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Synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates via three-component reactions of 2-(2-formylphenyl)ethanone, amine, and diethyl phosphite

Shengqing Ye [a], Haibo Zhou [a], Jie Wu [a,b,*]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

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ABSTRACT

Synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates via CuI-catalyzed three-component tandem reactions of 2-(2-formylphenyl)ethanone, amine, and diethyl phosphite is described. The reactions proceed smoothly under mild conditions leading to the desired products in good yields.

1. Introduction

The prominence of 1,2-dihydroisoquinoline as a basic scaffold in natural products and biologically active molecules[1] has promoted considerable efforts toward their synthesis.[2–5] As part of a continuing effort in our laboratory for the expeditious synthesis of biologically relevant heterocyclic compounds, we have developed novel and efficient methods to construct the 1,2-dihydroisoquinoline scaffold.[4,5] Small library of 1,2-dihydroisoquinolines was generated meanwhile. Following biological screening showed that this kind of compound was active as PTP1B (protein tyrosine phosphatase) inhibitor (IC_{50} 4.6 μM). With a hope of finding more active hits for our particular biological assay, it is highly desired to develop novel methods to build up the new 1,2-dihydroisoquinoline-based structures.

Organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems.[6,7] Recent studies have indicated that a lot of heterocycle analogues containing phosphorus showed excellent bioactivities. For example, phosphacoumarins showed good inhibitory activity against SHP-1.[8] Prompted by these results, we envisioned that phosphorus incorporated 1,2-dihydroisoquinolines might be the choice for methodology development and library construction. Among the strategies used for the construction of small molecules, design and synthesis of natural product-like compounds via tandem reactions have attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis.[9] In particular, the development of tandem reactions for the efficient construction of small molecules is an important goal in combinatorial chemistry from the viewpoints of operational simplicity and assembly efficiency. The construction of 1,2-dihydroisoquinolin-1-ylphosphonate has been reported via AgOTf-catalyzed reaction of α-amino (2-alkynylphenyl)methylphosphonate through 6-*endo*-cyclization.[5a] It also could be generated via copper(I) iodide or silver triflate catalyzed three-component reactions of 2-alkynyl benzaldehyde, amine, and diethyl phosphite.[5b–d] We conceived that the desired 1,2-dihydroisoquinolin-1-ylphosphonate **4** could be obtained under suitable conditions in an alternative route via three-component tandem reaction of dicarbonyl compound **1**, amine **2**, and diethyl phosphite **3** (Scheme 1). In the reaction process, intermediated **A** would be formed. Following tandem nucleophilic addition of phosphite to imine and subsequent condensation of generated secondary amine with ketone would give rise to the target compound **4** in the presence of suitable catalyst. Lewis acid-catalyzed addition of diethyl phosphite to aldimine has been well known, which provides useful method for the preparation of α-amino phosphonate.[10] Moreover, three-component synthesis starting from aldehyde, amine, and diethyl phosphite or triethyl phosphite has been also reported by use of Lewis acids or Bronsted acid.[11] For this kind of transformation, the presence of Lewis acid or Bronsted acid promoted the reaction

* Corresponding author. Tel.: +86 215 566 4619; fax: +86 216 510 2412.
E-mail address: jie_wu@fudan.edu.cn (J. Wu).

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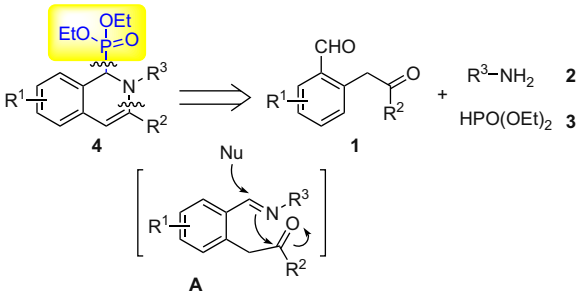
significantly. Based on these results, to verify the practicability of the projected route as shown in Scheme 1, a set of experiments were carried out using 2-(2-formylphenyl)ethanone **1a**, *p*-anisidine **2a**, and diethyl phosphite **3** as model substrates, materials, which are either commercially available or can be readily synthesized (Table 1).



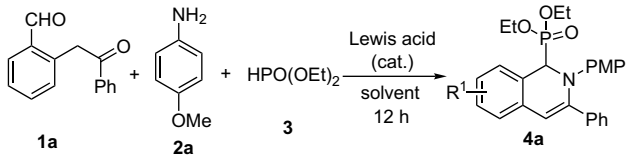
Scheme 1. Projected route for three-component tandem reactions of dicarbonyl compound **1**, amine **2**, and diethyl phosphite **3**.

2. Results and discussion

To identify suitable conditions for the proposed three-component tandem reaction process, reaction screening involving a series of metal catalysts was carried out. Results of this preliminary survey were shown in Table 1. Initially, only a trace amount of product was detected in the absence of catalyst when the reaction was performed at room temperature in 1,2-dichloroethane (Table 1, entry 1). Product **4a** (10% yield) was isolated when the reaction temperature was increased to 70 °C (Table 1, entry 2). Further screening of Lewis acid catalysts revealed that the yield could be dramatically improved when copper(I) iodide was utilized as the catalyst, and the desired 1,2-dihydroisoquinolin-1-ylphosphonate **4a** was obtained in 85% yield (Table 1, entry 11). Other Lewis acids employed displayed inferior results (Table 1, entries 3–10). Solvent screening revealed that dichloroethane was the best choice (Table 1, entries 12–14). Decreasing the amount of copper(I) catalyst diminished the yield (Table 1, entry 15).

With this promising result in hand, we started to investigate the three-component reactions of 2-(2-formylphenyl)-ethanone **1**, amine **2**, and diethyl phosphite **3** catalyzed by copper(I) iodide under optimized reaction conditions [CuI (10 mol %), 1,2-dichloroethane, 70 °C]. The results are shown in Table 2. From Table 2, we rapidly noticed the broad field of application of the process and the conditions were highly effective for the three-component reactions. For all cases the desired products were furnished in good to excellent yields. For instance, reaction of 2-(2-formylphenyl)ethanone **1a**, 4-methylbenzeneamine **2b**, with diethyl phosphite **3** under the standard conditions gave rise to the desired product **4b** in 82% yield (Table 2, entry 2). A 60% yield was obtained when aniline **2c** was utilized as a replacement (Table 2, entry 3). Anilines with electron-withdrawing groups attached on the aromatic ring were also employed in the reaction of **1a**, and the similar yields were observed (Table 2, entries 4 and 5). We also examined aliphatic amine in this reaction. However, no desired product was isolated when benzyl amine was used as substrate in the reaction of 2-(2-formylphenyl)ethanone **1a** with diethyl phosphite **3** (data not shown in Table 2). Other 2-(2-formylphenyl)ethanones were tested in the three-component tandem reactions. For example, when the phenyl group attached on the carbonyl unit was replaced by *p*-methoxyphenyl or cyclopropyl group, similar yield was isolated (Table 2, entries 6–10). The reactions also worked well when fluoro-substituted 2-(2-formylphenyl)ethanone **1d** was utilized in the reactions.

Table 1
Condition screening for three-component tandem reactions of 2-(2-formylphenyl)ethanone **1a**, *p*-anisidine **2a**, and diethyl phosphite **3**[a]



Entry	Lewis acid	Solvent	Temp	Yield[b] (%)
1	—	$ClCH_2CH_2Cl$	rt	Trace
2	—	$ClCH_2CH_2Cl$	70 °C	10
3	$Cu(OTf)_2$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	49
4	$Dy(OTf)_3$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	55
5	$In(OTf)_3$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	44
6	$Bi(OTf)_3$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	37
7	$Zn(OTf)_2$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	51
8	AgOTf (10 mol %)	$ClCH_2CH_2Cl$	70 °C	50
9	$Yb(OTf)_3$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	59
10	$PdCl_2$ (10 mol %)	$ClCH_2CH_2Cl$	70 °C	25
11	CuI (10 mol %)	$ClCH_2CH_2Cl$	70 °C	85
12	CuI (10 mol %)	THF	70 °C	69
13	CuI (10 mol %)	Toluene	70 °C	50
14	CuI (10 mol %)	CH_3CN	70 °C	47
15	CuI (5 mol %)	$ClCH_2CH_2Cl$	70 °C	56

[a] Reaction conditions: 2-(2-formylphenyl)ethanone **1a** (0.30 mmol), *p*-anisidine **2a** (1.1 equiv), diethyl phosphite (2.0 equiv), solvent (2.0 mL), 70 °C, 4 Å molecular sieves.
[b] Isolated yield based on 2-(2-formylphenyl)ethanone **1a**.

3. Conclusions

In conclusion, we have described an efficient route for the synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates via CuI-catalyzed three-component tandem reactions of 2-(2-formylphenyl)ethanone, amine, and diethyl phosphite. The reactions proceed smoothly under mild conditions leading to the desired products in good yields. The efficiency of this method combined with the operational simplicity of the present process makes it potentially attractive for library construction. The focused library generation and screening for biological activity of these small molecules are under investigation in our laboratory.

4. Experimental section

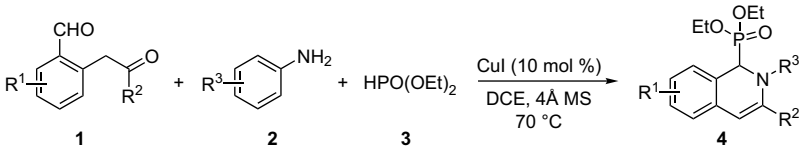
4.1. General

All reactions were performed in reaction tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale.

4.2. General procedure for three-component reactions of 2-(2-formylphenyl)ethanone, amine, and diethyl phosphite

Diethyl phosphite **3** (0.6 mmol, 2.0 equiv) was added to a mixture of 2-(2-formylphenyl)ethanone **1** (0.30 mmol, 1.0 equiv), amine **2** (0.33 mmol, 1.1 equiv), CuI (0.03 mmol, 10 mol %), and molecular sieves (150 mg) in DCE (2.0 mL). The mixture was then stirred at 70 °C. After completion of reaction as indicated by TLC,

Table 2
CuI-catalyzed three-component tandem reactions of 2-(2-formylphenyl)ethanone **1**, amine **2**, and diethyl phosphite **3**[a]



1 **2** **3** **4**

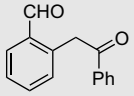
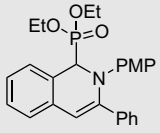
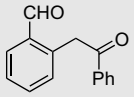
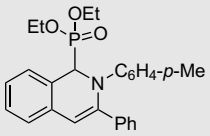
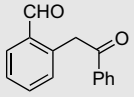
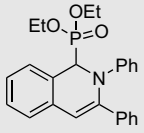
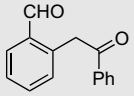
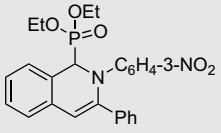
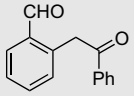
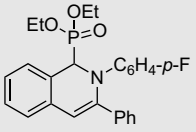
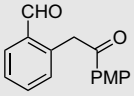
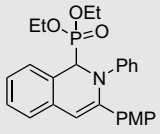
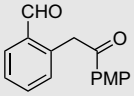
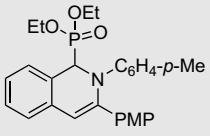
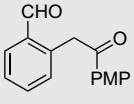
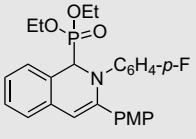
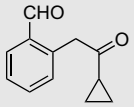
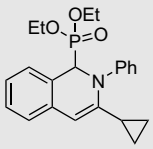
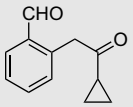
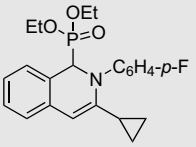
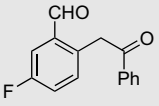
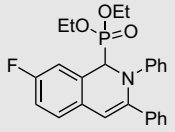
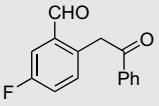
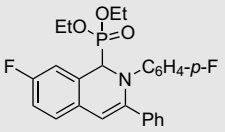
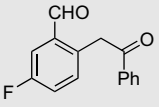
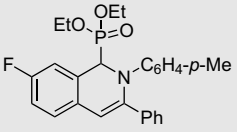
Entry	Substrate **1**	R^3	Product **4**	Yield[b] (%)
1	 **1a**	4-OMe	 **4a**	85 (12 h)
2	 **1a**	4-Me	 **4b**	82 (12 h)
3	 **1a**	H	 **4c**	60 (14 h)
4	 **1a**	3-NO_2	 **4d**	64 (24 h)
5	 **1a**	4-F	 **4e**	66 (16 h)
6	 **1b**	H	 **4f**	75 (18 h)
7	 **1b**	4-Me	 **4g**	65 (24 h)
8	 **1b**	4-F	 **4h**	77 (18 h)
9	 **1c**	H	 **4i**	56 (24 h)

Table 2 (*continued*)

Entry	Substrate **1**	R^3	Product **4**	Yield[b] (%)
10	 **1c**	4-F	 **4j**	61 (24 h)
11	 **1d**	H	 **4k**	47 (24 h)
12	 **1d**	4-F	 **4l**	70 (20 h)
13	 **1d**	4-Me	 **4m**	75 (20 h)

[a] Reaction conditions: 2-(2-formylphenyl)ethanone **1** (0.30 mmol), amine **2** (1.1 equiv), diethyl phosphite (2.0 equiv), 1,2-dichloroethane (2.0 mL), 70 °C.
[b] Isolated yield based on 2-(2-formylphenyl)ethanone **1**. PMP: *p*-methoxyphenyl.

the solvent was evaporated and the residue was quenched with water (10 mL), extracted with EtOAc (2×10 mL), dried by anhydrate Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **4**.

*4.2.1. Diethyl-2-(4-methoxyphenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4a**)*[5b]

Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18–1.24 (m, 6H), 3.64 (s, 3H), 3.91–4.12 (m, 4H), 5.33 (d, J=19 Hz, 1H), 6.44 (s, 1H), 6.62 (d, J=8.8 Hz, 2H), 7.04 (d, J=8.8 Hz, 2H), 7.08–7.26 (m, 7H), 7.57 (d, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.5, 55.3, 62.5, 62.6, 64.9 (d, $^1J_{CP}$=163.0 Hz), 111.1, 113.9, 124.1, 124.5, 125.0, 126.4, 127.3, 127.5, 127.8, 127.9, 128.2, 133.3, 137.5, 141.5, 142.6, 155.4.

*4.2.2. Diethyl-3-phenyl-2-p-tolyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4b**)*[5b]

Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17–1.23 (m, 6H), 2.16 (s, 3H), 3.92–4.08 (m, 4H), 5.40 (d, J=19 Hz, 1H), 6.48 (s, 1H), 6.88 (d, J=7.8 Hz, 2H), 6.97 (d, J=7.8 Hz, 2H), 7.09–7.25 (m, 7H), 7.58 (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.5, 20.5, 62.5, 62.6, 64.4 (d, $^1J_{CP}$=163.0 Hz), 111.7, 122.7, 124.1, 125.3, 126.4, 127.2, 127.6, 127.8, 128.1, 128.2, 129.1, 131.8, 133.1, 137.4, 142.2, 145.4.

*4.2.3. Diethyl-2,3-diphenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4c**)*[5b]

Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18–1.24 (m, 6H), 3.93–4.10 (m, 4H), 5.45 (d, J=19 Hz, 1H), 6.51 (s, 1H), 6.85 (m, 1H), 7.06–7.27 (m, 11H), 7.58 (d, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.5, 62.5, 62.7, 64.2 (d, $^1J_{CP}$=162.0 Hz), 112.2, 122.3, 122.6, 124.3, 125.6, 126.5, 127.2, 127.6, 127.9, 128.2, 128.5, 133.0, 137.3, 142.0, 147.6.

*4.2.4. Diethyl-2-(3-nitrophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4d**)*

Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.29 (m, 6H), 3.97–4.12 (m, 4H), 5.44 (d, J=19 Hz, 1H), 6.58 (s, 1H), 7.17–7.33 (m, 9H), 7.55 (d, J=7.4 Hz, 2H), 7.68 (d, J=8.3 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.5, 62.8, 62.9, 63.4 (d, $^1J_{CP}$=162.0 Hz), 113.9, 116.4, 116.6, 124.8, 125.8, 127.1, 127.2, 127.5, 127.8, 128.4, 128.6, 128.7, 129.0, 132.4, 136.3, 140.7, 148.3, 148.5. IR (KBr): ν_{max}/cm^{-1} 3063, 2914, 1608, 1527, 1445. HRMS calcd for $C_{25}H_{25}N_2O_5P$: 464.1501, found: 464.1505.

*4.2.5. Diethyl-2-(4-fluorophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4e**)*[5b]

Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.23 (m, 6H), 3.90–4.09 (m, 4H), 5.34 (d, J=19 Hz, 1H), 6.48 (s, 1H), 6.78 (t, J=8.8 Hz, 2H), 7.04–7.07 (m, 2H), 7.07 (d, J=7.8 Hz, 1H), 7.15–7.28 (m, 6H), 7.56 (d, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 16.5, 62.5, 62.6, 64.5 (d, $^1J_{CP}$=163.0 Hz), 111.8, 115.1 (d, $^2J_{CF}$=23.0 Hz), 124.3, 124.4, 125.2, 126.6, 127.2, 127.7, 128.0, 128.3, 133.0, 137.1, 142.1, 143.9, 158.5 (d, $^1J_{CF}$=241.0 Hz).

*4.2.6. Diethyl-3-(4-methoxyphenyl)-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4f**)*

Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18–1.23 (m, 6H), 3.75 (s, 3H), 3.93–4.10 (m, 4H), 5.43 (d, J=19 Hz, 1H), 6.42 (s, 1H), 6.77 (d, J=8.8 Hz, 2H), 6.85 (t, J=6.8 Hz, 1H), 7.06–7.18 (m, 7H), 7.23 (d, J=6.8 Hz, 1H), 7.50 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 55.1, 62.6, 62.7, 64.2 (d, $^1J_{CP}$=163.0 Hz), 110.9, 113.7, 122.2, 122.8, 124.1, 125.5, 126.2, 127.2, 128.2, 128.5, 128.9, 129.8, 133.3, 141.8, 147.8, 159.4; IR (KBr): ν_{max}/cm^{-1} 3063, 2976, 1598, 1506, 1491, 1450. MS (ESI) m/z 450 (M^++H); HRMS calcd for $C_{26}H_{28}NO_4P$ (M^++H): 450.1837, found: 450.1837.

*4.2.7. Diethyl-3-(4-methoxyphenyl)-2-p-tolyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4g**)*

Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19–1.23 (m, 6H), 2.17 (s, 3H), 3.74 (s, 3H), 3.91–4.11 (m, 4H), 5.38 (d, J=19 Hz, 1H), 6.39 (s, 1H), 6.76 (d, J=8.3 Hz, 2H), 6.89 (d, J=8.3 Hz, 2H), 6.97 (d, J=7.8 Hz, 2H), 7.07–7.25 (m, 4H), 7.50 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 16.4, 16.5, 20.6, 55.1, 62.5, 62.6, 64.5 (d, $^1J_{CP}$=163.0 Hz), 110.4, 113.6, 122.8, 123.9, 125.2, 126.1, 127.2, 128.1, 128.9, 129.1, 129.9, 131.8, 133.4, 141.9, 145.5, 159.4; IR (KBr): ν_{max}/cm^{-1} 3022, 2980, 1608, 1510. MS (ESI) *m*/*z* 464 (M^++H); HRMS calcd for $C_{27}H_{30}NO_4P$ (M^++H): 464.1991, found: 464.2001.

4.2.8. Diethyl-2-(4-fluorophenyl)-3-(4-methoxyphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (**4h**)

Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91–1.25 (m, 6H), 3.75 (s, 3H), 3.92–4.13 (m, 4H), 5.31 (d, *J*=19 Hz, 1H), 6.39 (s, 1H), 6.76–6.80 (m, 4H), 7.03–7.26 (m, 6H), 7.48 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 55.1, 62.6, 62.7, 64.6 (d, $^1J_{CP}$=163.0 Hz), 110.5, 113.7, 115.2 (d, $^2J_{CF}$=23.0 Hz), 124.1, 124.4, 125.1, 126.3, 127.2, 128.3, 129.0, 129.5, 133.2, 141.8, 144.1, 158.5 (d, $^1J_{CF}$=241.0 Hz), 159.5; IR (KBr): ν_{max}/cm^{-1} 3053, 2986, 1613, 1506, 1445. MS (ESI) *m*/*z* 468 (M^++H); HRMS calcd for $C_{26}H_{27}FNO_4P$ (M^++H): 468.1740, found: 468.1748.

4.2.9. Diethyl-3-cyclopropyl-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4i**)

Yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68–0.84 (m, 4H), 1.22–1.30 (m, 6H), 1.41–4.48 (m, 1H), 3.89–4.11 (m, 4H), 5.23 (d, *J*=18 Hz, 1H), 5.83 (s, 1H), 6.97 (d, *J*=7.3 Hz, 1H), 7.00–7.07 (m, 3H), 7.16 (t, *J*=7.3 Hz, 1H), 7.26–7.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 10.3, 14.1, 16.4, 16.5, 62.7, 62.8, 64.5 (d, $^1J_{CP}$=161.0 Hz), 104.9, 123.0, 123.2, 123.4, 124.0, 125.4, 127.0, 128.1, 128.7, 133.2, 145.7, 147.3; IR (KBr): ν_{max}/cm^{-1} 3058, 2986, 1619, 1593, 1485. MS (ESI) *m*/*z* 384 (M^++H); HRMS calcd for $C_{22}H_{26}NO_3P$ (M^++H): 384.1729, found: 384.1728.

4.2.10. Diethyl-3-cyclopropyl-2-(4-fluorophenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (**4j**)

Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66–0.70 (m, 2H), 0.77–0.81 (m, 2H), 1.22–1.26 (m, 6H), 1.32–1.39 (m, 1H), 3.94–4.12 (m, 4H), 5.11 (d, *J*=18 Hz, 1H), 5.78 (s, 1H), 6.94–6.98 (m, 4H), 7.06 (t, *J*=7.3 Hz, 1H), 7.17 (t, *J*=7.3 Hz, 1H), 7.29–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 10.4, 14.0, 16.4, 16.5, 62.7, 62.8, 64.8 (d, $^1J_{CP}$=162.0 Hz), 104.2, 115.3 (d, $^2J_{CF}$=22.0 Hz), 123.1, 123.6, 125.4, 125.5, 125.6, 127.0, 128.2, 133.2, 143.4, 145.7, 159.2 (d, $^1J_{CF}$=241.0 Hz); IR (KBr): ν_{max}/cm^{-1} 3068, 2986, 1634, 1501. MS (ESI) *m*/*z* 402 (M^++H); HRMS calcd for $C_{22}H_{25}FNO_3P$ (M^++H): 402.1634, found: 402.1627.

4.2.11. Diethyl-7-fluoro-2,3-diphenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4k**)

Yield: 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.26 (m, 6H), 3.97–4.10 (m, 4H), 5.90 (d, *J*=19 Hz, 1H), 6.49 (s, 1H), 6.85–6.88 (m, 2H), 6.96 (t, *J*=8.8 Hz, 1H), 7.05–7.12 (m, 4H), 7.15–7.26 (m, 4H), 7.57 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 62.7, 62.8, 63.9 (d, $^1J_{CP}$=164.0 Hz), 111.3, 114.3 (d, $^2J_{CF}$=23.0 Hz), 115.2 (d, $^2J_{CF}$=22.0 Hz), 122.5, 122.6, 125.6, 127.5, 127.6, 128.0, 128.3, 128.6, 129.4, 137.0, 141.5, 147.6, 161.5 (d, $^1J_{CF}$=245.0 Hz); IR (KBr): ν_{max}/cm^{-1} 3058, 2981, 1603, 1491, 1450. MS (ESI) *m*/*z* 438 (M^++H); HRMS calcd for $C_{25}H_{25}FNO_3P$ (M^++H): 438.1634, found: 438.1640.

4.2.12. Diethyl-7-fluoro-2-(4-fluorophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4l**)

Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.26 (m, 6H), 4.00–4.10 (m, 4H), 5.29 (d, *J*=19 Hz, 1H), 6.46 (s, 1H), 6.77–6.81 (m, 2H), 6.85 (d, *J*=8.8 Hz, 1H), 6.97 (t, *J*=8.3 Hz, 1H), 7.03–7.07 (m, 2H), 7.15–7.26 (m, 4H), 7.55 (d, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 62.7, 62.8, 64.3 (d, $^1J_{CP}$=165.0 Hz), 110.9, 114.3 (d, $^2J_{CF}$=23.0 Hz), 115.2 (d, $^2J_{CF}$=22.0 Hz), 115.3 (d, $^2J_{CF}$=22.0 Hz), 124.3, 125.6, 127.2, 127.6, 128.1, 128.3, 129.3, 136.8, 141.5, 143.8, 158.6 (d, $^1J_{CF}$=241.0 Hz), 161.6 (d, $^1J_{CF}$=247.0 Hz); IR (KBr): ν_{max}/cm^{-1} 3053, 2986, 1593, 1501, 1445. MS (ESI) *m*/*z* 456 (M^++H); HRMS calcd for $C_{25}H_{24}F_2NO_3P$ (M^++H): 456.1540, found: 456.1546.

4.2.13. Diethyl-7-fluoro-3-phenyl-2-p-tolyl-1,2-dihydroisoquinolin-1-ylphosphonate (**4m**)

Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 2.17 (s, 3H), 3.96–4.12 (m, 4H), 5.34 (d, *J*=19 Hz, 1H), 6.46 (s, 1H), 6.83 (d, *J*=8.3 Hz, 1H), 6.89 (d, *J*=7.8 Hz, 2H), 6.92–6.98 (m, 3H), 7.12–7.25 (m, 4H), 7.57 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 20.6, 62.7, 62.8, 64.2 (d, $^1J_{CP}$=164.0 Hz), 110.8, 114.3 (d, $^2J_{CF}$=23.0 Hz), 115.1 (d, $^2J_{CF}$=22.0 Hz), 122.7, 125.5, 127.3, 127.5, 127.9, 128.2, 129.2, 129.4, 132.2, 137.2, 141.7, 145.3, 161.5 (d, $^1J_{CF}$=245.0 Hz); IR (KBr): ν_{max}/cm^{-1} 3053, 2976, 1609, 1516, 1501, 1450. MS (ESI) *m*/*z* 452 (M^++H); HRMS calcd for $C_{26}H_{27}FNO_3P$ (M^++H): 452.1791, found: 452.1810.

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