

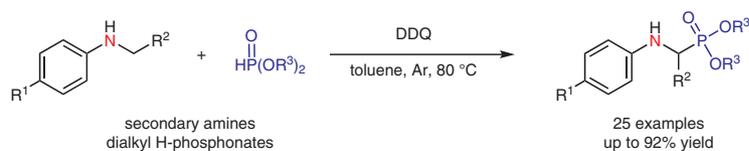
DDQ-Mediated Cross-Dehydrogenative-Coupling Reaction of Secondary Amines with Dialkyl Phosphonates

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- Metal free
- Mild reaction condition
- C–P bond formation
- A gram-scale synthesis

Received: 29.09.2018

Accepted after revision: 09.11.2018

Published online: 30.11.2018

DOI: 10.1055/s-0037-1611362; Art ID: st-2018-w0625-l

Abstract This work reports a DDQ-mediated cross-dehydrogenative-coupling reaction of secondary amines with dialkyl phosphonates under mild conditions. This reaction proceeds efficiently without involving visible light or transition-metal catalysis. This new approach provides efficient access to biologically important α -aminophosphonates.

Key words DDQ, cross-dehydrogenative-coupling, phosphorylation, allylic amines, dialkyl phosphonates, aminophosphonates

α -Aminophosphonates and their derivatives have attracted widespread attention in organic and medicinal chemistry because of their range of biological applications, for example as enzyme inhibitors,¹ catalytic antibodies,² anti-HIV agents,³ antibacterials,⁴ or antifungal agents⁵ (Figure 1).

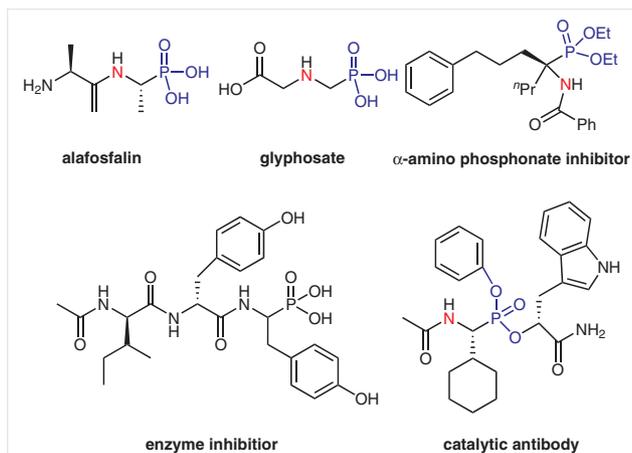
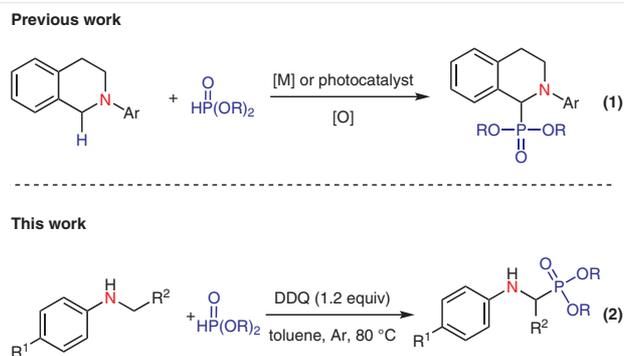


Figure 1 Representative examples of α -aminophosphonates and their derivatives

A simple approach to the synthesis of α -aminophosphonates involves the addition of phosphites to imines, known as the aza-Pudovik reaction.⁶ Another conventional strategy involves the Kabachnik–Fields reaction⁷ of aldehydes, amines, and dialkyl phosphonates. Recently, a new method for the synthesis of α -aminophosphonates by cross-dehydrogenative-coupling (CDC) of tertiary amines with H–P compounds has been developed (Scheme 1, eq 1).^{8–10} In 2009, Baslé and Li reported an efficient CDC reaction between sp^3 C–H and P–H bonds with a copper salt as catalyst and molecular oxygen as the terminal oxidant.^{8a} In the same year, Han and Ofial reported an Fe-catalyzed CDC reaction of *N,N*-dimethylanilines with dialkyl phosphonates in the presence of *tert*-butyl hydroperoxide (TBHP).^{8b} Then, Zhu and co-workers reported an Au-catalyzed oxidative phosphorylation of tertiary amines.^{8c} More recently, Kumar and co-workers reported a cobalt(II)/*N*-hydroxyphthalimide-catalyzed CDC reaction of *N*-aryltetrahydroisoquinolines with dialkyl phosphonates.^{8d} On the other hand, photoredox-catalyzed phosphorylations of tertiary amines



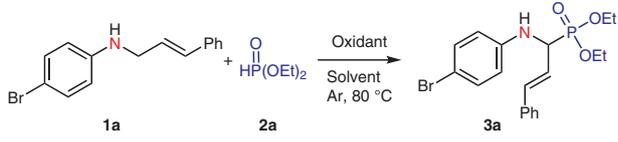
Scheme 1 Oxidative phosphorylation of tertiary amines and secondary amines with dialkyl phosphonates

have been developed by the groups of Rueping,^{9a} Kobayashi,^{9b} König,^{9c} and others.^{9d–j} Finally, a catalyst-free oxidative phosphorylation of tertiary amines has been reported.¹⁰ However, the oxidative phosphorylation of secondary amines has rarely been reported.¹¹ Here, we report a DDQ-mediated CDC reaction of allylic amines with dialkyl phosphonates under mild reaction conditions (Scheme 1, eq 2).

Initially, we used 4-bromo-*N*-cinnamylaniline (**1a**) and diethyl phosphite (**2a**) as starting materials to optimize the reaction conditions. When a mixture of **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), and 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ; 0.24 mmol, 1.2 equiv) was stirred in toluene (2.0 mL) at 80 °C, the desired oxidative phosphorylation product **3a** was isolated in 83% yield (Table 1, entry 1). Inspired by this result, we tested a series of oxidants [1,4-benzoquinone (BQ), Ag₂O, PhI(OAc)₂, K₂S₂O₈, 2-iodoxybenzoic acid (IBX), potassium monopersulfate triple salt

(Oxone), and TBHP] for this coupling reaction. However, no better results were achieved compared with DDQ (24–64% yield; entries 2–9). When O₂ was used to test this reaction,

Table 1 Optimization of the Reaction Conditions^a



Entry	Oxidant	Solvent	Yield ^b (%)
1	DDQ	toluene	83
2	BQ	toluene	45
3	Ag ₂ O	toluene	40
4	PhI(OAc) ₂	toluene	47
5	K ₂ S ₂ O ₈	toluene	61
6	IBX	toluene	24
7	Oxone	toluene	43
8 ^c	TBHP	toluene	55
9 ^d	TBHP	toluene	64
10	O ₂	toluene	trace
11	DDQ	MeCN	71
12	DDQ	DCE	75
13	DDQ	1,4-dioxane	64
14	DDQ	PhCl	78
15	DDQ	MeNO ₂	35
16 ^e	DDQ	toluene	76
17 ^f	DDQ	toluene	47
18 ^g	DDQ	toluene	92

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.24 mmol), solvent (2.0 mL), 80 °C, 48 h.

^b Isolated yield.

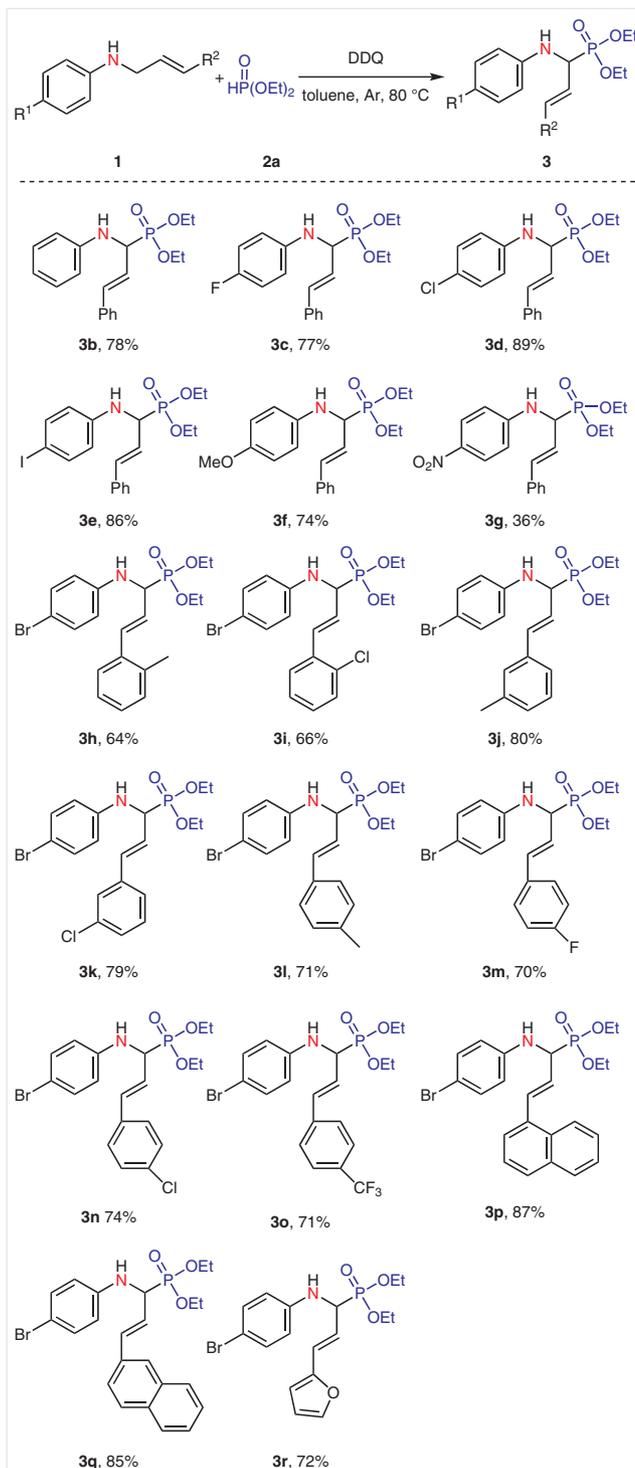
^c TBHP (5.5 M in decane)

^d TBHP (70% in H₂O)

^e At 60 °C.

^f At 100 °C.

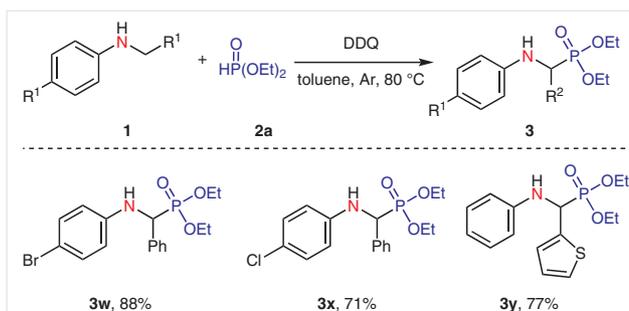
^g **2a** (0.36 mmol) was used.



only a trace of the product **3a** was isolated (entry 10). A series of solvents (MeCN, DCE, 1,4-dioxane, PhCl, MeNO₂) were also tested for this coupling reaction, but toluene emerged as the most suitable solvent (entries 11–15). Lowering the temperature to 60 °C or raising it to 100 °C did not improve the yield of product **3a** (entries 16 and 17). When the amount of diethyl phosphite (**2a**) was decreased to 1.8 equivalents, the best result was obtained (92% yield; entry 18).

With the optimized conditions in hand, we examined the scope of the coupling reaction (Scheme 2). First, we screened the influence of the *N*-substituent on the allylamine. With no substituent on the *N*-aryl ring, the reaction occurred successfully, and product **3b** was obtained in moderate yield (78%). The target products **3c–f** were also obtained in moderate yields of 74–89% when the *N*-aryl ring was substituted with 4-F, 4-Cl, 4-I, or 4-OMe groups, respectively. However, the presence of a 4-NO₂ substituent decreased the yield of **3g** sharply to 36%. Next, we explored the scope in terms of aromaticity. Electron-donating or -withdrawing groups, as well as halogen substituents, were well tolerated. Regardless of the position of the substituent on the aromatic ring, the reaction occurred smoothly, and the corresponding products **3h–o** were obtained in yields of 64–80%. Substrates with a 1- or 2-naphthyl substituent instead of a phenyl substituent also afforded the corresponding coupling products **3p** and **3q** in high yields of 87 and 85%, respectively. To our delight, a substrate with a heteroaromatic substituent was suitable for this CDC reaction, and the corresponding phosphonate **3r** was obtained in a yield of 72%.

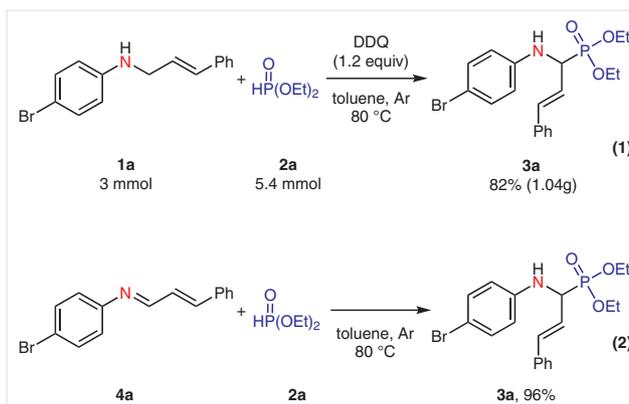
We also tested the scope of the dialkyl phosphonate, and the results are shown in Scheme 3. Dimethyl phosphite, diisopropyl phosphite, dibutyl phosphite, and di-*tert*-butyl phosphite all gave the corresponding phosphorylation products in this CDC reaction. It was noted that the yield decreased gradually with increasing steric hindrance of the substrate.



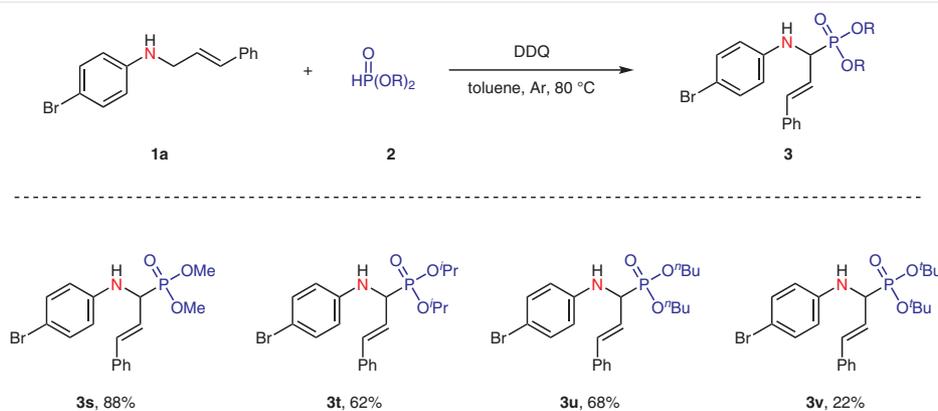
Scheme 4 CDC reaction of secondary *N*-alkylanilines and diethyl phosphite (**2a**). Reaction conditions: **1** (0.2 mmol), **2a** (0.36 mmol), DDQ (0.24 mmol), toluene (2.0 mL), 80 °C, 48 h. Isolated yields are reported.

Next, secondary *N*-alkylanilines were tested as substrates, and the results are shown in Scheme 4. *N*-Benzyl-4-bromoaniline, *N*-benzyl-4-chloroaniline, and *N*-(2-thienylmethyl)aniline were suitable substrates for this coupling reaction and gave the corresponding phosphonates **3w–y** in good yields of 71–88%.

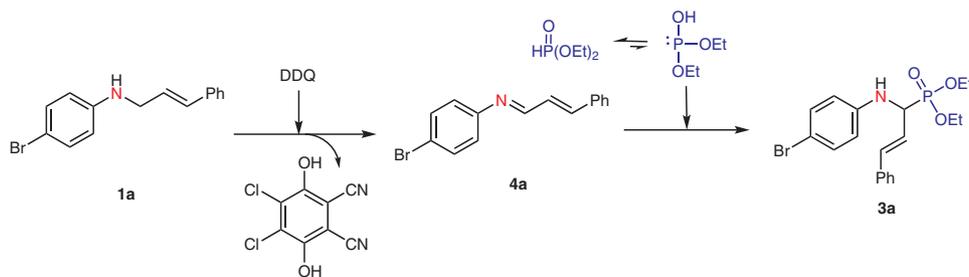
Note that this synthesis of α-aminophosphonates could be scaled up effectively with high efficiency. For example,



Scheme 5 Application study and exploration of the mechanism



Scheme 3 CDC reaction of 4-bromo-*N*-cinnamylamine (**1a**) with various dialkyl phosphonates **2**. Reaction conditions: **1a** (0.2 mmol), **2b–e** (0.36 mmol), DDQ (0.24 mmol), toluene (2.0 mL), 80 °C, 48 h. Isolated yields are reported.



Scheme 6 Plausible reaction mechanism for the coupling reaction

1a (3 mmol), **2a** (5.4 mmol), and DDQ (1.2 equiv) in toluene at 80 °C for 48 hours gave the corresponding product **3a** in 82% yield (Scheme 5, eq 1). Moreover, to our delight, the target product **3a** was obtained in high yield when we used the (1*E*,2*E*)-*N*-(4-bromophenyl)-3-phenylprop-2-en-1-imine (**4a**) and diethyl phosphite (**2a**) as starting materials (Scheme 5, eq 2). This result indicates that allylimine **4a** might be the reaction intermediate.

On the basis of our experimental results and previous reports,¹¹ we propose the mechanism for the DDQ-mediated CDC reaction of allylamines with dialkyl phosphonates shown Scheme 6. Initially, allylimine **4a** might be generated in situ from allylamine **1a** under oxidative conditions. Next, diethyl phosphite isomerizes to the active trivalent phosphorus compound. Finally, the active trivalent phosphorus compound attacks allylimine **4a** to afford the target product **3a**.

In summary, we have developed a novel DDQ-mediated simple method for the CDC reaction of secondary amines with dialkyl phosphonates to give α -aminophosphonates.^{12,13} The reaction proceeded efficiently without involving visible light or transition-metal catalysts. This practical protocol provides a convenient and efficient approach to biologically important α -aminophosphonates. Further investigations on transition-metal-free catalytic reactions are in progress.

Funding Information

Financial support from the Project of Science and Technology of Henan Province (No. 162102310448).

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611362>.

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- (12) **α -Aminophosphonates 3; General Procedure**
A Schlenk tube charged with secondary amine **1** (0.2 mmol) and DDQ (0.24 mmol, 1.2 equiv) was purged three times with argon. Anhyd toluene (2.0 mL) and phosphite **2** (0.36 mmol, 1.8 equiv) were added, and the mixture was stirred at 80 °C under Ar for 48 h. When the reaction was complete (TLC), the mixture was washed with sat. aq Na₂CO₃, concentrated, and purified by column chromatography (silica gel).
- (13) **Diethyl {(2*E*)-1-[(4-Bromophenyl)amino]-3-phenylprop-2-en-1-yl}phosphonate (3a)**
Viscous oil; yield: 78 mg (92%). ¹H NMR (400 MHz, CDCl₃): δ = 7.46–7.16 (m, 7 H), 6.67 (dd, *J* = 15.9, 4.8 Hz, 1 H), 6.62–6.50 (m, 2 H), 6.23 (dt, *J* = 16.0, 5.4 Hz, 1 H), 4.41 (dd, *J* = 19.4, 6.6 Hz, 2 H), 4.29–4.06 (m, 4 H), 1.30 (td, *J* = 7.1, 4.6 Hz, 6 H). ¹³C NMR (101 MHz, CDCl₃): δ = 145.48 (d, *J* = 12.5 Hz), 136.00 (d, *J* = 3.2 Hz), 133.11 (d, *J* = 12.3 Hz), 131.93, 128.53, 127.93, 126.51 (d, *J* = 1.8 Hz), 122.83 (d, *J* = 4.6 Hz), 115.36 (d, *J* = 8.5 Hz), 110.15, 63.44 (d, *J* = 7.1 Hz), 63.08 (d, *J* = 7.2 Hz), 54.71, 53.18, 16.43 (t, *J* = 5.2 Hz). ³¹P NMR (162 MHz, CDCl₃): δ = 21.92. MS (ESI): *m/z* = 424.1 [M + H]⁺.