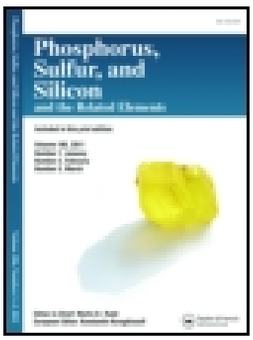

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Iron-catalyzed Aerobic Oxidative Phosphonation of N-aryl Tetrahydroisoquinolines

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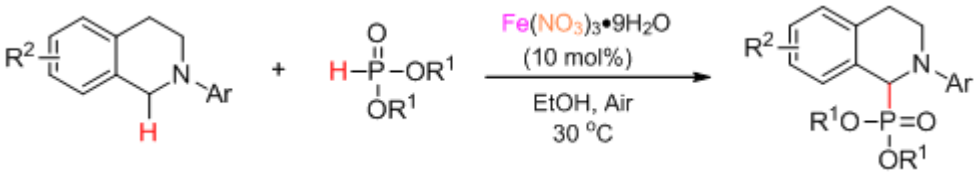
Abstract

We report herein a novel and efficient method for iron-catalyzed aerobic oxidative phosphonation of N-aryl tetrahydroisoquinolines for the synthesis of biologically interesting α-aminophosphonates. This new C-P bond formation reaction features the employment of a sustainable and cost-effective iron salt [$Fe(NO_3)_3 \cdot 9H_2O$] as catalyst, the utilization of air as environmental-benign oxidant, as well as the user-friendly open-flask reaction conditions.



Keywords

Oxidative Phosphonation; Iron Catalysis; Coupling; α-Aminophosphonate.

Introduction

Organophosphorus compounds are of great interest to synthetic chemists due to the broad applications in the fields of organic synthesis, materials, agrochemicals and pharmaceuticals[1]. α-Aminophosphonates and related α-aminophosphonic acids, containing amino and phosphonyl groups, are privileged structure motifs in the organophosphorus family. As the analogues of α-amino acids[2], these compounds shows promising potential in the regulation of binding affinity of target proteins which enables them to be good candidates for the discovery of potent enzyme inhibitors[3], antitumor[4] and antifungal agents[5]. In addition, α-aminophosphonates have also been served as useful precursors in Horner--Wadsworth--Emmons (HWE) reactions for the construction of enamine moieties[6]. Therefore, the development of simple and efficient methods to access the valuable α-aminophosphonate molecules is highly desirable.

Traditional operative methods to obtain α-aminophosphonates are using Kabachnik-Fields reaction[7] or Pudovik reaction[8] which is characterized by the addition of dialkyl phosphite to an imine intermediate. In contrast, the recent disclosed cross-dehydrogenative coupling (CDC)[9] between the C(sp^3)-H bond of tertiary amines and P-H bond of dialkyl phosphite represents an appealing alternative strategy to produce α-aminophosphonates owing to bypassing the necessity of prefunctionalization of the starting materials prior to the coupling event. Pioneered by Genies' electrical oxidation method[10], transition-metal-catalyzed chemical oxidative versions have already become important techniques for the dehydrogenative coupling of tertiary amines and

dialkyl phosphite (**Scheme 1**). Li and coworkers have established copper-catalyzed α-phosphonation of N-phenyl tetrahydroisoquinoline under aerobic conditions by using oxygen as sacrificial oxidant (**Scheme 1a**) [11]. Further, the Ofial group has found that sustainable and cost-effective iron catalysts are highly efficient for the construction of C-P bond in N,N-dimethylaniline substrates ($ArNMe_2$) (**Scheme 1b**) [12]. It is worth noting that N-phenyl tetrahydroisoquinoline substrates failed to produce the α-phosphonation products in Ofial's iron catalysis protocol, only delivering the corresponding lactam as an over-oxidation product (**Scheme 1c**) [13]. We speculate that the major challenges of desired transformation in **Scheme 1c** lie in the proper regulation of iron-catalyzed oxidation process on the sensitive α-sites of N-phenyl tetrahydroisoquinoline substrates and the cooperative interception of iminium ions by the nucleophilic dialkyl phosphite.

In this context, choosing a suitable combination of iron catalyst and oxidant could be very crucial to the success of oxidative phosphonation of N-phenyl tetrahydroisoquinoline substrates. It is well known that air is a ubiquitous and environment-friendly oxidant source which has versatile profiles in chemical oxidative transformations[14]. To take advantage of the joint synthetic merits from iron catalysis[15] and aerobic oxidation, we report herein our efforts to an iron-catalyzed aerobic oxidative phosphonation of N-phenyl tetrahydroisoquinolines to access biologically interesting α-aminophosphonate molecules.

Result and Discussion

Initial studies were focused on the screening of effective iron catalysts with using N-phenyl tetrahydroisoquinoline (**1a**) as the standard substrate and diethyl phosphite (**2a**) as the phosphonate source (**Table 1**). The ferrous salts which had superior catalytic activities in Ofial's reports[12,13] were found to be sluggish in our aerobic oxidation cases (entries 1-2). The ferric salts displayed improved catalytic performance on this transformation (entries 3-5). For the iron(III) nitrate nonahydrate [$Fe(NO_3)_3 \cdot 9H_2O$] (10 mol% catalyst loading), the desired product **3** can be smoothly obtained in 93% yield (entry 5). In comparison, iron(III) chloride hexahydrate [$FeCl_3 \cdot 6H_2O$] and iron(III) sulfate [$Fe_2(SO_4)_3$] gave inferior catalytic activities with prolonged time and decreased yield. These results revealed that the oxidizing nitrate [NO_3^-] played an important role in accelerating this iron-catalyzed oxidation process[16]. Heterogeneous iron(III) oxide (entry 6) and control experiment (entry 7) confirmed that iron(III) ionic species were essential factors for the activation of α position of tertiary amines. Further investigation of solvent effects indicated that ethanol are preferential solvent for this cross-dehydrogenative coupling (entries 5, 9-11).

With the optimized conditions in hand, the substrate scope of this iron-catalyzed aerobic oxidative phosphonation was examined (**Table 2**). A variety of dialkyl phosphites (including diethyl phosphite **2a**, diisopropyl phosphite **2b**, dibutyl phosphite **2c** and dibenzyl phosphite **2d**) were proved to be effective substrates to afford the corresponding coupling products in

satisfactory yields (entries 1-4). Next, we continued to explore the variability of N-aryl tetrahydroisoquinolines substrates. Gratifyingly, N-aryl tetrahydroisoquinolines (**1a**-**1e**) bearing either electron-withdrawing or electron-donating substituents on the aryl ring could be smoothly transformed into the desired phosphonation products (entries 5-8). For the substrate **1e**, an elevated temperature and oxygen atmosphere were required to obtain satisfactory conversion (entry 8). The larger oxidation barrier in **1e** was rationalized by the drastic decrease of electron density of α C-H bond in light of the presence of a strong electron-withdrawing nitro group. Additionally, the substrate **1f** was found to be amenable to the established conditions to furnish the corresponding products **13**-**15** (entries 11-13) which could allow further elaboration of the chloro group on the quinoline ring through coupling chemistry.

Consistent with the previous reports of iron-catalyzed CDC reactions[13,17], an analogous putative mechanism involving radical and iminium intermediates was proposed (**Scheme 2**). It was found that when one equivalent of radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was added in the reaction system of **1a** and **2a** (**Scheme 3a**), the reaction was partially suppressed and the yield dropped to 37% (vs **Table 2, entry 1**). The interruption effect was highly likely to be caused by TEMPO's coordinative deactivation towards catalytic iron species. This speculation was supported by the observation of [(TEMPO)Fe$(NO_3)_3$ + K^+] peak (*m/z* 437.3) in ESI-MS. In addition, the iminium intermediate and derivative species were also identified by ESI-MS monitoring of the reaction mixture (see supplemental materials). Next, preliminary

studies to examine the role of oxidizing nitrate in this catalysis were also conducted. We found that nitric acid[9k,16b] exhibited catalytic activities in the oxdative coupling of **1a** and **2a** albeit being lower than the optimal catalyst $Fe(NO_3)_3 \cdot 9H_2O$ (**Scheme 3b**). This observation indicated that the nitrate species (acidified) [9k] could play important roles within the oxidative catalysis process. Further, a mixed catalyst combination of $FeCl_3 \cdot 6H_2O$ and nitric acid displayed improved catalytic efficiency which supported the synergistic effects of Fe(III) and nitrate on this phosphonation reaction (**Scheme 3c**). Taken together, the innate and cooperative catalytic roles exerted by $Fe(NO_3)_3 \cdot 9H_2O$ were the key to achieve this aerobic oxidative phosphonation of N-aryl tetrahydroisoquinolines.

Conclusion

In summary, we have demonstrated a facile and sustainable iron-catalyzed α-phosphonation reaction of N-aryl tertrahydroisoquinoline derivatives. Various dialkyl phosphites and N-aryl tertrahydroisoquinolines were effective substrates to access the biologically active α-aminophosphonates under the mild ambient conditions. Further work to extend this methodology to other nucleophiles and systematic mechanistic study are in progress, and the result will be reported in due course.

Experimental

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AM-400 spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard; *J*-values are in hertz. Mass spectra

were recorded by EI methods, and high-resolution mass spectral analyses (HRMS) was measured on a Waters Micromass GCT Premier mass spectrometer. Commercially obtained reagents were used without further purification. All reactions were monitored by thin-layer chromatography (TLC) with Huanghai GF 254 silica gel-coated plates. Flash column chromatography was carried out using 300--400-mesh silica gel at increased pressure. The Supplemental Materials contain ^{1}H, ^{13}C and ^{31}P NMR spectra of samples **3**-**15** (Figures S 1--S 47 are available online in Supplemental Materials).

General Procedure for Iron-catalyzed Aerobic Oxidative Phosphonation of N-aryl tetrahydroisoquinolines

To a solution of N-aryl tetrahydroisoquinoline **1** (0.4 mmol) in ethanol (2.0 mL) were added dialkyl phosphite **2** (0.8 mmol) and then $Fe(NO_3)_3 \cdot 9H_2O$ (16 mg, 0.04 mmol). The reaction mixture was stirred vigorously under an open atmosphere at 30 °C for 24−48 h until the N-aryl tertrahydroisoquinoline substrate disappeared by TLC monitoring. After completion of the reaction, the reaction mixture was poured into 5% aqueous $NaHCO_3$ solution (20 mL), then was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with saturated NaCl aqueous solution and then dried over sodium sulfate. After removing the solvent in vacuo, the residue was purified by flash chromatography on silica gel to afford the corresponding coupling products.

Diethyl (6-Chloro- 2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (13)

Column chromatography (hexane: ethyl acetate = 3: 1) on silica gel gave a light yellow solid (129 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$): δ7.32 (dd, *J* = 8.9 Hz, 2.2 Hz, 1H), 7.28 -- 7.20 (m, 2H), 7.15 (d, *J* = 6.6 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 5.13 (d, *J* = 20.7 Hz, 1H), 4.16 -- 3.98 (m, 4H), 3.92 (ddd, *J* = 17.2 Hz, 11.1 Hz, 7.1 Hz, 1H), 3.68 -- 3.59 (m, 1H), 3.06 -- 2.89 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.54 (s, 1P).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.40 (d, *J* = 6.3 Hz), 138.42 (d, *J* = 5.6 Hz,), 133.22 (d, *J* = 4.2 Hz), 129.57 (d, *J* = 4.5 Hz), 129.35 (s), 128.86 (d, *J* = 2.5 Hz), 119.04 (s, 2H), 115.21 (s), 63.57 (d, *J* = 7.3 Hz), 62.46 (d, *J* = 7.7 Hz), 58.47 (d, *J* = 159.9 Hz), 43.27 (s), 26.64 (s), 16.54 (dd, *J* = 9.2, 5.6 Hz); MS (EI) *m*/*z* 379 $[M]^+$; HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{19}H_{23}ClNO_3P$, 379.1104; found 379.1101.

Diisopropyl (6-Chloro- 2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (14)

Column chromatography (hexane: ethyl acetate = 3: 1) on silica gel gave a light yellow solid (127 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.9 Hz, 2.0 Hz, 1H), 7.28 -- 7.19 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 6.79 (t, *J* = 7.3 Hz, 1H), 5.07 (d, *J* = 22.0 Hz, 1H), 4.72 -- 4.57 (m, 2H), 4.12 -- 4.00 (m, 1H), 3.66 (dt, *J* = 13.0 Hz, 5.0 Hz, 1H), 2.94 (dt, *J* = 8.1 Hz, 4.1 Hz, 2H), 1.30 (dd, *J* = 8.7 Hz, 6.2 Hz, 6H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.98 (d, *J* = 6.2 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.15 (s, 1P); ^{13}C NMR (101 MHz, $CDCl_3$) δ

149.57 (d, *J* = 7.2 Hz), 138.45 (d, *J* = 5.7 Hz), 133.06 (d, *J* = 4.2 Hz), 129.89 (d, *J* = 4.5 Hz), 129.67 (d, *J* = 1.5 Hz), 129.24 (s,), 128.82 (d, *J* = 2.5 Hz), 125.98 (d, *J* = 2.9 Hz), 118.90 (s), 115.49 (s), 72.52 (d, *J* = 7.8 Hz), 71.07 (d, *J* = 8.1 Hz), 58.46 (d, *J* = 161.9 Hz), 43.34 (s), 26.42 (s), 24.70 (d, *J* = 2.9 Hz), 24.25 (d, *J* = 3.3 Hz), 23.93 (d, *J* = 5.5 Hz), 23.52 (d, *J* = 5.5 Hz); MS (EI) *m*/*z* 407 $[M]^+$; HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{21}H_{27}ClNO_3P$, 407.1417; found 407.1422.

Dibutyl (6-Chloro- 2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (15)

Column chromatography (hexane: ethyl acetate = 3: 1) on silica gel gave a light yellow solid (131 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.9 Hz, 2.2 Hz, 1H), 7.28 -- 7.21 (m, 2H), 7.15 (d, *J* = 6.3 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 5.14 (d, *J* = 20.6 Hz, 1H), 4.09 -- 3.77 (m, 5H), 3.71 -- 3.59 (m, 1H), 3.06 -- 2.89 (m, 2H), 1.57 (dd, *J* = 13.5, 6.7 Hz, 2H), 1.46 (td, *J* = 13.6 Hz, 6.7 Hz, 2H), 1.38 -- 1.21 (m, 4H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.70 (s, 1P); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.34 (d, *J* = 6.1 Hz), 138.39 (d, *J* = 5.6 Hz), 133.21 (d, *J* = 4.2 Hz), 129.64, 129.59, 129.57 (d, *J* = 0.86 Hz), 129.33 (s), 128.84 (d, *J* = 2.5 Hz), 126.20 (d, *J* = 2.8 Hz), 118.99 (s), 115.17 (s), 67.18 (d, *J* = 7.5 Hz), 66.12 (d, *J* = 7.9 Hz), 58.40 (d, *J* = 159.3 Hz), 43.23 (s), 32.69 (dd, *J* = 7.4, 5.6 Hz), 26.69 (s), 18.79 (d, *J* = 7.8 Hz), 13.65 (d, *J* = 4.8 Hz); MS (EI) *m*/*z* 435 $[M]^+$; HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{23}H_{31}ClNO_3P$, 435.1730; found 435.1738.

Complete experimental details are available online in the Supplemental Materials.

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ACCEPTED MANUSCRIPT

Table 1. Optimization of Reaction Conditions[a]

Entry	Iron catalysts	Solvent	Time	Yield[b]
1.	$FeCl_2$	EtOH	48 h	33%
2.	$Fe(OAc)_2$	EtOH	48 h	31%
3.	$FeCl_3 \cdot 6H_2O$	EtOH	48 h	58%
4.	$Fe_2(SO_4)_3$	EtOH	48 h	45%
5.	$Fe(NO_3)_3 \cdot 9H_2O$	EtOH	24 h	93%
6.	Fe_2O_3	EtOH	48 h	none[c]
7.	no catalyst	EtOH	48 h	none[c]
8.	$Fe(NO_3)_3 \cdot 9H_2O$[d]	EtOH	48 h	19%
9.	$Fe(NO_3)_3 \cdot 9H_2O$	CH_2Cl_2	48 h	37%
10.	$Fe(NO_3)_3 \cdot 9H_2O$	DMF	48 h	24%
11.	$Fe(NO_3)_3 \cdot 9H_2O$	THF	48 h	12%

[a]General conditions: **1a** (0.2 mmol, 1.0 eq) and **2a** (0.4 mmol, 2.0 eq) was dissolved in solvent (1.0 mL), then added iron catalysts (0.02 mmol, 0.1 eq), stirring at ambient condition (open-flask, 30 °C).

[b]Isolated yield by column chromatography.

[c]No formation of **3**.

[d]The reaction was run under nitrogen atmosphere (O_2 free condition).

Table 2. Iron-catalyzed aerobic oxidative phosphonation of N-aryl tetrahydroisoquinolines [a]

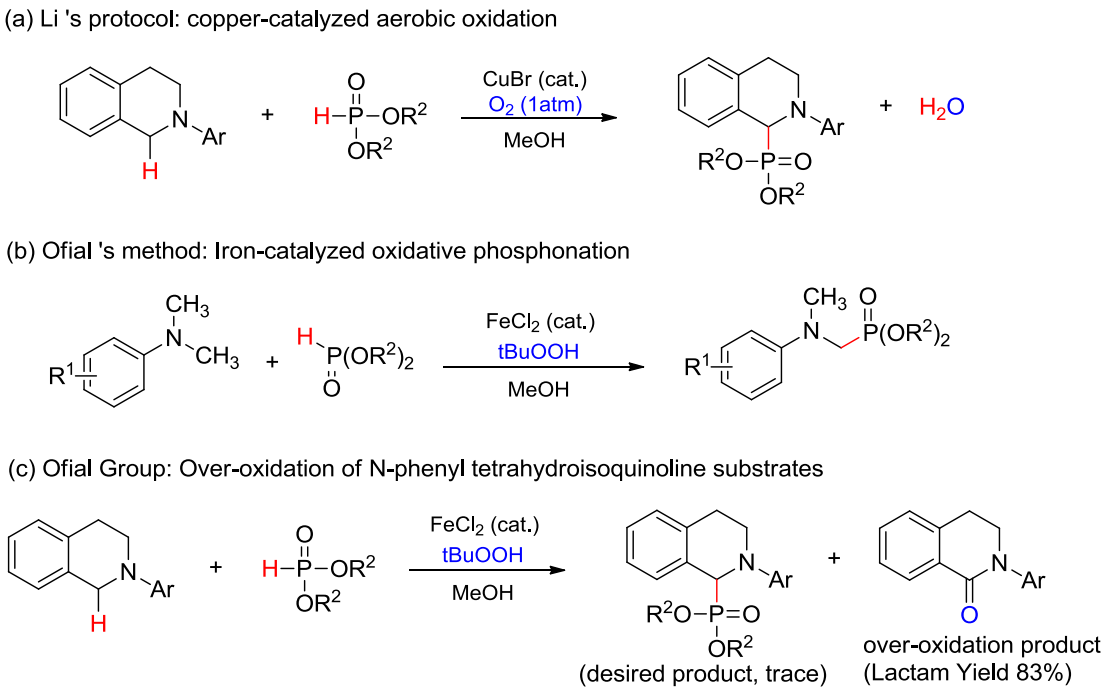
Entry	R^1	R^2	R^3	Product	Yield[b]
1.	Ph (**1a**)	H(**1a**)	Et (**2a**)	**3** [d]	93%
2.	Ph (**1a**)	H(**1a**)	^{i}Pr (**2b**)	**4**[d]	88%
3.	Ph (**1a**)	H(**1a**)	Bu (**2c**)	**5**[d]	82%
4.	Ph (**1a**)	H(**1a**)	Bn (**2d**)	**6**[d]	84%
5.	4-$MeOC_6H_4$ (**1b**)	H(**1b**)	Et (**2a**)	**7**[d]	80%
6.	2-$MeOC_6H_4$ (**1c**)	H(**1c**)	Et (**2a**)	**8**[d]	76%
7.	4-ClC_6H_4 (**1d**)	H(**1d**)	Et (**2a**)	**9**[d]	82%
8. [c]	3-$O_2NC_6H_4$ (**1e**)	H(**1e**)	Et (**2a**)	**10**[d]	55%
9.	4-$MeOC_6H_4$ (**1b**)	H(**1b**)	^{i}Pr (**2b**)	**11**[d]	77%
10.	4-ClC_6H_4 (**1c**)	H(**1c**)	^{i}Pr (**2b**)	**12**[d]	74%
11.	Ph (**1f**)	6-Cl(**1f**)	Et (**2b**)	**13**	85%
12.	Ph (**1f**)	6-Cl(**1f**)	^{i}Pr (**2b**)	**14**	78%
13.	Ph (**1f**)	6-Cl(**1f**)	Bu (**2c**)	**15**	75%

[a]General conditions: **1** (0.4 mmol, 1.0 eq) and **2** (0.8 mmol, 2.0 eq) was dissolved in EtOH (2.0 mL), then added iron catalysts (0.04 mmol, 0.1 eq), stirring at ambient condition (open-flask, 30 °C) for 24-48 h.

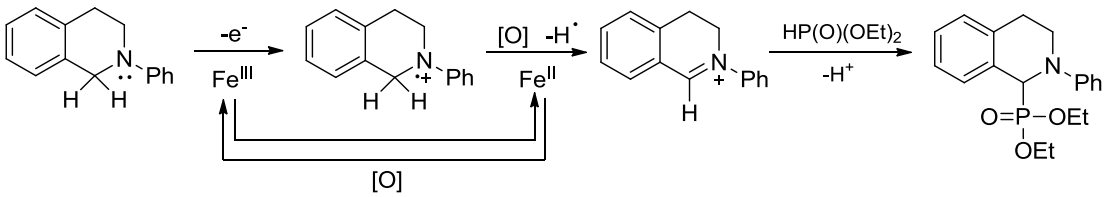
[b]Isolated yield by column chromatography.

[c]The reaction was performed under the condition of O_2 (1atm) atmosphere and 60 °C.

[d]The NMR spectra of compounds **3-12** was consistent with the reference 9.

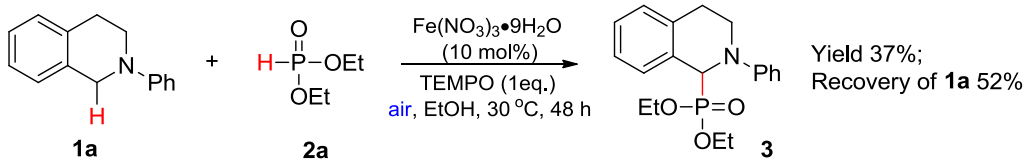


Scheme 1. Representative Base Metal Catalyzed Methods for the Oxidative Phosphonation of Tertiary Amines.



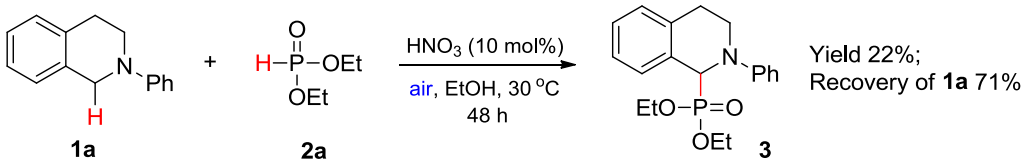
Scheme 2. Plausible Mechanism for Iron-catalyzed aerobic oxidative phosphonation

(a) Suppression effect of addition of radical scavenger



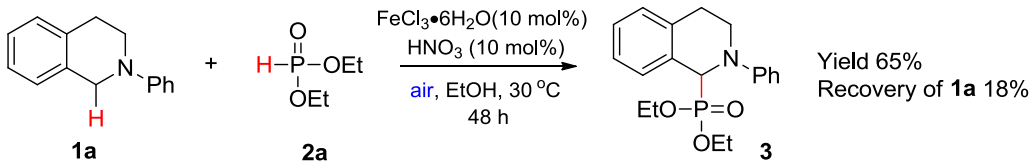
1a 2a 3

(b) Role of oxidizing nitrate in this oxidative coupling



1a 2a 3

(c) catalyitic activities of a Fe^{3+} and NO_3^- mixed system



1a 2a 3

Scheme 3. Preliminary Mechanistic Investigations