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An efficient route to 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates via CuI-catalyzed three-component reactions

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Abstract—Copper(I) iodide catalyzed three-component reactions of 2-alkynyl benzaldehyde, amine, and diethyl phosphite provide a facile and efficient route to 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonate. Palladium(II) chloride gives the similar results. An isoquinolinium intermediate may be involved in the reaction process.

1. Introduction

A goal of chemical genetics is to find small molecules that modulate the individual functions of gene products with high potency and high specificity.[1] Natural products and natural product-derived compounds provide many of the most striking examples, particularly, in terms of their specificity. Efficient methods for preparing natural product-like compounds are in great demand in the field of chemical genetics.[1] On the other hand, multicomponent reactions (MCR) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive compounds.[2] However, the range of easily accessible and functionalized small heterocycles is rather limited. Thus, the development of new, rapid, and robust routes toward focused libraries of such heterocycles is of great importance.

Recently, we have described three-component reactions of aldehydes, amines, and diethyl phosphite catalyzed by Lewis acid affording the corresponding α-amino phosphonates in excellent yields.[3] Inspired by these results, we envisaged that the resulting α-amino phosphonate could serve as nucleophile if an electrophile is available in the reaction system. It is well-precedented that the transition metal or Lewis acid catalyzed cyclization of alkynes possessing a nucleophile in proximity to the triple bond is an important process in organic synthesis, which can construct various heterocycles in an efficient and atom-economic way.[4–11] Meanwhile, Yamamoto and Takemoto described that functionalized 1,2-dihydroisoquinoline skeletons could be generated through the direct addition of various carbon pronucleophiles to *ortho*-alkynylaryl aldimines catalyzed by Lewis acid.[10a–c] Yamamoto also reported that the reaction could be performed in the absence of catalyst when chloroform was utilized as carbon pronucleophile.[10d] In connection with our ongoing program for the construction of natural product-like compounds,[12] we conceived that we could employ 2-alkynyl benzaldehyde **1** as substrate in the reaction of amine and diethyl phosphite in the presence of catalytic Lewis acid, with the hope to generate 1,2-dihydroisoquinolin-1-ylphosphonate scaffold (Scheme 1). Indeed, the reaction occurred in the presence of silver triflate as the catalyst.[12c] As described by Asao and Yamamoto,[10b] *ortho*-alkynylaryl aldimines reacted with AgOTf leading to isoquinoliniums in good yields. The observation indicated that, in the presence of silver salt, the triple bond might coordinate to the silver salt, and subsequently, the nitrogen atom could attack on the triple bond via 6-*endo*-cyclization to afford an isoquinolinium intermediate. Based on this result, we conceive that reaction of 2-alkynyl benzaldehyde **1**, amine, and diethyl phosphite catalyzed by other soft Lewis acid may undergo similar process. The results are disclosed herein.

2. Results and discussion

We tested this idea with 2-alkynyl benzaldehyde **1a**, *p*-anisidine **2a**, and diethyl phosphite **3**, which are either commercially available or can be readily synthesized

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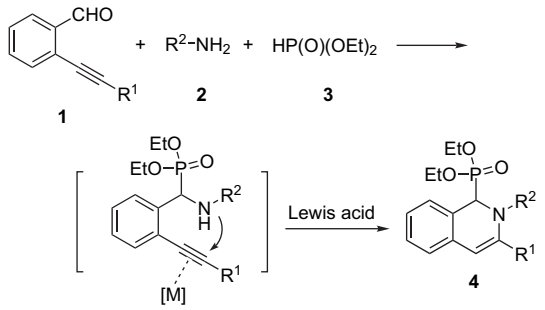
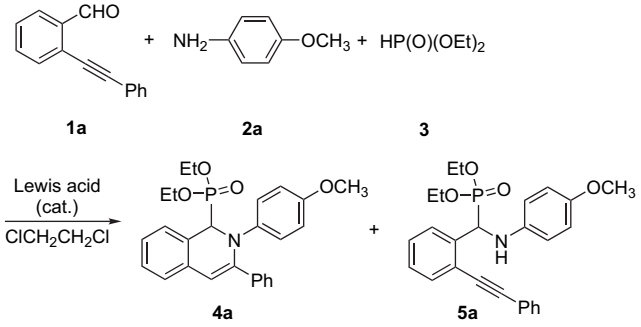


Scheme 1.

(Table 1). First, various Lewis acids were screened and the results are summarized in Table 1. We found that the desired 1,2-dihydroisoquinolin-1-ylphosphonate **4a** could be obtained when copper(II) triflate or copper(I) iodide was utilized as the catalyst; while α-amino phosphonate **5a** was obtained when $Sc(OTf)_3$, $Bi(OTf)_3$, $In(OTf)_3$, $FeCl_3$, AuCl, or $AuCl_3$ was employed as the catalyst in the reaction. It is well-documented that copper salts have mild Lewis acidity and have been used as catalysts in organic synthesis. Among these salts, CuI is one of the most popular reagents for inducing transformations, which takes advantage of its affinity to carbon–carbon unsaturated bonds rather than oxygen functional groups.[13] Compound **4a** could be generated in 83% yield when the reaction was performed at 60 °C in dichloroethane and catalyzed by 10 mol % of CuI. Further studies showed that dichloroethane or toluene was the best solvent. Decreasing the temperature or the amount of catalyst retarded the reaction.

Table 1. Reaction of 2-alkynyl benzaldehyde **1a** and *p*-anisidine with diethyl phosphite catalyzed by various Lewis acids[a]



Entry	Lewis acid (mol %)	Solvent	*T* (°C)	Yield (%)[b]	
				4a	**5a**
1	$Sc(OTf)_3$ (10)	DCE	25	—	72
2	$Sc(OTf)_3$ (10)	DCE	60	—	82
3	$Bi(OTf)_3$ (10)	DCE	60	—	86
4	$In(OTf)_3$ (10)	DCE	60	—	86
5	$FeCl_3$ (10)	DCE	60	—	79
6	$Dy(OTf)_3$ (10)	DCE	60	—	89
7	$Yb(OTf)_3$ (10)	DCE	60	16	72
8	$Cu(OTf)_2$ (10)	DCE	60	68	—
9	$Cu(OTf)_2$ (5)	DCE	60	60	—
10	CuI (10)	DCE	60	83	—
11	CuI (5)	DCE	60	67	—
12	CuI (1)	DCE	60	44	—
13	$AuCl_3$ (10)	DCE	60	—	91
14	AuCl (10)	DCE	60	—	84
15	CuI (10)	DCE	25	67	—
16	CuI (10)	MeCN	60	55	—
17	CuI (10)	CH_2Cl_2	60	77	—
18	CuI (10)	Toluene	60	83	—
19	CuI (10)	THF	60	81	—
20	CuI (10)	H_2O[c]	60	41	—

DCE: 1,2-dichloroethane.

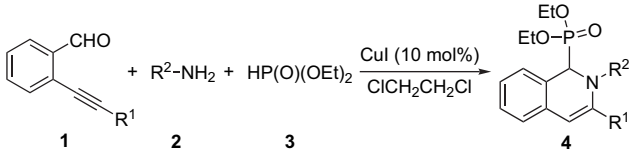
[a] Reaction conditions: 2-alkynyl benzaldehyde **1a** (0.50 mmol), *p*-anisidine (0.50 mmol), diethyl phosphite (1.2 equiv), Lewis acid (cat.), solvent (3.0 mL).

[b] Isolated yield based on 2-alkynyl benzaldehyde **1a**.

[c] In the presence of 20% SDS.

With this promising result in hand, we started to investigate the three-component reactions of 2-alkynyl benzaldehyde **1** and amine **2** with diethyl phosphite **3** catalyzed by copper(I) iodide under optimized reaction conditions [CuI (10 mol %), dichloroethane, and 60 °C]. The results are shown in Table 2. From Table 2, we found that these conditions were highly effective for the three-component reactions. For most cases, 2-alkynyl benzaldehydes **1** reacted smoothly with amines **2** and diethyl phosphite **3** leading to 1,2-dihydroisoquinolin-1-ylphosphonates **4** in good to excellent yields. However, reactions of 2-alkynyl benzaldehydes **1**, aliphatic amines, and diethyl phosphite **3** displayed inferior results. For example, reaction of **1a**, aniline **2g**, and diethyl phosphite **3** gave the corresponding product **4g** in 91% yield (Table 2, entry 7), while 61% yield of **4i** or 27% yield of **4j** was obtained, respectively, when benzyl amine or *n*-hexylamine was employed in this reaction (Table 2, entries 9 and 10). And also, a range of different aniline derivatives bearing electron-donating or electron-withdrawing groups are tolerated. Interestingly, this three-component reaction could also be

Table 2. Reaction of 2-alkynyl benzaldehyde **1** and amine **2** with diethyl phosphate **3** catalyzed by CuI (10 mol %)[a]



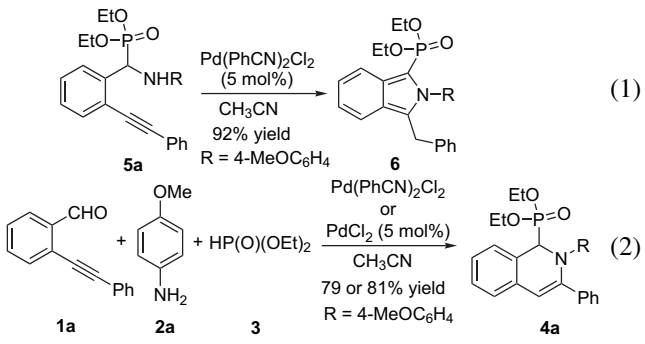
Entry	R^1	R^2	Product	Yield (%)[b]
1	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2a**)	**4a**	83
2	C_6H_5 (**1a**)	4-FC_6H_4 (**2b**)	**4b**	78
3	C_6H_5 (**1a**)	4-ClC_6H_4 (**2c**)	**4c**	79
4	C_6H_5 (**1a**)	C_6H_5 (**2d**)	**4d**	79
5	C_6H_5 (**1a**)	4-MeC_6H_4 (**2e**)	**4e**	83
6	C_6H_5 (**1a**)	3-$NO_2C_6H_4$ (**2f**)	**4f**	83
7	C_6H_5 (**1a**)	3-$CF_3C_6H_4$ (**2g**)	**4g**	91
8	C_6H_5 (**1a**)	2-Pyridinyl (**2h**)	**4h**	78
9	C_6H_5 (**1a**)	$C_6H_5CH_2$ (**2i**)	**4i**	61
10	C_6H_5 (**1a**)	*n*-Hexyl (**2j**)	**4j**	27
11	*n*-$C_5H_{11}C_6H_4$ (**1b**)	4-$MeOC_6H_4$ (**2a**)	**4k**	82
12	*n*-$C_5H_{11}C_6H_4$ (**1b**)	4-FC_6H_4 (**2b**)	**4l**	98
13	*n*-$C_5H_{11}C_6H_4$ (**1b**)	C_6H_5 (**2d**)	**4m**	96
14	*n*-$C_5H_{11}C_6H_4$ (**1b**)	$C_6H_5CH_2$ (**2i**)	**4n**	65
15	*n*-C_4H_9 (**1c**)	4-$MeOC_6H_4$ (**2a**)	**4o**	67
16	*n*-C_4H_9 (**1c**)	4-FC_6H_4 (**2b**)	**4p**	58
17	*n*-C_4H_9 (**1c**)	C_6H_5 (**2d**)	**4q**	53
18	1-Cyclohexenyl (**1d**)	4-$MeOC_6H_4$ (**2a**)	**4r**	79
19	1-Cyclohexenyl (**1d**)	4-FC_6H_4 (**2b**)	**4s**	64
20	1-Cyclohexenyl (**1d**)	C_6H_5 (**2d**)	**4t**	80
21	1-Cyclohexenyl (**1d**)	$C_6H_5CH_2$ (**2i**)	**4u**	38

[a] Reaction conditions: 2-alkynyl benzaldehyde **1** (0.50 mmol), amine **2** (0.50 mmol), diethyl phosphate **3** (1.2 equiv), CuI (10 mol %), DCE (3.0 mL), 60 °C, 4 h.

[b] Isolated yield based on 2-alkynyl benzaldehyde **1**.

applied to pyridine derivative **2h**, and 78% yield of the desired product **4h** was furnished (Table 2, entry 8).

As shown in Table 1, the reaction of 2-alkynyl benzaldehyde **1a**, *p*-anisidine **2a**, and diethyl phosphate **3** proceeded through compound **5a**, which may presumably involve the formation of π-complex via coordination of the alkynyl moiety of **5a** to Cu(I), thus activating the triple bond for nucleophilic attack by the amino group in the *endo* mode. However, the reaction of compound **5a** in the presence of CuI (5 mol %) afforded the desired product **4a** only in 14% yield. Recently, an unexpected result for the reaction of compound **5a** catalyzed by Pd(II) was observed. 2*H*-Isoindol-1-ylphosphonate **6** was generated instead of 1,2-dihydroisoquinolin-1-ylphosphonate **4a** (Scheme 2, Eq. 1).[12] Interestingly, when palladium(II) was employed in the reaction of 2-alkynyl benzaldehyde **1a**, *p*-anisidine **2a**, and diethyl phosphate **3**, 1,2-dihydroisoquinolin-1-ylphosphonate **4a** was obtained in good yield [$Pd(PPh_3)_2Cl_2$: 79% yield, $PdCl_2$: 81% yield] (Scheme 2, Eq. 2). This observation indicated that the reaction mechanism might be similar to that described by Asao and Yamamoto.[10b]



Scheme 2.

3. Conclusion

In summary, we have described copper(I) iodide catalyzed three-component reactions of 2-alkynyl benzaldehydes, amines, and diethyl phosphite, which provide a facile and efficient route to 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates. Isoquinolinium intermediate may be involved in the reaction process. 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 test tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade, Sorbent Technologies). 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). Solvents were re-distilled prior to use in the reactions. Other commercial reagents were used as-received. 2-Alkynyl benzaldehyde **1** was synthesized via Sonogashira coupling according to the literature report.[6a]

4.2. General procedure

A mixture of 2-alkynyl benzaldehyde **1** (0.5 mmol), amine **2** (0.5 mmol, 1.0 equiv), diethyl phosphite **3** (0.6 mmol, 1.2 equiv), and CuI (10 mol %) in dichloroethane (3.0 mL) was stirred at 60 °C under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2×10 mL). Evaporation of the solvent followed by purification of the residue on silica gel afforded pure 1,2-dihydroisoquinolin-1-ylphosphonate **4**.

4.2.1. Diethyl 2-(4-methoxyphenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4a). Yield 83%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 3.65 (s, 3H), 3.90–4.12 (m, 4H), 5.33 (d, J=19.0 Hz, 1H), 6.44 (s, 1H), 6.63 (d, J=8.8 Hz, 2H), 7.05 (d, J=8.8 Hz, 2H), 7.06–7.28 (m, 7H), 7.57 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 55.3, 62.5, 62.6, 64.9, 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; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.25; IR (cm^{-1}) ν_{max} 1031 (P–O), 1050 (P–O), 1246 (P═O); MS (ESI) m/z 450.20 (M^++1). HRMS calcd for $C_{26}H_{28}NO_4P$: 449.1756, found: 449.1752.

4.2.2. Diethyl 2-(4-fluorophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4b). Yield 78%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 3.90–4.12 (m, 4H), 5.34 (d, J=18.6 Hz, 1H), 6.47 (s, 1H), 6.7 (t, J=10.6 Hz, 2H), 7.04–7.28 (m, 9H), 7.56 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 62.6, 64.5, 111.8, 115.0, 115.3, 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; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.92; IR (cm^{-1}) ν_{max} 1025 (P–O), 1050 (P–O), 1251 (P═O); MS (ESI) m/z 438.20 (M^++1). HRMS calcd for $C_{25}H_{25}FNO_3P$: 437.1556, found: 437.1561.

4.2.3. Diethyl 2-(4-chlorophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4c). Yield 79%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 3.90–4.12 (m, 4H), 5.37 (d, J=18.6 Hz, 1H), 6.49 (s, 1H), 7.02–7.05 (m, 4H), 7.10–7.26 (m, 7H), 7.55 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 62.6, 62.7, 64.0, 112.5, 123.7, 124.4, 125.5, 126.7, 127.2, 127.5, 127.6, 128.1, 128.4, 128.5, 132.8, 136.9, 141.6, 146.2; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.59; IR (cm^{-1}) ν_{max} 1026 (P–O), 1051 (P–O), 1265 (P═O); MS (ESI) m/z 454.20 (M^++1). HRMS calcd for $C_{25}H_{25}ClNO_3P$: 453.1261, found: 453.1257. Anal. Calcd for $C_{25}H_{25}ClNO_3P$: C, 66.15; H, 5.55; N, 3.09. Found: C, 66.34; H, 5.86; N, 3.21.

4.2.4. Diethyl 2,3-diphenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4d). Yield 79%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 3.90–4.10 (m, 4H), 5.45 (d, J=18.6 Hz, 1H), 6.50 (s, 1H), 6.85–6.87 (m,

1H), 7.07–7.25 (m, 11H), 7.58 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 62.5, 62.7, 64.2, 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; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.33; IR (cm^{-1}) ν_{max} 1025 (P–O), 1052 (P–O), 1251 (P═O); MS (ESI) m/z 420.20 (M^++1). HRMS calcd for $C_{25}H_{26}NO_3P$: 419.1650, found: 419.1654.

4.2.5. Diethyl 3-phenyl-2-*p*-tolyl-1,2-dihydroisoquinolin-1-ylphosphonate (4e). Yield 83%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 2.16 (s, 3H), 3.88–4.13 (m, 4H), 5.40 (d, J=19.0 Hz, 1H), 6.47 (s, 1H), 6.88 (d, J=8.4 Hz, 2H), 6.98 (d, J=8.4 Hz, 2H), 7.09–7.25 (m, 7H), 7.58 (dd, J=8.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 20.5, 62.4, 62.6, 64.4, 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; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.31; IR (cm^{-1}) ν_{max} 1026 (P–O), 1052 (P–O), 1248 (P═O); MS (ESI): 434.20 (M^++1); HRMS calcd for $C_{26}H_{28}NO_3P$: 433.1807, found 433.1804. Anal. Calcd for $C_{26}H_{28}NO_3P$: C, 72.04; H, 6.51; N, 3.23. Found: C, 72.41; H, 6.33; N, 3.42.

4.2.6. Diethyl 2-(3-nitrophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4f). Yield 83%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 3.94–3.98 (m, 2H), 4.07–4.09 (m, 2H), 5.43 (d, J=18.6 Hz, 1H), 6.57 (s, 1H), 7.18–7.34 (m, 10H), 7.55 (d, J=8.0 Hz, 2H), 148.3 (d, J=7.0 Hz), 7.68 (d, J=7.2 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 62.8, 62.9, 63.4, 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; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.19; IR (cm^{-1}) ν_{max} 1022 (P–O), 1050 (P–O), 1264 (P═O); MS (ESI): m/z 465.20 (M^++1). HRMS calcd for $C_{25}H_{25}N_2O_5P$: 464.1501, found: 464.1505.

4.2.7. Diethyl 3-phenyl-2-(3-(trifluoromethyl)phenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4g). Yield 91%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J=7.2 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H), 3.94–3.96 (m, 2H), 4.07–4.09 (m, 2H), 5.42 (d, J=18.6 Hz, 1H), 6.53 (s, 1H), 7.08–7.10 (m, 1H), 7.16–7.18 (m, 4H), 7.19–7.24 (m, 3H), 7.25–7.29 (m, 2H), 7.34 (s, 1H), 7.53 (dd, J=6.8, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 62.6, 62.9, 63.6, 113.2, 118.6, 123.9, 124.6, 125.4, 125.7, 126.9, 127.2, 127.6, 128.2, 128.4, 128.5, 128.9, 130.9, 132.7, 136.8, 141.3, 147.8; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.72; IR (cm^{-1}) ν_{max} 1026 (P–O), 1050 (P–O), 1250 (P═O); MS (ESI): m/z 488.20 (M^++1). HRMS calcd for $C_{26}H_{25}F_3NO_3P$: 487.1524, found 487.1521. Anal. Calcd for $C_{26}H_{25}F_3NO_3P$: C, 64.06; H, 5.17; N, 2.87. Found: C, 64.43; H, 5.11; N, 3.21.

4.2.8. Diethyl 3-phenyl-2-(pyridin-2-yl)-1,2-dihydroisoquinolin-1-ylphosphonate (4h). Yield 78%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.2 Hz, 3H), 1.19 (t, J=7.2 Hz, 3H), 3.95–3.98 (m, 2H), 4.11–4.13 (m, 2H), 6.60 (t, J=4.4 Hz, 1H), 6.65 (s, 1H), 6.80 (d, J=21.0 Hz, 1H), 7.19–7.37 (m, 8H), 7.62 (d, J=7.2 Hz, 2H), 8.24 (d, J=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.3, 55.8, 62.5, 62.6, 113.0, 116.3, 125.5, 125.9, 126.9, 127.0, 127.1, 127.3, 128.1, 129.1, 132.8, 138.4, 139.8, 157.2, 160.0; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.82; IR (cm^{-1}) ν_{max} 1029 (P–O), 1050 (P–O), 1265 (P═O); MS (ESI): m/z 421.20 (M^++1). HRMS calcd for $C_{24}H_{25}N_2O_3P$: 420.1603, found: 420.1606. Anal. Calcd for $C_{24}H_{25}N_2O_3P$: C, 68.56; H, 5.99; N, 6.66. Found: C, 68.33; H, 5.82; N, 6.83.

4.2.9. Diethyl 2-benzyl-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4i). Yield 61%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J=7.2 Hz, 3H), 1.22 (t, J=7.2 Hz, 3H), 3.80–3.95 (m, 3H), 4.00–4.16 (m, 2H), 4.30 (d, J=15.6 Hz, 1H), 4.81 (d, J=18.6 Hz, 1H), 5.97 (s, 1H), 6.90–6.95 (m, 1H), 7.04–7.08 (m, 2H), 7.15–7.20 (m, 6H), 7.35–7.40 (m, 3H), 7.69 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 55.9, 59.2, 62.2, 62.4, 107.1, 123.6, 124.3, 125.9, 127.1, 127.2, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 134.0, 137.5, 138.5, 146.9; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.92; IR (cm^{-1}) ν_{max} 1027 (P–O), 1052 (P–O), 1248 (P═O); MS (ESI): m/z 434.20 (M^++1). HRMS calcd for $C_{26}H_{28}NO_3P$: 433.1807, found: 433.1802.

4.2.10. Diethyl 2-hexyl-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4j). Yield 27%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (t, J=6.8 Hz, 3H), 1.00–1.17 (m, 6H), 1.19 (t, J=7.2 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H), 1.40–1.42 (m, 2H), 2.91–2.95 (m, 1H), 3.17–3.21 (m, 1H), 3.86–4.11 (m, 4H), 4.86 (d, J=18.6 Hz, 1H), 5.87 (s, 1H), 7.00 (d, J=8.0 Hz, 1H), 7.12–7.15 (m, 2H), 7.18–7.22 (m, 1H), 7.32–7.40 (m, 3H), 7.58–7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.4, 16.5, 22.3, 26.1, 28.6, 31.3, 53.3, 60.5, 62.2, 62.4, 106.7, 123.4, 124.4, 125.8, 126.9, 128.1, 128.2, 134.3, 137.8, 146.8; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.59; IR (cm^{-1}) ν_{max} 1027 (P–O), 1050 (P–O), 1245 (P═O); MS (ESI): m/z 428.20 (M^++1). HRMS calcd for $C_{25}H_{34}NO_3P$: 427.2276, found: 427.2273.

4.2.11. Diethyl 2-(4-methoxyphenyl)-3-(4-pentylphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4k). Yield 82%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J=6.8 Hz, 3H), 1.21–1.25 (m, 6H), 1.28–1.32 (m, 4H), 1.55–1.60 (m, 2H), 2.51 (t, J=8.0 Hz, 2H), 3.65 (s, 3H), 3.90–4.12 (m, 4H), 5.32 (d, J=19.0 Hz, 1H), 6.41 (s, 1H), 6.62 (d, J=8.8 Hz, 2H), 7.02–7.05 (m, 4H), 7.06–7.18 (m, 3H), 7.22 (d, J=7.2 Hz, 1H), 7.47 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 16.4, 22.4, 30.8, 31.5, 35.6, 55.2, 62.4, 62.6, 64.85, 110.3, 113.7, 123.9, 124.4, 124.8, 126.1, 127.2, 127.6, 128.1, 128.2, 133.3, 134.6, 141.6, 142.5, 142.7, 155.1; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.26; IR (cm^{-1}) ν_{max} 1028 (P–O), 1054 (P–O), 1264 (P═O); MS (ESI): m/z 520.30 (M^++1). HRMS calcd for $C_{31}H_{38}NO_4P$: 519.2538, found: 519.2534.

4.2.12. Diethyl 2-(4-fluorophenyl)-3-(4-pentylphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4l). Yield 98%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J=7.2 Hz, 3H), 1.21–1.25 (m, 6H), 1.28–1.34 (m, 4H), 1.56–1.62 (m, 2H), 2.52 (t, J=7.6 Hz, 2H), 3.90–4.12 (m, 4H), 5.32 (d, J=18.6 Hz, 1H), 6.44 (s, 1H), 6.77 (t, J=8.8 Hz, 2H), 7.03–7.06 (m, 4H), 7.09–7.19 (m, 3H), 7.24 (t, J=7.2 Hz, 1H), 7.45 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 16.4, 22.4, 30.8, 31.5, 35.6, 62.6, 64.5, 110.1, 115.1, 124.1, 124.2, 124.3, 125.1, 126.3, 127.1, 127.5, 128.2, 133.1, 134.3, 142.1, 143.0, 144.0,

158.43; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.92; IR (cm^{-1}) ν_{max} 1025 (P–O), 1051 (P–O), 1253 (P═O); MS (ESI): *m/z* 508.30 (M^++1). HRMS calcd for $C_{30}H_{35}FNO_3P$: 507.2339, found: 507.2335.

4.2.13. Diethyl 3-(4-pentylphenyl)-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4m). Yield 96%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=7.2 Hz, 3H), 1.22–1.26 (m, 6H), 1.26–1.30 (m, 4H), 1.55–1.60 (m, 2H), 2.51 (t, *J*=8.0 Hz, 2H), 3.89–4.12 (m, 4H), 5.44 (d, *J*=18.6 Hz, 1H), 6.47 (s, 1H), 6.85–6.90 (m, 1H), 7.03 (d, *J*=8.0 Hz, 2H), 7.07–7.10 (m, 4H), 7.12–7.16 (m, 2H), 7.18–7.22 (m, 1H), 7.23–7.25 (m, 1H), 7.47 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 16.4, 22.4, 30.8, 31.4, 35.5, 62.4, 62.6, 64.1, 111.5, 122.1, 122.6, 124.1, 125.5, 126.3, 127.1, 127.4, 128.1, 128.2, 128.4, 133.2, 134.6, 142.0, 142.8, 147.8; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.34; IR (cm^{-1}) ν_{max} 1027 (P–O), 1053 (P–O), 1251 (P═O); MS (ESI): *m/z* 490.30 (M^++1). HRMS calcd for $C_{30}H_{36}NO_3P$: 489.2433, found: 489.2437.

4.2.14. Diethyl 2-benzyl-3-(4-pentylphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4n). Yield 65%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.8 Hz, 3H), 1.15 (t, *J*=7.2 Hz, 3H), 1.22 (t, *J*=7.2 Hz, 3H), 1.34–1.40 (m, 4H), 1.63–1.66 (m, 2H), 2.62 (t, *J*=7.6 Hz, 2H), 3.83–4.09 (m, 4H), 4.13 (dd, *J*=15.6, 3.2 Hz, 1H), 4.32 (d, *J*=15.6 Hz, 1H), 4.80 (d, *J*=18.6 Hz, 1H), 5.94 (s, 1H), 6.90–6.95 (m, 1H), 7.02–7.05 (m, 2H), 7.14–7.21 (m, 8H), 7.59 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 16.4, 16.5, 22.4, 31.0, 31.5, 35.7, 55.8, 59.2, 62.1, 62.3, 106.4, 123.4, 124.2, 125.7, 127.0, 127.1, 127.7, 127.9, 128.0, 128.2, 128.4, 134.1, 134.7, 138.6, 143.5, 146.9; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.05; IR (cm^{-1}) ν_{max} 1026 (P–O), 1052 (P–O), 1264 (P═O); MS (ESI): *m/z* 504.30 (M^++1). HRMS calcd for $C_{31}H_{38}NO_3P$: 503.2589, found: 503.2584.

4.2.15. Diethyl 3-butyl-2-(4-methoxyphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4o). Yield 67%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.2 Hz, 3H), 1.20–1.38 (m, 8H), 1.50–1.55 (m, 2H), 2.09–1.13 (m, 1H), 2.26–2.30 (m, 1H), 3.77 (s, 3H), 4.01–3.87 (m, 4H), 5.03 (d, *J*=18.6 Hz, 1H), 5.93 (s, 1H), 6.79 (d, *J*=8.0 Hz, 2H), 6.99 (d, *J*=8.0 Hz, 2H), 7.05 (t, *J*=7.6 Hz, 1H), 7.14–7.16 (m, 1H), 7.18 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.4, 22.3, 30.2, 33.0, 55.4, 62.2, 62.6, 65.03, 107.8, 113.9, 123.0, 125.4, 126.0, 127.0, 128.0, 129.7, 133.4, 140.6, 144.7, 156.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.02; IR (cm^{-1}) ν_{max} 1025 (P–O), 1050 (P–O), 1251 (P═O); MS (ESI): *m/z* 428.30 (M^+−1). HRMS calcd for $C_{24}H_{32}NO_4P$: 429.2069, found: 429.2065. Anal. Calcd for $C_{24}H_{32}NO_4P$: C, 67.12; H, 7.51; N, 3.26. Found: C, 67.44; H, 7.70; N, 3.45.

4.2.16. Diethyl 3-butyl-2-(4-fluorophenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4p). Yield 58%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.2 Hz, 3H), 1.20–1.38 (m, 8H), 1.52–1.56 (m, 2H), 2.12–2.15 (m, 1H), 2.26–2.30 (m, 1H), 3.88–4.05 (m, 4H), 5.04 (d, *J*=18.6 Hz, 1H), 5.99 (s, 1H), 6.95 (t, *J*=8.0 Hz, 2H), 7.00 (d, *J*=8.0 Hz, 2H), 7.08 (t, *J*=7.6 Hz, 1H), 7.20–7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.4, 22.3, 30.1, 32.9, 62.3, 62.7, 64.8, 109.1, 115.4, 123.2, 125.6, 125.8, 125.9, 127.0, 128.1, 133.1, 143.3, 144.0, 159.4; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.70; IR (cm^{-1}) ν_{max} 1025 (P–O), 1049 (P–O), 1250 (P═O); MS (ESI): *m/z* 416.20 (M^+−1). HRMS calcd for $C_{23}H_{29}FNO_3P$: 417.1869, found 417.1864.

4.2.17. Diethyl 3-butyl-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4q). Yield 53%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.2 Hz, 3H), 1.22–1.28 (m, 8H), 1.56–1.60 (m, 2H), 2.17–2.21 (m, 1H), 2.33–2.36 (m, 1H), 3.86–4.02 (m, 4H), 5.15 (d, *J*=19.0 Hz, 1H), 6.04 (s, 1H), 6.97–7.06 (m, 4H), 7.18–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.4, 22.4, 30.3, 32.9, 62.2, 62.7, 64.6, 109.8, 123.2, 123.3, 123.6, 123.7, 125.6, 127.0, 128.1, 128.7, 133.2, 144.0, 147.2; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.91; IR (cm^{-1}) ν_{max} 1024 (P–O), 1050 (P–O), 1253 (P═O); MS (ESI): *m/z* 400.20 (M^++1). HRMS calcd for $C_{23}H_{30}NO_3P$: 399.1963, found 399.1967.

4.2.18. Diethyl 3-cyclohexenyl-2-(4-methoxyphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4r). Yield 79%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.30 (m, 6H), 1.46–1.52 (m, 4H), 1.92–2.12 (m, 4H), 3.74 (s, 3H), 3.93–4.07 (m, 4H), 5.16 (d, *J*=19.6 Hz, 1H), 6.13 (t, *J*=4.0 Hz, 1H), 6.20 (s, 1H), 6.73 (t, *J*=8.8 Hz, 2H), 7.02–7.08 (m, 5H), 7.18–7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 22.0, 22.6, 25.6, 26.2, 55.3, 62.3, 62.5, 64.6, 108.9, 113.6, 123.5, 123.9, 124.7, 125.8, 127.1, 127.9, 129.4, 133.3, 133.6, 142.4, 144.5, 155.2; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.12; IR (cm^{-1}) ν_{max} 1026 (P–O), 1050 (P–O), 1252 (P═O); MS (ESI): *m/z* 452.20 (M^+−1). HRMS calcd for $C_{26}H_{32}NO_4P$: 453.2069, found: 453.2065.

4.2.19. Diethyl 3-cyclohexenyl-2-(4-fluorophenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4s). Yield 64%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.30 (m, 6H), 1.45–1.56 (m, 4H), 1.90–2.13 (m, 4H), 3.92–4.08 (m, 4H), 5.17 (d, *J*=19.6 Hz, 1H), 6.11 (t, *J*=4.0 Hz, 1H), 6.24 (s, 1H), 6.87 (t, *J*=8.8 Hz, 2H), 7.04–7.10 (m, 5H), 7.20–7.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 22.0, 22.6, 25.6, 26.2, 62.4, 62.5, 64.4, 109.7, 115.0, 123.4, 124.1, 125.0, 126.1, 127.1, 128.1, 129.7, 133.1, 133.2, 144.0, 144.9, 158.47; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.86; IR (cm^{-1}) ν_{max} 1031 (P–O), 1050 (P–O), 1249 (P═O); MS (ESI): *m/z* 442.20 (M^++1). HRMS calcd for $C_{25}H_{29}FNO_3P$: 441.1869, found: 441.1865.

4.2.20. Diethyl 3-cyclohexenyl-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4t). Yield 80%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.31 (m, 6H), 1.45–1.58 (m, 4H), 1.92–2.15 (m, 4H), 3.92–4.05 (m, 4H), 5.29 (d, *J*=19.6 Hz, 1H), 6.13 (t, *J*=4.0 Hz, 1H), 6.27 (s, 1H), 6.92 (t, *J*=6.8 Hz, 1H), 7.03–7.10 (m, 5H), 7.16–7.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 22.1, 22.6, 25.7, 26.2, 62.4, 62.6, 64.0, 110.0, 121.7, 122.0, 124.2, 125.5, 126.0, 127.1, 128.0, 128.4, 129.4, 133.2, 133.4, 144.0, 148.7; ^{31}P NMR (161 MHz, $CDCl_3$) δ 20.83; IR (cm^{-1}) ν_{max} 1025 (P–O), 1050 (P–O), 1248 (P═O); MS (ESI): *m/z* 424.30 (M^++1). HRMS calcd for $C_{25}H_{30}NO_3P$: 423.1963, found: 423.1966.

4.2.21. Diethyl 2-benzyl-3-cyclohexenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4u). Yield 38%, yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.25 (m, 6H), 1.58–1.78 (m, 4H), 2.16–2.23 (m, 3H), 2.41–2.45 (m, 1H), 4.01–3.80 (m, 4H), 4.14–4.20 (m, 2H), 4.61 (d, J=19.6 Hz, 1H), 5.84 (s, 1H), 6.31 (t, J=4.0 Hz, 1H), 6.88 (d, J=7.2 Hz, 1H), 6.95 (d, J=7.2 Hz, 1H), 7.00 (t, J=7.2 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 7.18–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 22.2, 22.7, 25.6, 27.1, 55.6, 58.5, 62.0, 62.2, 105.2, 123.6, 124.1, 125.5, 127.1, 127.3, 127.8, 127.9, 128.3, 128.4, 134.1, 134.2, 138.7, 149.0; ^{31}P NMR (161 MHz, $CDCl_3$) δ 21.32; IR (cm^{-1}) ν_{max} 1025 (P–O), 1050 (P–O), 1252 (P═O); MS (ESI): m/z 438.30 (M^++1). HRMS calcd for $C_{26}H_{32}NO_3P$: 437.2120, found: 437.2122.

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