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Nano-Iron Oxide as a Recyclable Catalyst for Intramolecular C−N Cross-Coupling Reactions under Ligand-Free Conditions: One-Pot Synthesis of 1,4-Dihydroquinoline Derivatives

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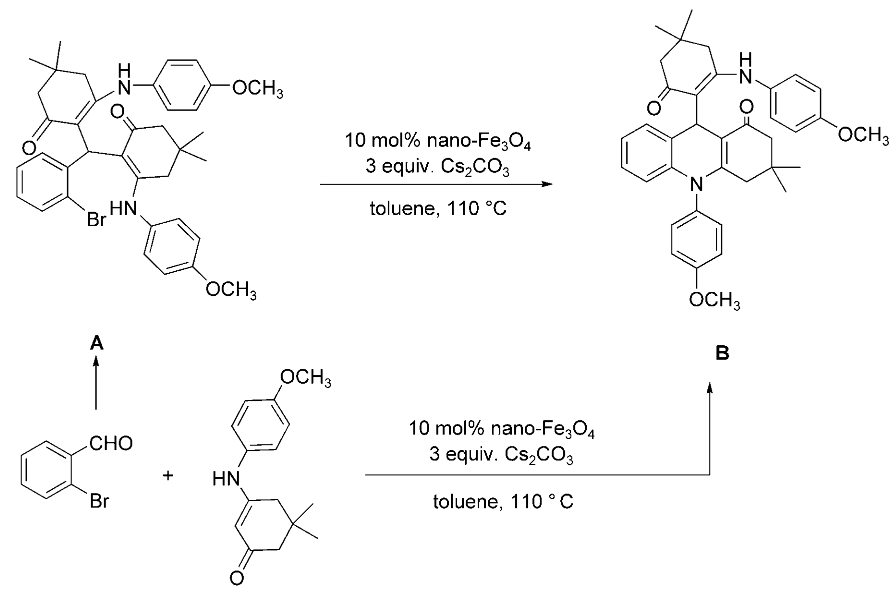
Abstract: The ligand-free nanoparticle ferroferric oxide catalytic system has been developed to promote the intramolecular C−N cross-coupling reaction. With this protocol, various 1,4-dihydroquinoline derivatives were synthesized from *o*-halobenzaldehydes and β-enaminones in moderate to good yields.

Keywords: C−N-cross-coupling; 1,4-dihydroquinoline derivatives; ligand-free conditions; nano-iron oxide; synthesis

The transition metal-catalyzed C−N cross-coupling process is considered as an important methodology, which has been widely applied in pharmaceutical and medicinal chemistry.[1] Although remarkable success in both palladium[2] and copper[3] catalyzed versions of this strategy has been achieved, the development of alternative catalysts involving more cheap, non-toxic, and environmentally friendly metals is still highly desired. Since the pioneering work of Kochi in 1971, iron salts have emerged as a ready available, low price and environmentally friendly catalyst for many organic transformations.[4] In the past few years, Taillefer firstly reported a novel iron-copper cooperative catalysis to accomplish the C−N cross-coupling reaction. The potential drawback of this methodology is the demand of using two metals in the catalyst system.[5] Shortly thereafter Bolm actualized the C−N cross-coupling reaction utilizing exclusively iron as the metal of choice. This iron catalyst appears promising for industrial-scale synthesis and further research could focus on operationally simple and cost-effective processes. The main limitation of the system relates to the facts that only a few successful examples with aryl bromides and aryl chlorides as the electrophilic partners have been reported so far, and that it generally involves eco-disadvantageous ligands such as *N,N*′-dimethylethylenediamine to catalyze the coupling reaction effectively.[6] Although significant progress in the field of iron-catalyzed C−N cross-coupling reaction has been achieved, these limitations still lead to continued interest and challenges.

Recently, nanoparticles have been employed as novel catalysts for various organic transformations,[7] which inspired us to focus our attention on the aspect of an iron oxide nanoparticle-catalyzed C−N cross-coupling reaction. As we know, nanoscale catalysts can provide higher surface areas and lower coordinating sites, which are responsible for the higher catalytic activity.[8] In contrast to our expectations, until now, the investigation of iron oxide nanoparticle as catalysts for the C−N cross-coupling process has never been reported.

On the other hand, since Buchwald constructed *N*-benzylindoline *via* an intramolecular C−N cross-coupling reaction in 1995,[9] this protocol has made a large impact on the synthesis of nitrogen heterocycles.[10] Quinoline, as an important drug intermediate,[11] has been prepared *via* many approaches.[12] However, very few studies on the synthesis of the quinoline ring by a C−N cross-coupling reaction were reported.[13] Therefore, we wished to develop a new approach to construct the quinoline ring *via* the intramolecular C−N cross-coupling reaction involving the iron oxide nanoparticle catalytic system. To the best of our knowledge, *β*-enaminones, as a highly efficient synthon, have been extensively applied for the construction of nitrogen-containing heterocycles.[14] In



Scheme 1. Synthesis of 1,4-dihydroquinoline derivative **B**.

view of this, we designed **A** as a building block, which could be obtained *via* the Baylis–Hillman reaction[15] followed by the nucleophilic substitution reaction from *β*-enaminone and *o*-bromobenzaldehyde, to carry out our trials (Scheme 1). Initially, we proved the feasibility of the intramolecular C–N cross-coupling reaction of **A** with the classical Pd(OAc)$_2$ catalytic system. Considering the drawback of the palladium catalyst system, we then attempted to replace it with the nano-Fe$_3$O$_4$. Fortunately, the strategy was successfully actualized. A 1,4-dihydroquinoline derivative **B** was synthesized in good yield, and the definite structure of **B** was confirmed by an X-ray crystal structure analysis (Figure 1).[16] It was very interestingly to find that no extra ligand was required in our catalytic system. Considering that **A** could also be obtained in the presence of a base which was needed in the intramolecular Buchwald–Hartwig reaction as well,[9,17] we tried to accomplish these processes in one-pot. As expected, the target **B** was generated in good yield by using the original substrates [*o*-bromobenzaldehyde (0.25 mmol), 3-(4-methoxyphenylamino)-5,5-dimethylcyclohex-2-enone (0.5 mmol)] in the presence of the nano-Fe$_3$O$_4$ catalytic system (Scheme 1).

Next, sets of experiments were performed to optimize the reaction conditions. As shown in Table 1, the nano *γ*-Fe$_2$O$_3$ could also afford the target in 56% yield (entry 1). Compared with the reaction in the air, the nano-Fe$_3$O$_4$-catalyzed reaction in an argon atmosphere is more efficient (entries 2 and 3). The influence of the amount of nano-Fe$_3$O$_4$ was also evaluated (entries 3–5), 10 mol% of the catalyst was the best choice.

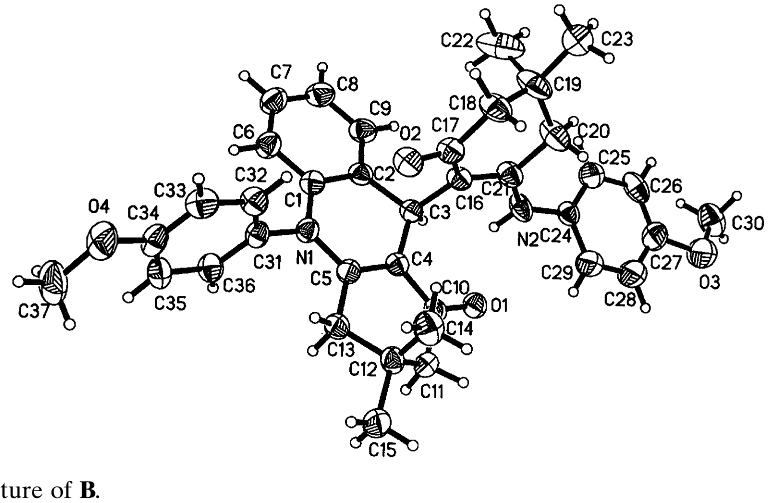


Figure 1. The crystal structure of **B**.

Table 1. Influence of the catalysts for the reaction of **1a** with **2a**.[a]

Entry	Catalyst	Yield [%][b]
1	nano-γ-Fe_2O_3 (10 mol%)	56
2	nano-Fe_3O_4 (10 mol%, air)	65
3	nano-Fe_3O_4 (10 mol%, argon)	89
4	nano-Fe_3O_4 (5 mol%, argon)	69
5	nano-Fe_3O_4 (15 mol%, argon)	87

[a] *Reaction conditions:* **1a** (0.25 mmol), **2a** (0.5 mmol), Cs_2CO_3 (3 equiv.), 3.0 mL of toluene at 110 °C for 24 h.

[b] Isolated yield.

Table 2. Optimization of conditions for the reaction of **1a** with **2a**.[a]

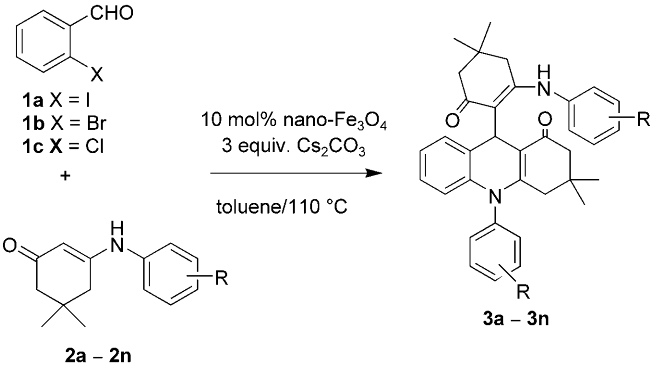
Entry	Base	Solvent	Yield[b] [%]
1	Cs_2CO_3	toluene	89
2	K_2CO_3	toluene	12
3	K_3PO_4	toluene	51
4	NaOAc	toluene	<10
5	*t*-BuOK	toluene	<10
6	Cs_2CO_3	THF	<10
7	Cs_2CO_3	CH_3CN	<10
8	Cs_2CO_3	Dioxane	<10
9	Cs_2CO_3	NMP	13
10	Cs_2CO_3	DMSO	26

[a] *Reaction conditions:* **1a** (0.25 mmol), **2a** (0.5 mmol), nano Fe_3O_4 (0.025 mmol), base (3 equiv.), solvent (3.0 mL) at 110 °C under argon atmosphere for 24 h.

[b] Isolated yield.

We next made a study on the effect of bases and solvents in the reaction. As shown in Table 2, the utilization of the commonly used bases (such as K_2CO_3, K_3PO_4, NaOAc and *t*-BuOK) only gave the desired product in poor yields (entries 2–5). Cs_2CO_3 was found to be the most appropriate base. Then we turned our attention to the solvents: THF, CH_3CN and dioxane were not suitable solvents for the reaction (entries 6–8). The commonly used solvents for the coupling reaction, such as NMP, DMSO, also gave disappointing results (entries 9 and 10). Finally, toluene was found to be act as the optimal solvent (entry 1).

Table 3. Scope for nano-Fe_3O_4-catalyzed synthesis of 1,4-dihydroquinoline derivatives.[a]



Entry	Substrate		Product	Yield[b] [%]
	X	R		
1	**1a**	4-OCH_3 (**2a**)	**3a**	88
2	**1a**	4-CH_3 (**2b**)	**3b**	86
3	**1a**	3-CH_3 (**2c**)	**3c**	71
4	**1a**	2-CH_3 (**2d**)	**3d**	78
5	**1a**	H (**2e**)	**3e**	77
6	**1a**	4-Cl (**2f**)	**3f**	70
7	**1a**	3-Cl (**2g**)	**3g**	67
8	**1a**	4-Br (**2h**)	**3h**	73
9	**1a**	4-I (**2i**)	**3i**	83
10	**1a**	2-Cl (**2j**)	**3j**	54
11	**1b**	**2a**	**3a**	89
12	**1b**	**2b**	**3b**	82
13	**1b**	**2c**	**3c**	71
14	**1b**	**2d**	**3d**	73
15	**1b**	**2e**	**3e**	75
16	**1b**	**2f**	**3f**	70
17	**1b**	**2g**	**3g**	64
18	**1b**	**2h**	**3h**	72
19	**1b**	**2i**	**3i**	81
20	**1b**	**2j**	**3j**	48
21	**1c**	**2a**	**3a**	81
22	**1c**	**2b**	**3b**	78
23	**1c**	**2c**	**3c**	67
24	**1c**	**2d**	**3d**	64
25	**1c**	**2e**	**3e**	68
26	**1c**	**2f**	**3f**	65
27	**1c**	**2g**	**3g**	60
28	**1c**	**2h**	**3h**	63
29	**1c**	**2i**	**3i**	62
30	**1c**	**2j**	**3j**	47
31	**1a**	4-NO_2 (**2k**)	**3k**	0
32	**1a**	4-CN (**2l**)	**3l**	0
33	**1a**	4-COMe (**2m**)	**3m**	0
34	**1a**	4-COOEt (**2n**)	**3n**	0

[a] *Reaction conditions:* **1** (0.25 mmol), **2** (0.5 mmol), nano-Fe_3O_4 (0.025 mmol), Cs_2CO_3 (0.75 mmol), toluene (3.0 mL) at 110 °C under argon for 24 h.

[b] Isolated yield.

After having optimized the conditions, we continued to examine the generality of the reaction, as shown in Table 3. We firstly introduced a series of *o*-halobenzaldehydes to the strategy. It was worthwhile to note that there was not much obvious decrease in activity among aryl bromides, chlorides and iodides in our catalytic conditions (entries 1, 11, 12), although aryl chlorides were inactive in the traditional iron-mediated C–N coupling reaction. Then the functional compatibility of *β*-enaminones to the approach was explored with 2-iodobenzaldehyde as substrate. This catalytic system has a good tolerance toward electron-donating groups and a few weak electron-withdrawing groups (4-OMe, 4-Me, 4-I, 4-Br, 4-Cl, 3-Me and 3-Cl) on the β-enaminones (entries 1–3, 6–9), but it is not compatible with strong electron-withdrawing groups, such as 4-NO_2, 4-CN, 4-COMe, 4-COOEt (entries 31–34). Moreover, 5,5-methyl-3-(phenylamino)-cyclohex-2-enone could also afford the target in good yield (entry 5). In order to study the steric influence of the approach, we next tested several β-enaminones with substituent groups in different positions. Notably, our catalytic system was also efficient for a 2-substituted β-enaminone which reacted to furnish the corresponding product in 78% yield (entry 4). Unfortunately, this catalytic system was less effective for the 2-chloro-substituted β-enaminone (entry 10), which maybe the result of both steric and electron-withdrawing influences. Satisfactory yields were also obtained in the reactions of 2-bromo- or 2-chlorobenzaldehyde with β-enaminones (entries 11–30). The influence of steric and electronic effects was similar to the reaction results when using 2-iodobenzaldehyde as substrate. Therefore, the representative examples illustrated the generality of this reaction. Taking the poor solubility of nano-Fe_3O_4 in toluene into consideration, we explored the recyclability of the unmodified magnetite. To our delight, we found that the yields were almost constant in a range between 80% and 89% after 5 cycles of the reaction for the preparation of compound **3a**, with the magnetite being maintained inside the flask by the help of a magnet (Figure 2).

In order to explore the possible degradation of the naked magnetite under the reaction conditions, we observed SEM images of the unmodified magnetite and the 5-fold reused one (Figure 3). This did not show any marked difference between them, which indicated that there was no significant sinter process under the reaction conditions. The simple recyclability makes this catalyst suitable for continuous industrial processes.

Furthermore, we explored if the reaction occurred in solution, completely or in part, with the nanoparticles leached from the solid surface.[18] A simple test with the reaction of **1a** and **2a** was carried out: The reaction mixture (see the Typical Experimental Procedure in the Experimental Section) was first refluxed in toluene for an hour, then hot-filtered. Subsequently, we subjected the resulting solution to standard conditions.[19] The system was then stirred at 110 °C for 24 h, after work-up, but only a 35% yield of desired product was obtained. Therefore, we considered that the reaction only occurs in solution partly.

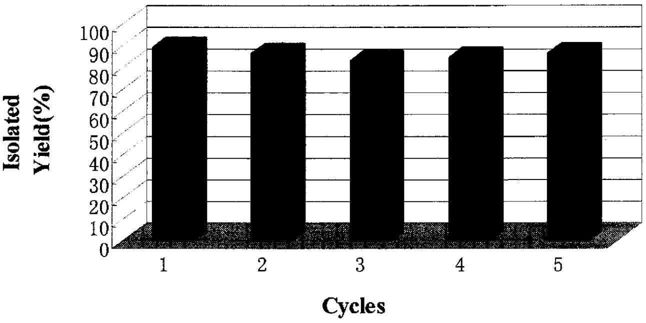


Figure 2. Investigation to the reuse of nano-Fe_3O_4 in the reactions: **1a** (0.25 mmol), **2a** (0.5 mmol), nano-Fe_3O_4 (0.025 mmol), Cs_2CO_3 (3 equiv.), 3.0 mL of toluene at 110 °C under argon for 24 h.

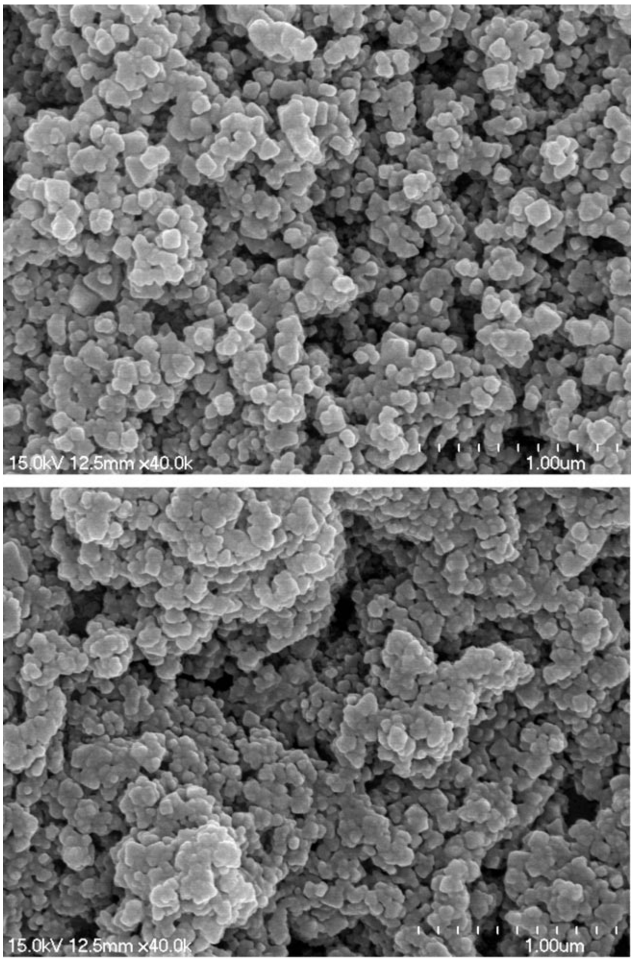
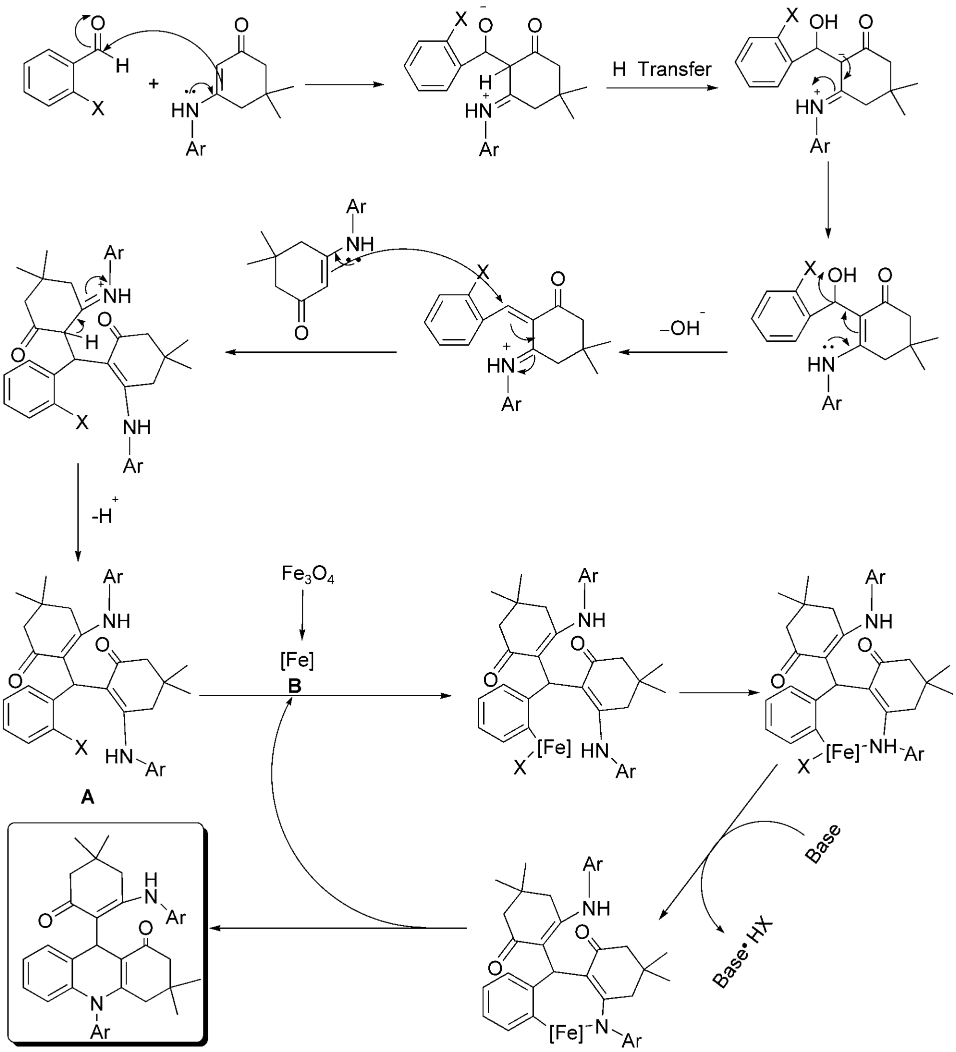


Figure 3. SEM images of unmodified nanopowder magnetite (*above*) and the same magnetite after having been used in 5 cycles (*below*).

Finally, a possible reaction mechanism for the formation of 1,4-dihydroquinoline derivatives from *o*-halobenzaldehyde and a wide range of β-enaminones was proposed (Scheme 2).

First, the intermediate **A** was generated through Baylis–Hillman-type reaction and nucleophilic substitution of another β-enaminone. Then, the intramolecular C–N cross-coupling reaction catalyzed by nano-Fe_3O_4 was accomplished to generate the final product. The possible way is proposed as follows: a low-oxidation state iron species [Fe] **B** was firstly generated by rapid electron transfer between the Fe sites in Fe_3O_4,[20] then oxidative addition of 2-substituted aryl



Scheme 2. Possible mechanism for the formation of 1,4-dihydroquinoline derivatives.

halide to **B** occurred. Subsequently, the classical cross-coupling route involving coordination and deprotonation of the arylamine fragment, followed by reductive elimination was performed to get the final product.[21]

In summary, ligand-free nano-Fe_3O_4 has been shown to be an active, stable and recyclable catalyst for the intramolecular C–N cross-coupling reaction for the first time. By using of this catalytic system, we have developed a novel and efficient method for the synthesis of various 1,4-dihydroquinoline derivatives from *o*-halobenzaldehyde and a wide range of β-enaminones. Noteworthy, the novel Fe catalyst is highly efficient for the inactive aryl chlorides and arylamine derivatives. The simple recyclability also makes this catalyst suitable for continuous industrial processes. Further study on the wider applications of the catalytic system is currently in progress.

Experimental Section

General Experimental Methods

All reactions were carried out under an argon atmosphere. All *o*-halobenzaldehydes, were purchased from Aldrich or Alfa. The nano-Fe_3O_4 catalyst and β-enaminones were prepared according to the known methods.[22] The average diameter of Fe_3O_4 particles is about 100 nm and they have a narrow size distribution. Analytical thin-layer chromatography was performed using glass plates precoated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Melting points were recorded on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a Varian FT-1000 spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ on a Varian Inova-400 NMR spectrometer with TMS as an internal reference. High resolution mass spectra were obtained using Microma GCT-TOF instrument. X-ray diffraction data were recorded on a Rigaku Mercury CCD area detector with graphite monochromated Mo-Kα radiation.

Typical Experimental Procedure for the Synthesis of Quinoline Derivative 3a

A mixture of **1a** (0.25 mmol), **2a** (0.5 mmol), nano-Fe_3O_4 (5.8 mg, 0.025 mmol), Cs_2CO_3 (144.7 mg, 0.75 mmol) and toluene (3.0 mL) was stirred at 110 °C under argon for 24 h. After that, the mixture was poured into water, and extracted with ethyl acetate, then the organic phase was dried by anhydrous $MgSO_4$, filtered and evaporated under vacuum, the residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1:6 v/v) to afford the product **3a**.

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[16] CCDC 736552 contains the supplementary crystallographic data for compound **3a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [E-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; fax: (+44)-01223–336–033]. Structural parameters for **3a**: data collection: Rigaku Mercury CCD area detector; crystal size: $0.30 \times 0.25 \times 0.18$ mm^3; $C_{37}H_{40}N_2O_4$, Mr = 576.71, monoclinic, space group P 21/c, $a = 10.5730(12)$ Å, $b = 24.150(3)$ Å, $c = 12.1542(13)$ Å, $\alpha = 90°$, $\beta = 93.107(4)°$, $\gamma = 90°$, $V = 3098.8(6)$ Å^3, $Z = 4$, $D_{calcd} = 1.236$ mg cm^{-3}, R $[I > 2\sigma(I)] = 0.1015$, wR $[I > 2\sigma(I)] = 0.2107$.

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[19] In Jones's case (see Ref.[18d]), no additional reagent was added, but in our case, the reaction could not proceed without base, so according to a referee's suggestion, Cs_2CO_3 was added to subject the resulting solution to standard conditions.

[20] Cotton and Wilkinson stated that Fe_3O_4 demonstrated an electrical conductivity about 10^6 times than that of Fe_2O_3, which is probably due to rapid valence oscillation between the Fe sites, see: F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th edn., John Wiley & Sons, Inc., New York, **1988**, p 712. We suppose the rapid valence oscillation can be interpreted as rapid electron transfer. This process may lead to the instantaneous formation of low oxidation state of iron species. Furthermore, we tested the catalytic activity of Fe(II) and Fe(III), respectively. But both of them showed lower activity than that of Fe_3O_4 in this transformation, which, to some extent, implies that a cooperation should exist between Fe(II) and Fe(III) in Fe_3O_4. The cooperation may be the exhibition of rapid electron transfer.

[21] The loading level of Cu in nano-iron oxide was determined *via* ICP-AES: 2.53×10^{-5} mmol Cu/mmol Fe. Thus, the effect of Cu was examined for the reaction of **1a** with **2a** in the presence of Cs_2CO_3 (3.0 equiv.), and toluene (3 mL): 16% yield (10 mol% nano-Cu), 32% yield (10 mol% CuI) and 43% yield (10 mol% nano-CuO). These results suggest that nano-Fe_3O_4 plays the key role in the present reaction, but we cannot rule out the effect of Cu completely.

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