AgOTf-Catalyzed Three-Component Reactions of 2-Alkynylbenzaldehydes, Amines, and Diethylphosphite. An Efficient Route to 2,3-Disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates

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AgOTf was discovered as a highly efficient catalyst in reactions of 2-alkynylbenzaldehydes, amines, and diethylphosphite, which provided a facile and efficient pathway for the synthesis of 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates.

Introduction

The availability of practical route for generation of small molecules based natural products is of utmost urgency and importance in the biomedical research.[1] Realizing such a critical need, we have focused on the development of methodologies for the facile synthesis of natural-product-like molecules.[2] Recently, we also described reactions of aldehydes, amines, and diethyl phosphite catalyzed by Lewis acid, and the corresponding α-amino phosphonates could be produced in excellent yields.[3] It is well-known that α-amino phosphonate derivatives have broad applications because of their antibacterial[4] and antifungal[5] activity and because they function as inhibitors of phosphatase activity.[6] Meanwhile, as a privileged fragment, 1,2-dihydroisoquinoline is a ubiquitous subunit in many 1,2-dihydroisoquinoline-containing natural products with remarkable biological activity.[7] Because of the importance of α-amino phosphonate and 1,2-dihydroisoquinoline, our continued interest in building a 1,2-dihydroisoquinoline-based combinatorial library led us to devote our efforts to the developement of efficient methods for the synthesis of diversified 1,2-dihydroisoquinolin-1-ylphosphonate molecules, with a hope of finding more active hits or leads for our particular biological assays[8] (Figure 1). Herein, we would like to describe a simple, efficient, and practical synthesis of 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonate via AgOTf-catalyzed reaction of 2-alkynylbenzaldehyde, amine, and diethylphosphite.

Recently, Yamamoto and Takemoto described the generation of functionalized 1,2-dihydroisoquinoline skeletons through the direct addition of various carbon pronucleophiles to *ortho*-alkynylaryl aldimines catalyzed by Lewis acid.[9a,9c] Subsequently, Yamamoto also reported that the reaction could be performed in the absence of catalyst when chloroform was used as carbon pronucleophile.[9b] Prompted by these results[9] and our efforts for the α-amino phosphonate synthesis,[3] we conceived that 1,2-dihydroisoquino-lin-1-ylphosphonate may be synthesized from 2-alkynylbenzaldehyde, amine, and diethylphosphite under suitable conditions. It is well-known that multicomponent reactions (MCR) have emerged as a powerful tool for the delivery of the molecular diversity needed in combinatorial approaches for the preparation of bioactive compounds.[10] This multicomponent one-pot procedure will provide a new, rapid, and robust route toward a focused library of such heterocycles. Thus, we started to investigate the possibility of this reaction.

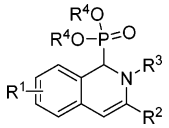

Figure 1. Diversified 1,2-dihydroisoquinolin-1-ylphosphonate scaffold.

Results and Discussion

The initial study was performed by treatment of 2-alkynylbenzaldehyde **1a**, *p*-anisidine **2a**, and diethylphosphite **3** in $ClCH_2CH_2Cl$ in the presence of a catalytic amount of $Mg(ClO_4)_2$ (10 mol %) at room temperature. To our delight, the reaction was highly efficient and completed in 4 h (85% yield). However, from spectral characterization, the product found was not the expected one (**4a**). Structure elucidation by ^1H and ^{13}C NMR and mass spectroscopy revealed this compound to be the normal addition adduct **5a**. (Scheme 1) Without catalyst, the reaction displayed an inferior result with generation of compound **5a**. Further studies by screening various Lewis acids revealed that $FeCl_3$, CBr_4, $In(OTf)_3$, $Bi(OTf)_3$, and $Yb(OTf)_3$ also gave compound **5a** in moderate to good yields. Increasing the temperature to 60 °C did not change the results. Fortunately, when silver triflate (10 mol %) was used as catalyst in the reaction at 60 °C, the reaction proceeded smoothly to afford the desired product **4a** in 74% yield. Encouraged by this result, we then screened other

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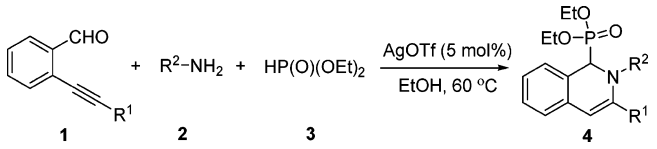
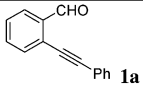
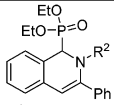
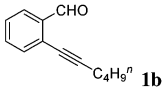
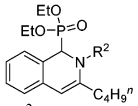
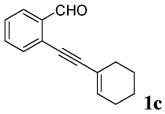
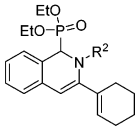
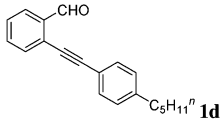
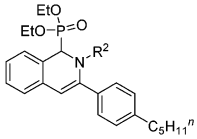
Table 1. Reaction of 2-Alkynylbenzaldehyde **1**, Amine **2**, and Diethyl Phosphate **3** Catalyzed by AgOTf (5 mol %)[a]

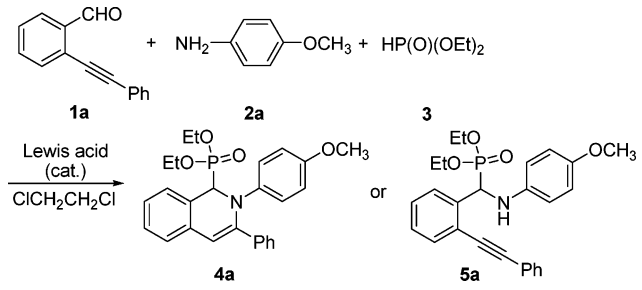


1 2 3 4

Entry	Aldehyde **1**	Amine **2**	Product **4**	Yield (%)[b]
1	 **1a**	4-OMeC$_6$H$_4$NH$_2$ **2a**	 **4a**: R^2 = 4-OMeC$_6$H$_4$	98
2	**1a**	4-MeC$_6$H$_4$NH$_2$ **2b**	**4b**: R^2 = 4-MeC$_6$H$_4$	87
3	**1a**	C$_6$H$_5$NH$_2$ **2c**	**4c**: R^2 = C$_6$H$_5$	88
4	**1a**	4-ClC$_6$H$_4$NH$_2$ **2d**	**4d**: R^2 = 4-ClC$_6$H$_4$	80
5	**1a**	3-CF$_3$C$_6$H$_4$NH$_2$ **2e**	**4e**: R^2 = 3-CF$_3$C$_6$H$_4$	72
6	**1a**	4-FC$_6$H$_4$NH$_2$ **2f**	**4f**: R^2 = 4-FC$_6$H$_4$	78
7	**1a**	C$_6$H$_5$CH$_2$NH$_2$ **2g**	**4g**: R^2 = C$_6$H$_5$CH$_2$	96
8	**1a**	^{n}C$_6$H$_{13}$NH$_2$ **2h**	**4h**: R^2 = ^{n}C$_6$H$_{13}$	51
9	 **1b**	**2a**	 **4i**: R^2 = 4-OMeC$_6$H$_4$	80
10	**1b**	**2c**	**4j**: R^2 = C$_6$H$_5$	80
11	**1b**	**2f**	**4k**: R^2 = 4-FC$_6$H$_4$	97
12	 **1c**	**2a**	 **4l**: R^2 = 4-OMeC$_6$H$_4$	92
13	**1c**	**2c**	**4m**: R^2 = C$_6$H$_5$	76
14	**1c**	**2f**	**4n**: R^2 = 4-FC$_6$H$_4$	96
15	**1c**	**2g**	**4o**: R^2 = C$_6$H$_5$CH$_2$	77
16	 **1d**	**2a**	 **4p**: R^2 = 4-OMeC$_6$H$_4$	79
17	**1d**	**2c**	**4q**: R^2 = C$_6$H$_5$	72
18	**1d**	**2f**	**4r**: R^2 = 4-FC$_6$H$_4$	80
19	**1d**	**2g**	**4s**: R^2 = C$_6$H$_5$CH$_2$	73

[a] Reaction conditions: 2-alkynylbenzaldehyde **1** (0.5 mmol), amine **2** (0.5 mmol, 1.0 equiv), diethyl phosphite **3** (0.5 mmol, 1.0 equiv), AgOTf (5 mol %), EtOH (2.0 mL), 60 °C, 4−6 h. [b] Isolated yield based on 2-alkynylbenzaldehyde **1**.

Scheme 1. Reaction of 2-Alkynyl Benzaldehyde **1a**, *p*-Anisidine, and Diethylphosphite Catalyzed by Various Lewis Acids



solvents in the presence of AgOTf (10 mol %) at 60 °C. It was found that ethanol was the best choice of solvent, leading to the corresponding product **4a** in 98% yield after 6 h (MeCN, 6 h, 81%; toluene, 6 h, 76%; THF, 6 h, 84%; EtOH, 6 h, 98%; DCE, 4 h, 74%). Similar results were obtained when the catalytic loading was decreased to 5 mol %. However, the reaction was retarded when 1 mol % of AgOTf was used.

To demonstrate the generality of this method, we started to investigate the reactions of 2-alkynyl benzaldehyde **1**, amine **2**, and diethyl phosphate **3** catalyzed by silver triflate under optimized reaction conditions [AgOTf (5 mol %), EtOH, 60 °C], and the results are shown in Table 1. From Table 1, we found that this condition was highly effective for the reactions, and all reactions afforded the corresponding products **4** in moderate to good yields. For different types of aromatic amines, a range of different groups with different electronic demands on the aromatic rings involving electron-donating and electron-withdrawing groups were also found to be tolerated. When benzyl amine **2g** was employed in this reaction instead of anilines, the generated product **4g** was also isolated in excellent yield (96%, entry 7). However, a

yield of only 51% for compound **4h** was obtained when an aliphatic amine, such as *n*-hexylamine **2h**, was involved in this reaction (entry 8). We also tried other 2-alkynyl benzaldehydes, for example, substrates **1b**, **1c**, and **1d**. Similarly, these reactions proceeded smoothly to give the desired products in good yields.

Conclusion

In summary, we described silver triflate-catalyzed reactions of 2-alkynyl benzaldehydes, amines, and diethyl phosphate, which provide a novel and efficient route to 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonate. It is likely that the efficiency and novelty of this method combined with the operational simplicity of this process will make it potentially attractive for library construction. Focused library generation and screening for biological activity of these small molecules are under investigation in our laboratory.

Experimental Section

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 redistilled 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.[11]

General Procedure for Synthesis of Compound 4. 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 AgOTf (5 mol %) in ethanol (3.0 mL) was stirred at 60 °C under a 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 on silica gel afforded pure 1,2-dihydroisoquinolin-1-ylphosphonate **4**.

Diethyl 2-(4-Methoxyphenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (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. MS (ESI): m/z 450.20 ($M^+ + 1$). HRMS Calcd for $C_{26}H_{28}NO_4P$: 449.1756. Found: 449.1752.

Diethyl 3-Phenyl-2-p-tolyl-1,2-dihydroisoquinolin-1-ylphosphonate (4b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (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. MS (ESI): 434.20 ($M^+ + 1$). HRMS Calcd for $C_{26}H_{28}NO_3P$: 433.1807. Found: 433.1804.

Diethyl 2,3-Diphenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4c). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (m, 6H), 3.90−4.10 (m, 4H), 5.45 (d, J = 18.6 Hz, 1H), 6.50 (s, 1H), 6.85 (m, 1H), 7.07−7.25 (m, 11H), 7.58 (d, J = 6.8 Hz, 2H). ^{13C} 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. MS (ESI): m/z 420.20 ($M^+ + 1$). HRMS Calcd for $C_{25}H_{26}NO_3P$: 419.1650. Found: 419.1654.

Diethyl 2-(4-Chlorophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4d). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (m, 6H), 3.90−4.12 (m, 4H), 5.37 (d, J = 18.6 Hz, 1H), 6.49 (s, 1H), 7.02 (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. MS (ESI): m/z 454.20 ($M^+ + 1$). HRMS Calcd for $C_{25}H_{25}ClNO_3P$: 453.1261. Found: 453.1257.

Diethyl 3-Phenyl-2-(3-(trifluoromethyl)phenyl)-1,2-dihydroisoquinolin-1-yl-phosphonate (4e). ^{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 (m, 2H), 4.09 (m, 2H), 5.42 (d, J = 18.6 Hz, 1H), 6.53 (s, 1H), 7.08 (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. MS (ESI): m/z 488.20 ($M^+ + 1$). HRMS Calcd for $C_{26}H_{25}F_3NO_3P$: 487.1524. Found: 487.1521.

Diethyl 2-(4-Fluorophenyl)-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4f). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (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. MS (ESI): m/z 438.20 ($M^+ + 1$). HRMS Calcd for $C_{25}H_{25}FNO_3P$: 437.1556. Found: 437.1561.

Diethyl 2-Benzyl-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4g). ^{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 (m, 1H), 7.04 (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. MS (ESI): m/z 434.20 ($M^+ + 1$). HRMS Calcd for $C_{26}H_{28}NO_3P$: 433.1807. Found: 433.1802.

Diethyl 2-Hexyl-3-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4h). ^{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 (m, 2H), 2.91 (m, 1H), 3.17 (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 (m, 2H), 7.18 (m, 1H), 7.32−7.40 (m, 3H), 7.58 (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. MS (ESI): m/z 428.20

($M^+ + 1$). HRMS Calcd for $C_{25}H_{34}NO_3P$: 427.2276. Found: 427.2273.

Diethyl 3-Butyl-2-(4-methoxyphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4i). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.2 Hz, 3H), 1.20−1.38 (m, 8H), 1.50 (m, 2H), 2.09 (m, 1H), 2.26 (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), 7.15 (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. MS (ESI): m/z 428.30 ($M^+ - 1$). HRMS Calcd for $C_{24}H_{32}NO_4P$: 429.2069. Found: 429.2065.

Diethyl 3-Butyl-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4j). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.2 Hz, 3H), 1.22−1.28 (m, 8H), 1.56 (m, 2H), 2.17 (m, 1H), 2.33 (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. MS (ESI): m/z 400.20 ($M^+ + 1$). HRMS Calcd for $C_{23}H_{30}NO_3P$: 399.1963. Found: 399.1967.

Diethyl 3-Butyl-2-(4-fluorophenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4k). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.2 Hz, 3H), 1.20−1.38 (m, 8H), 1.52 (m, 2H), 2.12 (m, 1H), 2.26 (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 (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. MS (ESI): m/z 416.20 ($M^+ - 1$). HRMS Calcd for $C_{23}H_{29}FNO_3P$: 417.1869. Found: 417.1864.

Diethyl 3-Cyclohexenyl-2-(4-methoxyphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4l). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (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 (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. MS (ESI): m/z 452.20 ($M^+ - 1$). HRMS Calcd for $C_{26}H_{32}NO_4P$: 453.2069. Found: 453.2065.

Diethyl 3-Cyclohexenyl-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (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. MS (ESI): m/z 424.30 ($M^+ + 1$). HRMS Calcd for $C_{25}H_{30}NO_3P$: 423.1963. Found: 423.1966.

Diethyl 3-Cyclohexenyl-2-(4-fluorophenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4n). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (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 (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. MS (ESI): m/z 442.20 ($M^+ + 1$). HRMS Calcd for $C_{25}H_{29}FNO_3P$: 441.1869. Found: 441.1865.

Diethyl 2-Benzyl-3-cyclohexenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4o). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (m, 6H), 1.58−1.78 (m, 4H), 2.16 (m, 3H), 2.41 (m, 1H), 4.01−3.80 (m, 4H), 4.14 (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. MS (ESI): m/z 438.30 ($M^+ + 1$). HRMS Calcd for $C_{26}H_{32}NO_3P$: 437.2120. Found: 437.2122.

Diethyl 2-(4-Methoxyphenyl)-3-(4-pentylphenyl)-1,2-dihydroisoquinolin-1-yl-phosphonate (4p). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.21 (m, 6H), 1.28 (m, 4H), 1.55 (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. MS (ESI): m/z 520.30 ($M^+ + 1$). HRMS Calcd for $C_{31}H_{38}NO_4P$: 519.2538. Found: 519.2534.

Diethyl 3-(4-Pentylphenyl)-2-phenyl-1,2-dihydroisoquinolin-1-ylphosphonate (4q). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 7.2 Hz, 3H), 1.22 (m, 6H), 1.26 (m, 4H), 1.55 (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 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.07 (m, 4H), 7.12 (m, 2H), 7.18 (m, 1H), 7.23 (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. MS (ESI): m/z 490.30 ($M^+ + 1$). HRMS Calcd for $C_{30}H_{36}NO_3P$: 489.2433. Found: 489.2437.

Diethyl 2-(4-Fluorophenyl)-3-(4-pentylphenyl)-1,2-dihydroisoquinolin-1-yl-phosphonate (4r). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J = 7.2 Hz, 3H), 1.21 (m, 6H), 1.28 (m, 4H), 1.56 (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. MS (ESI): m/z 508.30 ($M^+ + 1$). HRMS Calcd for $C_{30}H_{35}FNO_3P$: 507.2339. Found: 507.2335.

Diethyl 2-Benzyl-3-(4-pentylphenyl)-1,2-dihydroisoquinolin-1-ylphosphonate (4s). ^{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 (m, 4H), 1.63 (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 (m, 1H), 7.02 (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. MS (ESI): *m/z* 504.30 ($M^+ + 1$). HRMS Calcd for $C_{31}H_{38}NO_3P$: 503.2589. Found: 503.2584.

Diethyl (4-Methoxyphenylamino)(2-(2-phenylethynyl)-phenyl)methylphosphonate (5a). A mixture of 2-alkynylbenzaldehyde **1a** (0.5 mmol), *p*-anisidine **2a** (0.5 mmol), diethylphosphite **3** (0.6 mmol), and $Mg(ClO_4)_2$ (10 mol %) in $ClCH_2CH_2Cl$ (3.0 mL) was stirred at room temperature under a 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 on silica gel, afforded compound **5a** as white solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (t, $J = 7.3$ Hz, 3H), 1.30 (t, $J = 7.3$ Hz, 3H), 3.60−3.70 (m, 4H), 3.85−3.93 (m, 1H), 4.18−4.25 (m, 2H), 4.80 (br, 1H), 5.49 (d, $J = 24.4$ Hz, 1H), 6.61 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 7.23 (t, $J = 7.3$ Hz, 1H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.36−7.40 (m, 3H), 7.53−7.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 16.5, 53.2, 54.7, 55.7, 63.4, 63.5, 87.2, 95.0, 114.9, 123.1, 123.3, 127.3, 127.4, 127.7, 128.6, 128.7, 129.0, 131.6, 132.1, 138.4, 140.2, 152.6. MS (EI): *m/z* 449 (M^+). HRMS Calcd for $C_{26}H_{28}NO_4P$: 449.1756. Found: 449.1752.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of compounds **4a**−**4s** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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