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Iron-catalyzed cross-dehydrogenative coupling of indolin-2-ones with active methylenes for direct carbon–carbon double bond formation†

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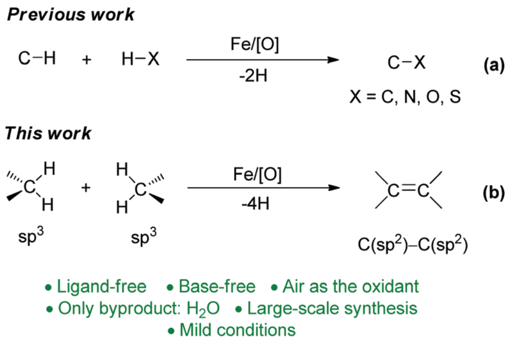
The iron-catalyzed cross-dehydrogenative coupling (CDC) of $C(sp^3)$–H/$C(sp^3)$–H bonds to afford olefins by 4H elimination is described. This method employs air (molecular oxygen) as an ideal oxidant, and is performed under mild, ligand-free and base-free conditions. H_2O is the only byproduct. Good tolerance of functional groups and high yields have also been achieved. Preliminary mechanistic investigations suggest that the present transformation involves a radical process.

Carbon–carbon double bonds have a central importance in organic chemistry. They can be directly transformed into any desirable functional groups.[1] Some very important organic reactions, such as the Heck reaction,[2] olefin metathesis[3] and Sharpless epoxidation,[4] are all based on olefins. Molecules with carbon–carbon double bonds are widespread in natural compounds; they constitute key intermediates for pharmaceuticals, agrochemicals, functional materials and bulk chemicals.[5] In the past few decades, a number of typical classic olefination methodologies have been established, such as the Wittig reaction,[6] Peterson olefination,[7] McMurry coupling,[8] and Julia olefination.[9] And very recently, some alternative methods for the synthesis of alkenes have been developed, such as carbene dimerization[10] and a three-membered ring for carbonyl olefination.[11] However, these reactions are based on substrates with specific unsaturated functional groups, and/or require extensive prefunctionalization of reactants. A large amount of waste was often generated due to the involvement of a stoichiometric amount of toxic reagents. Hence, the development of new catalytic methods for the construction of carbon–carbon double bonds from readily available starting materials is still a significant challenge.

Iron is the second most abundant metal in the Earth's crust. Iron salts are cheap and incorporated into biological systems. The characteristic of low toxicity is especially important in the pharmaceutical and food industry. These advantages make iron salts highly attractive catalysts or reagents in chemical transformations.[12] Iron salts are considered as the ideal material for catalyst development. Notable achievements have been made recently with iron salts for direct transformations of inert C–H bonds into C–C and C–X (X = heteroatom) bonds, which were often promoted by rare and expensive transition metal catalysts, such as Ru, Rh, and Pd (Scheme 1a).[13,14] However, iron-catalyzed direct coupling of two unactivated $C(sp^3)$–H alkyl groups to form a new C═C bond is unprecedented.

On the other hand, with the increasing interest in the development of green or sustainable chemistry, clean and environmentally benign technologies have attracted significant attention. Oxidation reactions using chemical oxidants are often expensive and cause secondary pollution, which may limit their applications in industrial production. Air is cheap and easily available. The use of air instead of chemical oxidants is considered to be an ideal oxidation process due to its economic and environmental benefits.[15] Herein, we report an iron-catalyzed cross-dehydrogenative coupling reaction (CDC) between two $C(sp^3)$–H bonds to form C–C double bonds



• Ligand-free • Base-free • Air as the oxidant
• Only byproduct: H_2O • Large-scale synthesis
• Mild conditions

Scheme 1 Iron-catalyzed cross-dehydrogenative coupling reactions.

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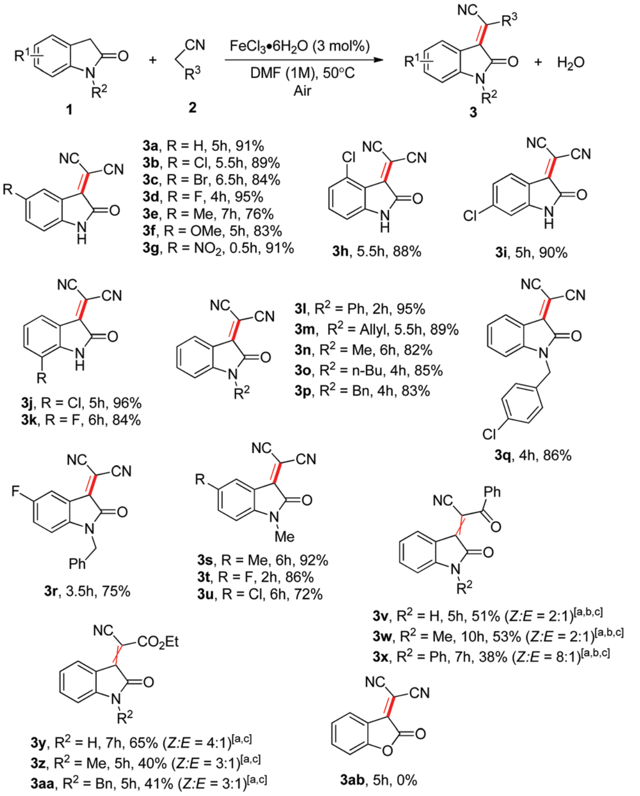
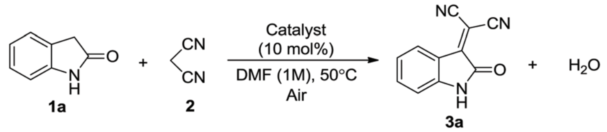
(Scheme 1b). The notable features of this process include (1) a readily available iron salt as a catalyst under ligand-free and base-free conditions, (2) air as a green and sustainable oxidant, and (3) low reaction temperature (50 °C).

At the outset of the project, various reaction conditions were investigated for the model reaction between indolin-2-one (**1a**) and malononitrile (**2**) with air as the oxidant to optimize and identify the reaction parameters (see Table 1, and Table S1 in the ESI†).[16] The effect of different solvents was evaluated in the presence of 10 mol% $FeCl_3·6H_2O$ under open air. To our delight, the corresponding alkene (**3a**) was obtained in 91% yield within 5 h in DMF (Table 1, entry 3). However, under the same reaction conditions, other metal salts such as indium, ytterbium, and scandium salts fell short in affording the desired alkene product **3a** (Table 1, entries 4–7). These results indicate that the iron catalysis of $FeCl_3·6H_2O$ has unique power in the oxidative coupling reaction for the construction of alkene, even at a reduced catalyst loading (Table 1, entries 8 and 9). To further improve the reaction conditions, different iron salts were tested, but no better results were obtained (Table 1, entries 10–14). Furthermore, no product was formed under the conditions without any catalyst (Table 1, entry 15).



Scheme 2 Substrate scopes of indolin-2-ones with nitriles. Unless otherwise noted, the reactions were performed on a 0.5 mmol scale under the standard reaction conditions, see Table 1, entry 9. [a] $FeCl_3·6H_2O$ (10 mol%). [b] DMSO was used as the solvent. [c] Determined by ^1H NMR.

Table 1 Optimization of the iron-catalyzed oxidative coupling reaction[a]

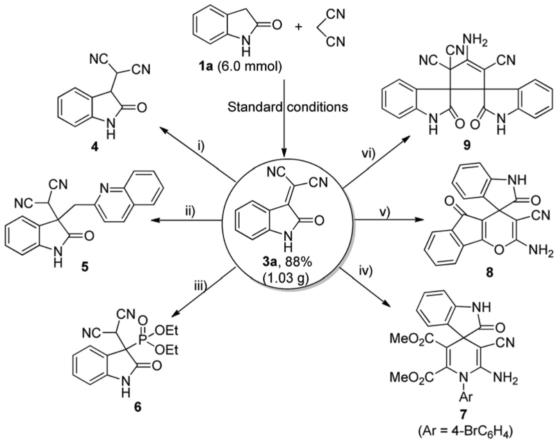


Entry	Cat. (10 mol%)	Solvent	Yield[b] (%)
1	$FeCl_3·6H_2O$	DMSO	78
2	$FeCl_3·6H_2O$	DCE	—
3	$FeCl_3·6H_2O$	DMF	91
4	$InCl_3$	DMF	—
5	$In(OTf)_3$	DMF	—
6	$Yb(OTf)_3$	DMF	—
7	$Sc(OTf)_3$	DMF	—
8[c]	$FeCl_3·6H_2O$	DMF	91
9[d]	$FeCl_3·6H_2O$	DMF	91
10[d]	$FeBr_3$	DMF	90
11[d]	$Fe(NO_3)_3·9H_2O$	DMF	82
12[d]	$Fe_2(SO_4)_3·xH_2O$	DMF	77
13[d]	$FeCl_2·4H_2O$	DMF	—
14[d]	$Fe(OAc)_2$	DMF	37
15	—	DMF	—

[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), **2** (0.6 mmol, 1.2 equiv.), catalyst (10 mol%), DMF (0.5 mL), 50 °C, under open air, 5 h. [b] Isolated yield. [c] With 5 mol% catalyst. [d] With 3 mol% catalyst.

With the optimized conditions in hand, we next examined the versatility with various substituted indolin-2-ones to explore the scope for the iron-catalyzed oxidative coupling olefination reaction. As is shown in Scheme 2, the reactions of indolin-2-ones with electron-donating and electron-withdrawing groups all proceeded smoothly to deliver the desired alkenes in good yields (**3a–g**). Indolin-2-ones with substituted groups at the 4-, 6-, and 7-positions were well tolerated, providing the corresponding alkenes in high yields (**3h–k**). Even the sterically hindered substrate 4-chloroindolin-2-one reacted smoothly to afford the desired product **3h** in a good yield of 88%. Indolin-2-ones possessing N-protecting groups, such as phenyl, allyl, methyl, *n*-butyl and benzyl, were found to be particularly compatible with this reaction (**3l–q**). Moreover, multiple substituted indolin-2-ones were also efficiently converted into the corresponding products (**3r–u**). Having demonstrated that the dehydrogenative process is compatible with various substituted indolin-2-ones, we investigated other nitriles. It was found that benzoylacetonitrile (**2b**) and ethyl cyanoacetate (**2c**) were less reactive, and the alkene products were isolated in moderate yields (**3v–3aa**). However, 2-benzofuranone could not be employed successfully (**3ab**).

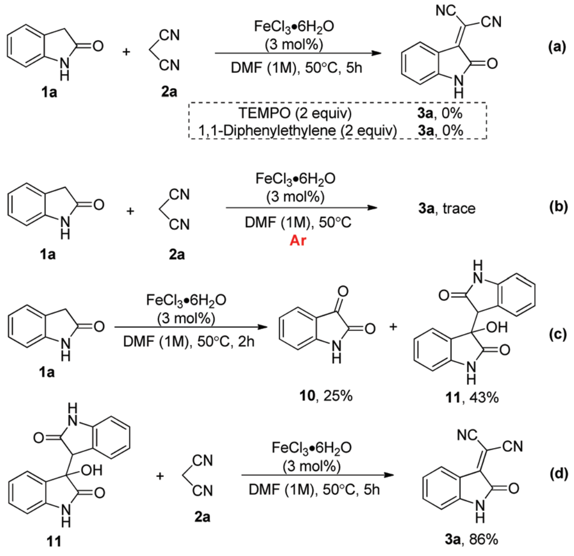
To demonstrate the further synthetic utility of this protocol, a gram-scale reaction was carried out and 1.03 g of **3a** was obtained in 88% yield (Scheme 3). Then several transformations were carried out. The double bond of **3a** could be reduced by treatment with the Hantzsch 1,4-dihydropyridine ester, affording the product **4** in 85% yield (Scheme 3i). Michael addition processes with 2-methylquinoline and diethyl phosphate were also explored, delivering the products



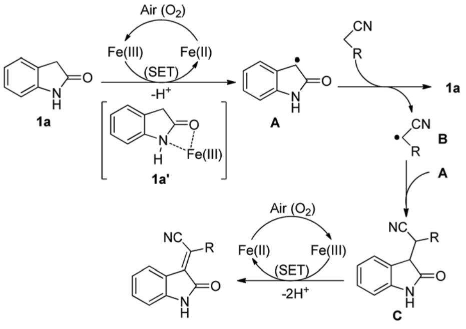
Scheme 3 Gram-scale synthesis and synthetic manipulations. Conditions: (i) Hantzsch 1,4-dihydropyridine ester (1.05 equiv.), ethanol, r.t., 15 min, 85% yield. (ii) 2-Methylquinoline (1.05 equiv.), H_2O, 100 °C, 2 h, 88% yield. (iii) Diethyl phosphate (1.05 equiv.), [DABCO-H]AcO (10 mol%), THF, r.t., 30 min, 97% yield. (iv) Dimethyl acetylenedicarboxylate (1.05 equiv.), 4-bromoaniline (1.0 equiv.), [DABCO-H]AcO (10 mol%), ethanol, 40 °C, 5 h, 85% yield. (v) 1,3-Indanedione (1.05 equiv.), [DABCO-H]Cl (10 mol%), ethanol, 50 °C, 91% yield. (vi) Hantzsch 1,4-dihydropyridine ester (0.5 equiv.), $InCl_3$ (20 mol%), ethanol, r.t., 2 h, 67% yield.

in good yields of 88% and 97% respectively (Scheme 3ii and iii). Furthermore, spiro 1,4-dihydropyridine (**7**) and spiro 4H-pyran (**8**) could be obtained in one step from **3a** (Scheme 3iv and v). Moreover, the reductive self-coupling cyclization product **9** could be obtained catalyzed by $InCl_3$ in the presence of the Hantzsch 1,4-dihydropyridine ester (Scheme 3vi).

To gain more insights into the reaction pathway, a few control experiments were performed as shown in Scheme 4. Firstly, when radical trapping reagents such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or 1,1-diphenylethylene were added in the reaction under the standard conditions, the present transformation was completely inhibited, suggesting that a radical intermediate might be involved in this transformation (Scheme 4a). On the other hand, we observed that only a trace amount of **3a** was obtained when the reaction was performed under an argon atmosphere (Scheme 4b). This result signifies the importance of air (molecular oxygen). Moreover, a mixture of isatin (**10**) and the oxidative coupling product (**11**) was obtained in the absence of malononitrile (**2a**) (Scheme 4c). This result suggests that a radical intermediate might be generated from indolin-2-one (**1a**) in the presence of $FeCl_3$ *via* a single-electron transfer (SET). In addition, compound **11** could be reacted with malononitrile (**2**) to afford **3a** in 96% yield under the standard conditions (Scheme 4d).



Scheme 4 Control experiments.



Scheme 5 Proposed reaction mechanism.

Based on the above control experiments and previous reports,[13c,17] a tentative mechanism is illustrated in Scheme 5. Initially, in the presence of Fe(III), indolin-2-one (**1a**) could be easily converted into the corresponding radical **A** *via* a single electron transfer (SET) and loss of H^+. In this step, the substrate **1a** acts as an auxiliary ligand with Fe(III) leading to a chelate Fe complex **1a′** which may play a key role in the oxidation step of **1a** to **A**. Then, indolin-2-one radicals (**A**) abstract hydrogen atoms from methylene nitriles to afford radical **B**, which may react with **A** to afford intermediate **C**. Finally, **C** was oxidized to provide the product *via* two single electron transfers (SET) and loss of two H^+.

Conclusions

In summary, we have developed an iron-catalyzed oxidative coupling reaction between two different $C(sp^3)$–H bonds to access carbon–carbon double bonds under ligand-free and base-free conditions. The use of iron salts as catalysts in the cross-dehydrogenative coupling reaction to construct olefins has not been described previously. Notably, this protocol employed air as a green and sustainable oxidant, and H_2O is the only byproduct. Two readily available methylene compounds directly lost four Hs to from a carbon–carbon double bond under mild conditions, providing a new way to access olefins. A wide range of substituted indolin-2-ones and nitriles could be well tolerated in the current catalytic system. We anticipate that this work will highlight the iron-catalyzed cross-dehydrogenative coupling (CDC) reactions. Further studies on the application of the cross-dehydrogenative coupling reaction are currently underway in our laboratory.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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