	$FeBr_3$	DMF	80	6	57
10	$Fe(NO_3)_3$•$9H_2O$	DMF	80	6	62
11	$Fe(OTf)_3$	DMF	80	5	21
12	$Fe_2(SO_4)_3$•xH_2O	DMF	80	7	65
13	$FeCl_2$•$4H_2O$	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] Conditions: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (10 mol%), solvent (1 mL), 80 °C, under open air, 5 h. [b] Isolated yields. [c] With 5 mol% catalyst. [d] With 1 mol% catalyst. [e] With 0.5 mol% catalyst.

With the optimized reaction conditions in hand (Table 1, entry 14), we then carried out the alkylation and hydroxylation reaction between 2-methylquinoline with various indolin-2-ones (Scheme 2). The 5-substituted indolin-2-ones with both electron-donating and electron-withdrawing substituents were all competent well in the reaction, giving the desired products in good to excellent yields (**3b**-**g**, 78-93%). 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*-substitued indolin-2-ones were also compatible with this reaction, delivering the desired products in satisfactory yields (**3l-n**, 81-85%).



Scheme 2. Reaction scope of 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 ºC, under open air. [b] Isolated yields.

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 electron withdrawing or 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, were 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-3ab** 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 the **3ae** in 39% yield. Strikingly, 2-methylbenzothiazole and 2-methylbenzoxazole could be also 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 products **3ah** in a good yield of 72%. However, 8-methylquinoline could not be employed successfully. These results indicated that nitrogen atom and alkyl substituent in the same heteroarene is essential in this transformation. The nitrogen atom has the following two functions: a) the formation of tautomerism, b) the lone pair on 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-

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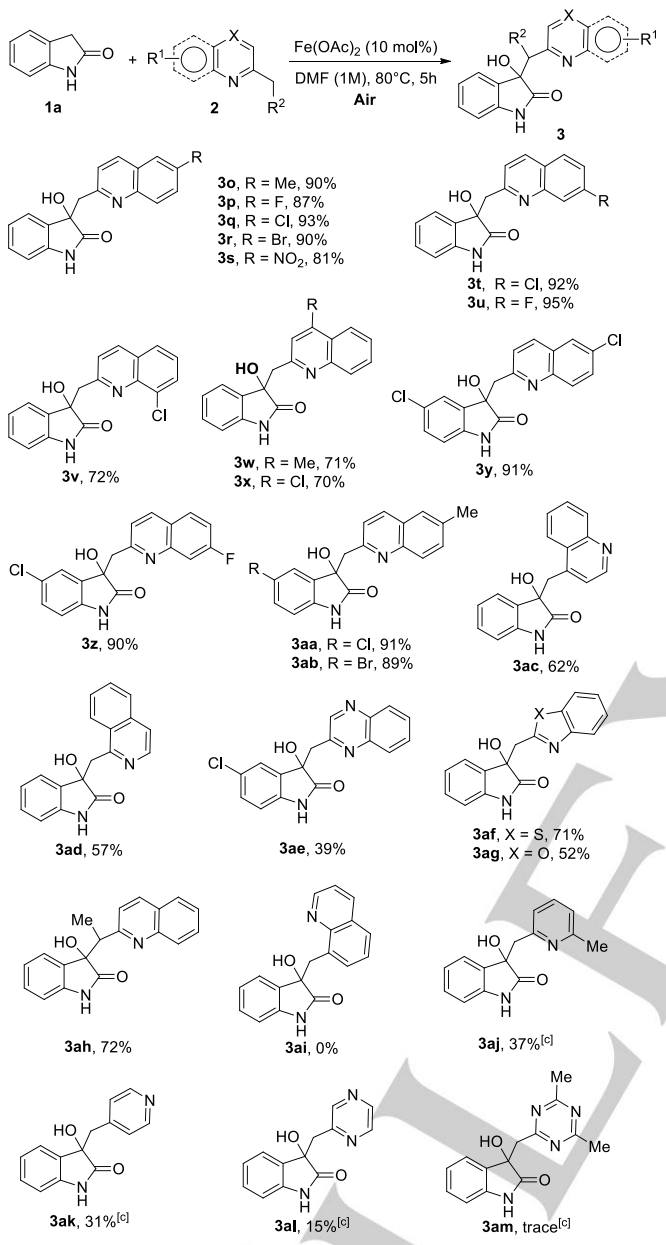
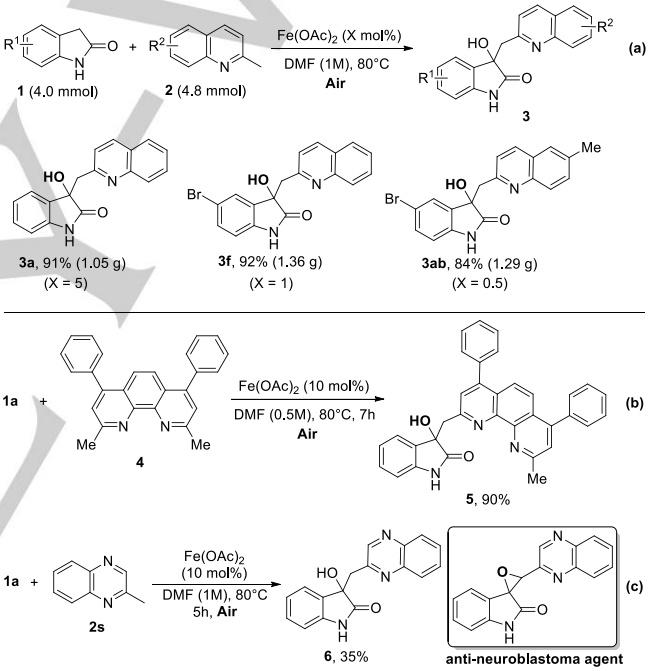
methylpyridine, 2-methylpyrazine and 2,4,6-trimethyl-1,3,5-triazine were also evaluated in the reaction, but the products were often isolated in low yields (3aj-am).



Scheme 3. Reaction scope of 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 ºC, under open air. [b] Isolated yields. [c] Reaction time 8 h.

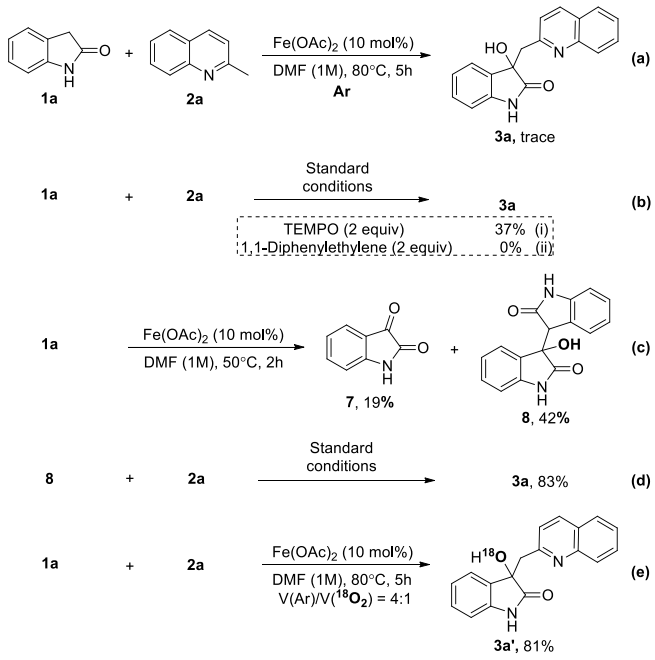
Encouraged by this unique alkylation and hydroxylation reaction between two different C(sp^3)-H bonds, we next show the practicality of this method. First, we conducted the gram-scale synthesis for **3a**, **3f** and **3ab** (Scheme 4a). Product **3a** was obtained in 91% (1.05g) yield under the optimized conditions in the presence of 5 mol% $Fe(OAc)_2$. To our delight, when we decreased the catalyst loading to 1 mol% or 0.5 mol%, the reactions smoothly proceeded to provide **3f** and **3ab** in 92% (1.36g) yield and 84% (1.29g) 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 for 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, performed the reaction of indolin-2-one (**1a**) with 2-methylquinoline (**2a**) under argon atmosphere conditions, 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 conditions. The product yield was sharply decreased in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (Scheme 5b, (i)). The reaction was



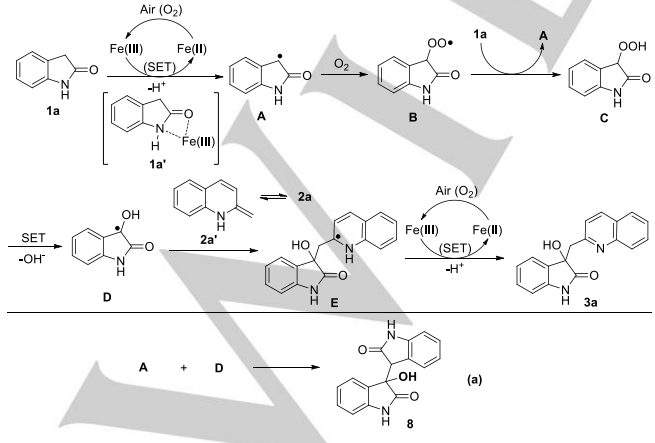
Scheme 4. Gram synthesis and synthetic manipulation.

completely inhibited when DPE (1,1-diphenylethylene) was added into the reaction (Scheme 5b, (ii)). These results indicate that a radical process may be involved in this transformation. In another control experiment, indolin-2-one (**1a**) could be transformed into the oxidation product isatin (**7**) and oxidative homo-coupling product **8** under a milder reaction conditions (Scheme 5c). The formation of the compound **8** suggests that two intermediates (**A** and **D**) may be generated in the reaction (Scheme 6). Furthermore, compound **8** could be reacted with 2-methylquinoline (**2a**) under the standard conditions, affording **3a** in 83% yield (Scheme 5d). In addition, an ^{18}O labelling experiment was clearly shown that the O in OH group was coming from oxygen (Scheme 5e).



Scheme 5. Control experiments.

On the basis of the preliminary experimental results and previous reports,[10] a possible mechanism for this transformation is proposed in Scheme 6. Initially, indolin-2-one (**1a**) was oxidized to the corresponding radical **A** through a single-electron-transfer (SET).[11] In this step, the substrate **1a** may play the role as an auxiliary ligand, and reacts with Fe(III) leading to a chelate Fe complex **1a′** which playing the key role in the oxidation step of **1a** to A. Next, the radical **A** reacts with O_2 to give radical **B,** which abstract a hydrogen atom from indolin-2-one (**1a**) to afford **A** and **C**. Then, the intermediate **C** loses a hydroxyl to give the radical **D**. After that, the attack of **D** to 2a′ and followed by a single-electron-transfer (SET) to form the desired alkylation and hydroxylation of indolin-2-one (**3a**). The lone pair on nitrogen atom of 2-methylquinoline could stabilize the intermediate E. This may be the reason that the lower yields



Scheme 6. Proposed Reaction Mechanism.

were obtained for 4-methylquinoline and 1-methylisoquinoline. The formation of intermediates **A** and **D** is supported by the isolation of oxidative homo-coupling product **8**, which could be formed by a cross-couple reaction from radicals **A** and **D** (Scheme 6a).

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, providing a simple and green approach toward C3-alkylated 3-hydroxyindolin-2-one derivatives. Moreover, iron is the one of the most abundant metal in the Earth's crust. Catalysis with iron salts will be helping us to save our rare noble-metal resources. Further investigations to observe more interesting reactivity of iron salts in novel transformation are currently in progress in our laboratory. The results will be reported soon.

Acknowledgements

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Keywords: iron • molecular oxygen • N-heteroarenes • oxidation • C(sp^3)- C(sp^3) bond formation

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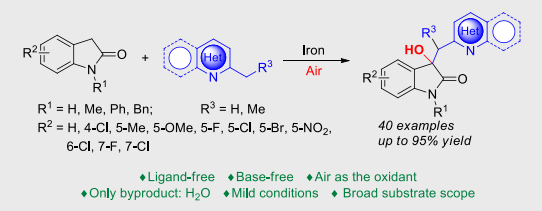

The direct alkylation and hydroxylation reaction between two different C(sp^3)-H bonds, indolin-2-ones and alkyl-substituted N-heteroarenes, is reported. The reaction is catalyzed by a simple iron salt and employed air (molecular oxygen) as the terminal oxidant and oxygen source for the synthesis of O-containing compounds, producing only water as the byproduct.

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