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Direct Phosphonylation of *N*-Carbamate-tetrahydroisoquinoline by Convergent Paired Electrolysis

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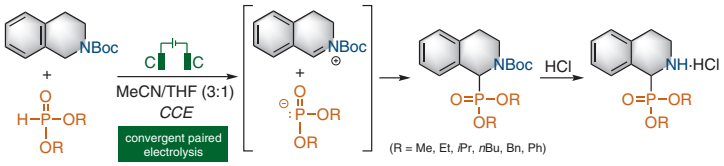

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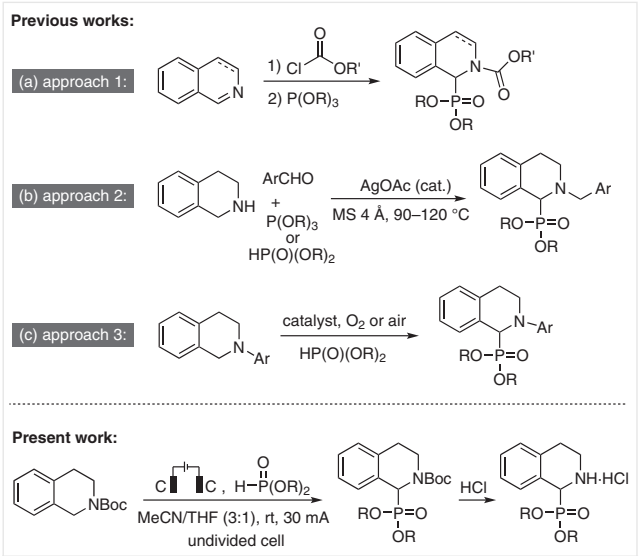
Abstract Mild experimental conditions for a direct phosphonylation of an easily cleavable *N*-carbamate-tetrahydroisoquinoline have been described under constant current electrolysis. The developed electrochemical process allowed to prepare α-aminophosphonates in moderate to good yields. On the basis of the experimental results, a mechanism proceeding through a convergent paired electrochemical process was enabled to be postulated.

Key words electrosynthesis, convergent paired electrolysis, phosphonylation, aminophosphonates, *N*-Boc-tetrahydroisoquinoline

The renewed interest in organic electrosynthesis in recent years is due, among others, to the easier access to carbon–carbon or carbon–heteroatom bonds.[1] The ability to generate selectively reduced or oxidized intermediates in situ, with a simplified and eco-compatible methodology, replacing conventional reducing and oxidizing agents, contributes to making the approach more attractive. The formation of C(sp^3)–P bonds has been the subject of the development of chemical or electrochemical methods for the synthesis of tetrahydroisoquinoline (THIQ) phosphonates by C1-phosphonylation. α-Aminophosphonic acids,[2] considered as bioisosteres of α-amino acids, have received special attention from the community in medicinal chemistry.[3] As our laboratory has an expertise in organic electrosynthesis,[4] it is envisaged to take the advantage of this know-how to develop a direct C(sp^3)–P bond formation on this amino substrate model, while focusing on the mechanistical study of the coupling. Among different documented chemical approaches to phosphonylate THIQ at the C1 position, three main approaches have been envisaged for the synthesis of tetrahydroisoquinoline phosphonates (Scheme 1).



Scheme 1 Described chemical approaches for the synthesis of tetrahydroisoquinoline phosphonates

In the first approach, isoquinoline or 3,4-dihydroisoquinoline is activated by alkyl chloroformate on its iminium salt form prior to react with trialkyl phosphite under heating (Scheme 1, a).[5] It can be noted that a further step is mandatory to reduce the double bond when isoquinoline was employed. Moreover, through this approach, Mukherjee and co-workers reported an elegant catalytic enantioselective dearomatized phosphonylation of *N*-acyl isoquinolinium.[6] In the second approach, *N*-benzyl-tetrahydroisoquinoline phosphonates were prepared by a silver-catalyzed three-component strategy starting from NH-free tetrahydroisoquinoline, benzaldehyde derivative, and trialkyl or dialkyl phosphite under heating (Scheme 1, b). Silver

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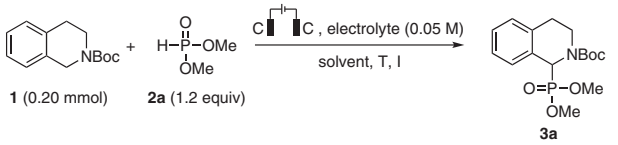
acetate is used to isomerize exocyclic iminium intermediate to the thermodynamically stable endocyclic isomer leading regioselectively to C1-phosphonylation of THIQ.[7]

The last approach, extensively reported compared to the two previous ones, constitutes the described traditional method for the synthesis of tetrahydroisoquinoline phosphonates from *N*-aryl tetrahydroisoquinoline using aerobic conditions in the presence of catalytic[8] or stoichiometric oxidant,[9] or by photoredox catalysis[10] to achieve C(sp^3)–H and P–H cross-dehydrogenative couplings via iminium intermediate formation (Scheme 1, c). However, the preparation of tetrahydroisoquinoline phosphonates by an electrochemical method is poorly explored to date[11] until recently, where Xiang and co-workers[12] have reported constant current electrochemical *N*-aryl-tetrahydroisoquinoline couplings with dialkyl phosphites. It is important to emphasize that the employed *N*-aryl protecting groups are hardly or not cleavable and the postulated mechanism is only based on literature reports. At the same time, Ding and co-workers[13] have described a less common protocol in organic electrosynthesis by employing controlled potential (with a potential difference of 6.6 V between the two electrodes) in the presence of additive base to phosphonylate successfully unprotected tetrahydroisoquinoline derivatives. In this present work, a simple electrochemical approach of C(sp^3)–P bond formation under constant current electrolysis and using an easily cleavable tetrahydroisoquinoline nitrogen protecting group was disclosed. Additionally, mechanistic aspects of such electrochemical process were investigated and proposed, supported by complementary experiments.

Initially, *N*-Boc-protected tetrahydroisoquinoline (THIQ-*N*-Boc) **1** was prepared in quantitative yield by treating the commercially available tetrahydroisoquinoline with di-*tert*-butyl dicarbonate in the presence of catalytic amount of 4-dimethylaminopyridine in dichloromethane. Some experimental parameters were then examined to optimize the electrooxidative phosphonylation of THIQ-*N*-Boc with dimethyl phosphite (**2a**) as model phosphorous reagent (Table 1).

Current intensity was first analyzed. It can be observed that 10 mA (J = 2.18 mA/cm^2) gave the best result in cross-coupled product when 2.0 F/mol had been passed (Table 1, entry 1). At higher current intensity (entry 2), the yield decreases slightly at the expense of *N*-Boc-deprotected cross-coupled product. By increasing the amount of charges to 2.4 F/mol (entry 3), the yield drops to 52% and degradation of the expected product was observed. In order to limit its degradation, some experimental parameters were examined. When lowering substrates concentration by 2 (entry 4), the yield drops to 50%. Conversely, the yield is not affected by doubling their concentration (entry 5). The increase of the amount of dimethyl phosphite to 2.4 equivalents has no effect on the yield (entry 6). The replacement of tetraethylammonium tetrafluoroborate by some other common electrolytes (entries 7 and 8) resulted in lower yields. Heating the reaction at 45 °C (entry 9) or lowering the temperature to 0 °C (entry 10) did not return a better yield. In the last series of experiments, the solvent was assessed. The addition of THF as co-solvent to acetonitrile in 1:3 ratio allowed to improve slightly the yield (entry 11). It is important to note that under these new conditions, no degradation of the product was observed. Indeed, it is noteworthy that when the reaction was carried out in acetonitrile without THF, more important amount of the *N*-Boc-deprotected product was observed which led to its degradation as this product is more easily oxidizable than the starting THIQ-*N*-Boc substrate. However, the use of an excess of THF versus acetonitrile has the inverse effect on the yield (entry 12). Finally, the yield was enhanced by increasing the amount of charge to 3 F/mol (entry 14) and 70% of phosphonylated compound was isolated. It noteworthy that, under these optimized experimental conditions, direct electrochemical phosphonylation of unprotected tetrahydroisoquinoline with dialkyl phosphite leads mainly to a mixture of side products, only traces of the expected product were observed.

Table 1 Experimental Parameters Optimization of THIQ-*N*-Boc for Direct Electrooxidative Phosphonylation with Dimethyl Phosphite[a]



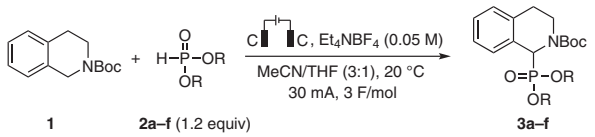
1 (0.20 mmol) **2a** (1.2 equiv) **3a**

Entry	Electrolyte	Solvent	Charge (F/mol)	I (mA)	Temp (°C)	Yield (%)[b]
1	Et_4NBF_4	MeCN	2.0	10	20	64
2	Et_4NBF_4	MeCN	2.0	15	20	53
3	Et_4NBF_4	MeCN	2.4	10	20	52
4	Et_4NBF_4	MeCN	2.0	10	20	50[c]
5	Et_4NBF_4	MeCN	2.0	10	20	63[d]
6	Et_4NBF_4	MeCN	2.0	10	20	64[e]
7	KBF_4	MeCN	2.0	10	20	61
8	$LiClO_4$	MeCN	2.0	10	20	45
9	Et_4NBF_4	MeCN	2.0	10	45	32
10	Et_4NBF_4	MeCN	2.0	10	0	50
11	Et_4NBF_4	MeCN/THF (3:1)	2.0	10	20	68
12	Et_4NBF_4	MeCN/THF (1:3)	2.0	10	20	32
13	Et_4NBF_4	MeCN/THF (3:1)	2.5	10	20	74
14	Et_4NBF_4	MeCN/THF (3:1)	3.0	10	20	80 (70)[f]

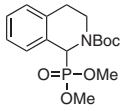
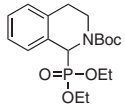
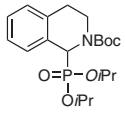
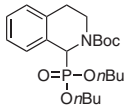
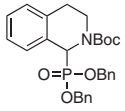
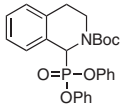
[a] Reaction conditions: undivided cell, graphite electrodes plates, solvent (2 mL), electrolyte (0.10 mmol), THIQ-*N*-Boc (0.20 mmol), dimethyl phosphite (0.24 mmol, 1.2 equiv), constant current, room temperature.
[b] Yields determined by ^{1}H NMR analysis.
[c] **1** (0.10 mmol).
[d] **1** (0.40 mmol).
[e] **2a** (0.48 mmol, 2.4 equiv).
[f] Isolated yield.

With the optimized conditions in hands,[14] the scope of phosphite reagents was explored (Table 2).[15]

Table 2 Scope of Phosphites Reagents[a]



1 **2a–f** (1.2 equiv) **3a–f**

Entry	R	Product		Isolated yield (%)
1	Me		**3a**	70
2	Et		**3b**	65
3	*i*-Pr		**3c**	50
4	*n*-Bu		**3d**	71
5	Bn		**3e**	45
6	Ph		**3f**	–

[a] Typical procedure: In a 15 mL electrochemical cell fitted with two graphite plate electrodes were successively added MeCN/THF (3:1, 10 mL, v/v), tetraethylammonium tetrafluoroborate (0.50 mmol), then THIQ-*N*-Boc (1 mmol) and dialkyl phosphite (1.20 mmol). The resulting solution was electrolyzed under stirring at 20 °C for 161 min (3.0 F/mol) at constant current of 30 mA (current density: 3.42 mA/cm^2).

Good yields were obtained with linear dialkyl phosphites (Table 2, entries 1, 2, and 4). When diisopropyl phosphite was used, the yield drops to 50% probably due to steric effect (entry 3). Phosphonylation can be applied with dibenzyl phosphite although moderate yield was obtained (2, entry 5). However, phosphonylation failed with diphenyl phosphite (entry 6). This result can be attributed to the oxidability of diphenyl phosphite (Ep = 1.55 V/SCE, Figure 1, c) unlike to other phosphites which are not oxidizable under the electrochemical couplings conditions (Figure 1, b). Indeed, diphenyl phosphite is more easily oxidizable than THIQ-*N*-Boc (Ep = 1.97 V/SCE, Figure 1, d) thus preventing the coupling to occur, contrary to what has been observed by Xiang et al.[12] with *N*-arylated THIQ substrates (Ep < 1.55 V/SCE). Moreover, it can be noted that the THIQ-*N*-Boc peak current intensity (Ip) is comparable with the two-electrons exchange (iminium formation) compared to that of a solution of ferrocene.

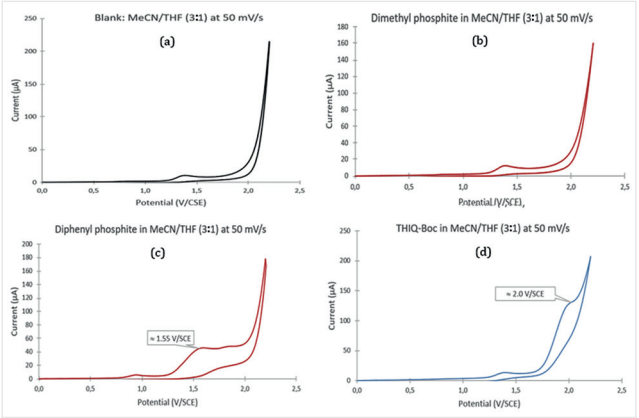
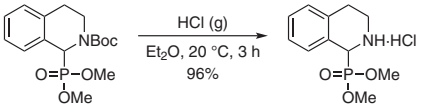


Figure 1 Cyclic voltammetries of substrates: (a) blank, (b) dimethyl phosphite, (c) diphenyl phosphite, (d) THIQ-*N*-Boc.

The deprotection of the coupled product **3a** was performed successfully at room temperature in a saturated hydrochloric chloride diethyl ether solution to afford the free amino-tetrahydroisoquinoline chlorhydrate salt in an excellent yield (Scheme 2).

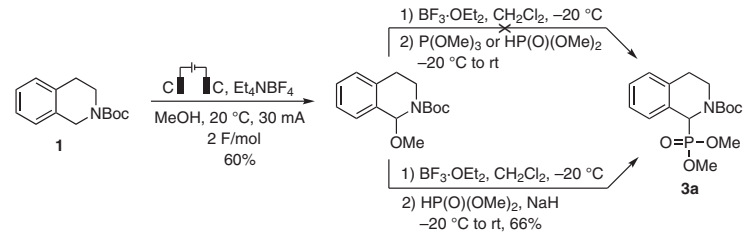


3a **3a'**

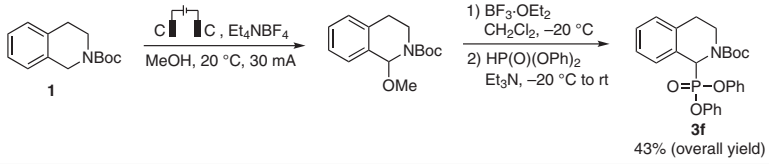
Scheme 2 Deprotection of THIQ-*N*-Boc in saturated HCl–diethyl ether solution

Our electrochemical process was then compared to indirect phosphonylation via Shono methoxylation sequence. For this purpose, THIQ-*N*-Boc was methoxylated using the Shono standard procedure in methanol under constant current electrolysis. The iminium intermediate is generated from methoxylated THIQ-*N*-Boc using boron trifluoride etherate, followed by trapping with dimethyl phosphite anion, prior deprotonated with sodium hydride, to afford the expected product in 66% yield. It is important to note that only traces of the expected product were observed either with trimethyl phosphite or with dimethyl phosphite non-deprotonated with a base (Scheme 3). This constitutes an important result for the mechanistic insight. Finally, this approach allowed to afford the product in 40% overall yield in three steps starting from THIQ-*N*-Boc, which is less efficient compared to our present electrochemical process.

In the case of diphenyl phosphite where our method failed due to the oxidability of the reagent under our conditions, the coupling was successfully performed via Shono



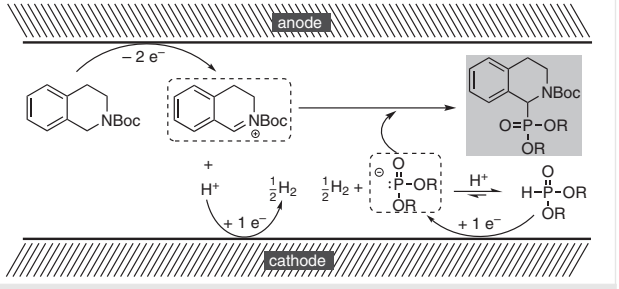
Scheme 3 Indirect phosphonylation of THIQ-*N*-Boc by Shono methoxylation sequence, followed by Lewis acid iminium generation and phosphite trapping



Scheme 4 Indirect phosphonylation of THIQ-*N*-Boc with diphenyl phosphite by Shono methoxylation sequence

methoxylation sequence in 43% overall yield (Scheme 4). A weaker base (triethylamine) was employed since the pK_a value of diphenyl phosphite was estimated to 9.0 unlike dimethyl phosphite, estimated to 18.4.[16] The weak reactivity of phosphite reagent was observed in the absence of triethylamine.

Based on the experimental results, the postulated mechanism for direct phosphonylation of *N*-carbamate-tetrahydroisoquinoline would proceed according to a convergent paired electrolysis (Scheme 5). The two-electron oxidation of THIQ-*N*-Boc substrate at the anode would lead to iminium intermediate with proton release, which can be reduced at the cathode into dihydrogen in a one-electron process. At the same time, the reactive phosphite anion is generated either by the one-electron direct reduction of dialkyl phosphite or via the deprotonation by the electrogenerated base from acetonitrile at the cathode. This key reactive phosphite anion is supported by chemical experiments (see Scheme 3). Both iminium and phosphite anion intermediates would then react in solution to afford the expected product.



Scheme 5 Postulated mechanism for the direct electrooxidative phosphonylation of THIQ-*N*-Boc via a convergent paired electrolysis

In summary, a direct electrochemical phosphonylation of easily cleavable *N*-carbamate-tetrahydroisoquinoline under constant current electrolysis was developed. Various phosphites were successfully coupled in moderate to good yields. The developed electrochemical process has shown a better efficiency compared to the three-step Shono approach. These studies allowed to postulate a mechanism involving a convergent paired electrochemical process where phosphite anion, formed at the cathode, reacts with iminium from THIQ-*N*-Boc generated at the anode to afford the coupling product.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690899.

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(14) **Experimental Procedure for Phosphonylation of *N*-Carbamate-tetrahydroisoquinoline**

In an electrochemical cell fitted with two graphite plate electrodes (thickness: 2 mm, submerged area: 8.78 cm^2, distance between the electrodes: 3–5 mm) was added a solution of tetraethylammonium tetrafluoroborate (109 mg, 0.50 mmol, 0.5 equiv) in MeCN/THF (3:1, 10 mL, v/v). The solution was bubbled with argon for 5 min before the successive addition of *N*-Boc-tetrahydroisoquinoline (233 mg, 1.00 mmol, 1.0 equiv) and dialkyl phosphite (1.20 mmol, 1.2 equiv). After 161 min (3.0 F/mol) of electrolysis (30 mA of current giving rise to a density of 3.42 mA cm^{-2}) under stirring at 20 °C, the reaction mixture was quenched with a 1 M HCl aqueous solution (20 mL) and diluted with Et_2O (20 mL). After layers separation, the aqueous layer was extracted by Et_2O (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography on silica gel column to afford the pure phosphonylated compound.

(15) **Characterization Data of Compounds 3a–f**

***tert*-Butyl 1-(Dimethoxyphosphoryl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3a)**

Colorless oil, yield 70% (237 mg). FC: ethyl acetate/petroleum ether (60:40). ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers in 55:45 ratio) = 7.45–7.41 (m, 1 H), 7.24–7.08 (m, 3 H), 5.71 (d, *J* = 20.5 Hz, 0.55 H), 5.52 (d, *J* = 20.6 Hz, 0.45 H), 4.28 (m, 0.45 H), 4.00 (m, 0.55 H), 3.83–3.37 (m, 7 H), 2.92–8.81 (m, 2 H), 1.48 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.5 (d, *J* = 3.4 Hz), 153.9 (d, *J* = 1.1 Hz), 135.0 (d, *J* = 4.1 Hz), 135.0 (d, *J* = 4.0 Hz), 130.8 (s), 129.4 (s), 128.9 (d, *J* = 1.9 Hz), 128.8 (s), 128.0 (d, *J* = 3.8 Hz), 127.7 (d, *J* = 3.6 Hz), 127.5 (d, *J* = 3.1 Hz), 127.3 (d, *J* = 3.1 Hz), 126.1 (d, *J* = 2.8 Hz), 126.1 (d, *J* = 2.8 Hz), 80.8 (s), 80.5 (s), 53.6 (d, *J* = 7.2 Hz), 53.4 (d, *J* = 6.7 Hz), 53.3 (d, *J* = 6.2 Hz), 53.2 (d, *J* = 149.7 Hz), 53.0 (d, *J* = 7.4 Hz), 51.8 (d, *J* = 152.3 Hz), 40.0 (s), 38.2 (s), 28.7 (s), 28.3 (s), 28.2 (s), 27.9 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ (mixture of rotamers) = 24.44, 23.99. HRMS (ESI$^+$): *m/z* calcd for $C_{16}H_{25}NO_5P$ [M + H]$^+$: 342.1465; found: 342.1467.

***tert*-Butyl 1-(Diethoxyphosphoryl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3b)**

Colorless oil, yield 65% (240 mg). FC: ethyl acetate/petroleum ether (60:40). ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers in 55:45 ratio) = 7.47–7.43 (m, 1 H), 7.22–7.11 (m, 3 H), 5.70 (d, *J* = 20.7 Hz, 0.55 H), 5.51 (d, *J* = 20.7 Hz, 0.45 H), 4.32–4.27 (m, 0.45 H), 4.15–3.93 (m, 4.4 H), 3.82–3.68 (m, 1 H), 3.55–3.48 (m, 0.45 H), 2.95–2.79 (m, 2 H), 1.49 and 4.48 (2 s, 9 H), 1.40–1.27 (m, 3 H), 1.19 (t, *J* = 7.1 Hz, 1.7 H), 1.12 (t, *J* = 7.0 Hz, 1.3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.5 (d, *J* = 4.0 Hz), 154.1 (d, *J* = 1.9 Hz), 135.2 (d, *J* = 5.6 Hz), 135.1 (d, *J* = 6.0 Hz), 129.8 (s), 129.4 (d, *J* = 1.1 Hz), 129.2 (s), 128.9 (d, *J* = 2.3 Hz), 128.2 (d, *J* = 3.9 Hz), 127.9 (d, *J* = 3.3 Hz), 127.4 (d, *J* = 3.3 Hz), 127.3 (d, *J* = 3.0 Hz), 126.0 (d, *J* = 2.7 Hz), 126.0 (d, *J* = 3.2 Hz), 80.7 (s), 80.30 (s), 63.2 (d, *J* = 7.3 Hz), 63.0 (d, *J* = 7.1 Hz), 62.6 (d, *J* = 7.0 Hz), 62.4 (d, *J* = 7.6 Hz), 53.6 (d, *J* = 153.0 Hz), 52.1 (d, *J* = 152.9 Hz), 40.0 (s), 38.2 (s), 28.4 (s), 28.2 (s), 27.9 (s), 16.4 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.92, 21.87. HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{29}NO_5P$ [M + H]$^+$: 370.1778; found: 370.1780.

***tert*-Butyl 1-(Diisopropoxyphosphoryl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3c)**

Colorless oil, yield 50% (198 mg). FC: ethyl acetate/petroleum ether (30:70). ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers in 55:45 ratio) = 7.49–7.40 (m, 1 H), 7.18–7.05 (m, 3 H), 5.64 (d, *J* = 21.7 Hz, 0.54 H), 5.45 (d, *J* = 21.1 Hz, 0.46 H), 4.70–4.59 (m, 1 H), 4.58–4.50 (m, 0.53 H), 4.45–4.35 (m, 0.47 H), 4.27 (dd, *J* = 13.4, 5.8 Hz, 0.45 H), 4.05–3.97 (m, 0.55 H), 3.73–3.64 (m, 0.53 H), 3.45 (ddd, *J* = 13.3, 11.6, 4.5 Hz, 0.47 H), 2.98–2.71 (m, 2 H), 1.45 and 1.44 (2 s, 9 H), 1.31–1.25 (m, 5 H), 1.25–1.20 (m, 4 H), 0.99 (d, *J* = 6.2 Hz, 1.6 H), 0.81 (d, *J* = 6.2 Hz, 1.4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.5 (d, *J* = 4.6 Hz), 154.1 (d, *J* = 1.8 Hz), 135.2 (d, *J* = 5.6 Hz), 135.1 (d, *J* = 5.7 Hz), 130.3 (s), 129.7 (s), 129.3 (s), 128.9 (s), 128.4 (d, *J* = 3.5 Hz), 128.0 (d, *J* = 3.3 Hz), 127.3 (d, *J* = 2.9 Hz), 127.1 (d, *J* = 2.9 Hz), 126.2 (s), 125.8 (d, *J* = 2.9 Hz), 80.5 (s), 80.1 (s), 72.0 (d, *J* = 7.4 Hz), 71.7 (d, *J* = 7.6 Hz), 71.1 (d, *J* = 7.5 Hz), 70.8 (d, *J* = 8.0 Hz), 54.1 (d, *J* = 151.2 Hz), 52.9 (d, *J* = 155.7 Hz), 39.9 (s), 38.0 (s), 28.4 (s), 28.19 (s), 27.9 (s), 24.41 (s), 24.2 (d, *J* = 3.0 Hz), 24.1 (s), 24.0 (d, *J* = 3.4 Hz), 23.8 (d, *J* = 5.7 Hz), 23.3 (d, *J* = 5.4 Hz), 23.1 (d, *J* = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ (mixture of rotamers) = 20.31, 20.17. HRMS (ESI$^+$): *m/z* calcd for $C_{20}H_{33}NO_5P$ [M + H]$^+$: 398.2091; found: 398.2092.

***tert*-Butyl 1-(Dibutoxyphosphoryl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3d)**

Colorless oil, yield 71% (302 mg). FC: ethyl acetate/petroleum ether (20:80). ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers in 55:45 ratio) = 7.49–7.38 (m, 1 H), 7.21–7.10 (m, 3 H), 5.70 (d, *J* = 20.8 Hz, 0.55 H), 5.51 (d, *J* = 20.8 Hz, 0.45 H), 4.30 (dd, *J* = 13.5, 5.2 Hz, 0.46 H), 4.06–3.97 (m, 3 H), 3.93 (dd, *J* = 10.0, 6.8 Hz, 0.4 H), 3.88–3.81 (m, 0.6 H), 3.75–3.62 (m, 1 H), 3.48 (ddd, *J* = 13.3, 11.4, 4.4 Hz, 0.54 H), 3.00–2.75 (m, 2 H), 1.66–1.57 (m,

2 H), 1.48 and 1.47 (2 s, 9 H), 1.43–1.33 (m, 3 H), 1.28–1.21 (m, 2 H), 0.95–0.86 (m, 4 H), 0.86–0.79 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.5 (d, *J* = 4.4 Hz), 154.1 (d, *J* = 2.9 Hz), 135.1 (d, *J* = 5.6 Hz), 129.9 (s), 129.4 (s), 129.4 (s), 128.9 (s), 128.2 (d, *J* = 3.8 Hz), 127.9 (s), 127.4 (s), 127.3 (s), 127.2 (s), 126.0 (s), 126.0 (s), 80.7 (s), 80.3 (s), 66.9 (d, *J* = 8.0 Hz), 66.6 (d, *J* = 7.2 Hz), 66.2 (d, *J* = 7.0 Hz), 66.1 (d, *J* = 7.5 Hz), 53.7 (d, *J* = 151.8 Hz), 52.2 (d, *J* = 154.4 Hz), 40.9 (s), 40.1 (s), 38.2 (s), 32.5 (d, *J* = 5.7 Hz), 28.4 (s), 28.2 (s), 27.9 (s), 23.9 (s), 18.7 (s), 18.6 (s), 13.6 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.94, 21.86. HRMS (ESI$^+$): *m/z* calcd for $C_{22}H_{37}NO_5P$ [M + H]$^+$: 426.2404; found: 426.2406.

***tert*-Butyl 1-[Bis(benzyloxy)phosphoryl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3e)**

Off-white solid, yield 45% (220 mg). FC: ethyl acetate/petroleum ether (20:80); mp 87–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers in 55:45 ratio) = 7.52–7.37 (m, 1 H), 7.39–7.01 (m, 13 H), 5.86 (d, *J* = 20.5 Hz, 0.55 H), 5.62 (d, *J* = 20.8 Hz, 0.45 H), 5.09–4.94 (m, 2.45 H), 4.94–4.80 (m, 1 H), 4.64 (dd, *J* = 20.4, 11.8 Hz, 0.55 H), 4.32–4.22 (m, 0.45 H), 4.03–3.93 (m, 0.55 H), 3.74– 3.62 (m, 0.55 H), 3.56–3.43 (m, 0.45 H), 2.95–2.72 (m, 2 H), 1.43 (s, 4.9 H), 1.37 (s, 4.1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.6 (d, *J* = 3.4 Hz), 154.0 (d, *J* = 2.0 Hz), 136.3 (d, *J* = 6.2 Hz), 136.1 (d, *J* = 5.8 Hz), 135.3 (d, *J* = 6.6 Hz), 135.2 (d, *J* = 6.3 Hz), 129.5 (d, *J* = 1.8 Hz), 129.4 (s), 129.1 (d, *J* = 1.7 Hz), 128.9 (s), 128.6 (s), 128.5 (s), 128.4 (s), 128.3 (s), 128.2 (s), 128.1 (s), 128.1 (s), 127.9 (s), 127.8 (s), 127.7 (s), 127.6 (d, *J* = 3.7 Hz), 127.5 (d, *J* = 3.3 Hz), 126.2 (s), 126.1 (d, *J* = 2.8 Hz), 80.9 (s), 80.5 (s), 68.5 (d, *J* = 7.2 Hz), 68.2 (d, *J* = 7.1 Hz), 67.9 (d, *J* = 6.5 Hz), 67.8 (d, *J* = 7.5 Hz), 53.8 (d, *J* = 149.2 Hz), 52.4 (d, *J* = 152.3 Hz), 40.1 (s), 38.3 (s), 28.4 (s), 28.3 (s), 28.2 (s), 27.9 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ (mixture of rotamers) = 22.74, 22.64. HRMS (ESI$^+$): *m/z* calcd for $C_{28}H_{33}NO_5P$ [M + H]$^+$: 494.2091; found: 494.2091.

***tert*-Butyl 1-(Diphenoxyphosphoryl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3f)**

Off-white solid, yield 43% (200 mg); mp 81–83 °C. FC: ethyl acetate/petroleum ether (10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers in 50:50 ratio) = 7.58 (dd, *J* = 18.2, 6.7 Hz, 1 H), 7.38–7.08 (m, 11 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 0.5 H), 6.19 (d, *J* = 21.0 Hz, 0.5 H), 5.97 (d, *J* = 19.6 Hz, 0.5 H), 4.50–4.34 (m, 0.5 H), 4.22–4.00 (m, 0.5 H), 3.92–3.78 (m, 0.5 H), 3.74–3.60 (m, 0.5 H), 3.12–2.86 (m, 2 H), 1.49 and 1.48 (2 s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 154.7 (d, *J* = 4.0 Hz), 154.1 (s), 150.9 (s), 150.8 (s), 150.4 (s), 150.3 (s), 150.2 (d, *J* = 2.7 Hz), 150.1 (s), 135.5 (d, *J* = 2.4 Hz), 135.5 (d, *J* = 2.8 Hz), 129.8 (s), 129.7 (s), 129.6 (s), 129.5 (s), 129.2 (d, *J* = 2.0 Hz), 128.9 (s), 128.4 (d, *J* = 4.3 Hz), 128.2 (s), 128.1 (s), 128.0 (d, *J* = 3.5 Hz), 127.9 (d, *J* = 3.4 Hz), 126.4 (s), 125.3 (s), 125.1 (d, *J* = 4.6 Hz), 124.9 (s), 120.8 (d, *J* = 4.2 Hz), 120.7 (d, *J* = 4.3 Hz), 120.4 (s), 120.3 (s), 120.2 (s), 81.3 (s), 80.8 (s), 54.4 (d, *J* = 150.8 Hz), 53.3 (d, *J* = 156.8 Hz), 40.4 (s), 38.6 (s), 28.4 (s), 28.3 (s), 28.2 (s), 28.0 (s). ^{31}P NMR (162 MHz, $CDCl_3$): δ (mixture of rotamers) = 14.35, 13.88. HRMS (ESI$^+$): *m/z* calcd for $C_{26}H_{29}NO_5P$ [M + H]$^+$: 466.1778; found: 466.1776.

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