Generation of Diverse 2*H*-Isoindol-1-ylphosphonates via Three-Component Reaction of 2-Alkynylbenzaldehyde, Aniline, and Phosphite

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Diverse 2*H*-isoindol-1-ylphosphonates as potential HCT-116 inhibitors are easily generated via a $FeCl_3$ and $PdCl_2$ cocatalyzed three-component reaction of 2-alkynylbenzaldehyde, aniline, and phosphite. The focused small library is constructed based on parallel diversity-oriented synthesis.

Introduction

Parallel diversity-oriented synthesis of discrete molecules has become a useful technology for the rapid preparation of focused libraries.[1] Among *N*-heterocycles, less attention has been paid to isoindoles.[2] Various isoindoles have become known for both their plant growth regulating[3a] and fluorescent properties.[2b] Recently, we described an efficient synthesis of 2,3-disubstituted-2*H*-isoindol-1-ylphosphonates via palladium(II)-catalyzed reaction of α-amino (2-alkynylphenyl)methylphosphonate.[2e,f] The 5-exo-cyclization and [1,5]-H shift were involved in this transformation. Subsequent biological assays revealed that several compounds of phosphonylated isoindoles displayed promising activity as HCT-116 (human colon cancer cells) inhibitors. Compound **A** shows the best activity with an IC_{50} 9.90 μM (Figure 1). In addition, mechanistic studies show that this compound causes destabilization of microtubules, leading to a cell cycle arrest at G2/M stage.[3b] The discovery of promising lead antitumor compounds with moderate activity prompted us to develop efficient and rapid synthesis protocol and test the resulting compounds to find better inhibitors. Consequently, we initiated a program to develop efficient methods for facile assembly of diverse 2*H*-isoindol-1-ylphosphonate molecules (Figure 1).

Recently, multicatalytic processes have attracted considerable interest.[4,5] Normally, several catalysts are combined in a reaction and promote two or more distinct chemical transformations in one pot. For instance, Lambert and coworkers described the multicatalytic synthesis of α-pyrrolidinyl ketones in the presence of palladium(II) and indium(III) catalysts.[5i] Silver triflate and bismuth triflate proved to be effective as cocatalysts for the tandem reaction of 2-alkynylbenzaldoxime with isocyanide.[5m] As mentioned above, the 2,3-disubstituted-2*H*-isoindol-1-ylphosphonates were generated from palladium(II)-catalyzed reaction of

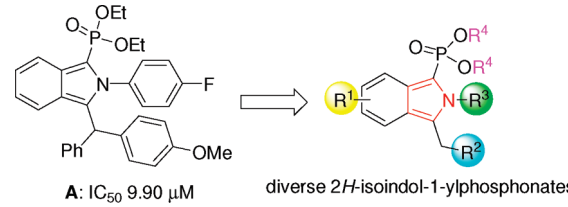

Figure 1. 2*H*-Isoindol-1-ylphosphonates.

α-amino (2-alkynylphenyl)methylphosphonate.[2e] The starting material, α-amino (2-alkynylphenyl)methylphosphonate, was traced back to the 2-alkynylbenzaldehyde, amine, and phosphite. However, the initial examination revealed that three-component reaction of 2-alkynylbenzaldehyde, amine, and phosphite, in the presence of palladium or copper catalyst, produced 1,2-dihydroisoquinolin-1-ylphosphonates via 6-endo cyclization.[6a] While selectivity and efficiency are the major concerns in this transformation, based on the different reactivity of Lewis acids[7] and the advancement of multicatalysis and tandem reactions,[8] we conceived that the phosphonylated isoindoles might be generated in a selective way using a suitable cocatalytic system. Thus, we started to explore the possibility to form the phosphorylated isoindoles via the three-component reaction of 2-alkynylbenzaldehyde, amine, and phosphite.

Result and Discussion

2-Alkynylbenzaldehydes **1** were synthesized via Sonogashira coupling reaction according to the literature report.[9] The initial idea was to react 2-alkynylbenzaldehyde **1**{*1*}, *p*-toluidine **2**{*3*}, and diethyl phosphite in the presence of different Lewis acids in using different solvents at 60 °C (Scheme 1). Starting with acetonitrile in the presence of 5 mol % of Lewis acids ($FeCl_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$, $Zn(OTf)_2$, AgOTf, $Sc(OTf)_3$, $In(OTf)_3$, $Mg(ClO_4)_2$) did not lead to the desired product **3**{*1,3*}. Only α-amino (2-alkynylphenyl)methylphosphonate or compound **4**{*1,3*} was generated (Scheme 1). Among the reactions, compound **4**{*1,3*} was isolated when AgOTf or $PdCl_2$ was used as the catalyst,[6] while α-amino (2-alkynylphenyl)methylphospho-

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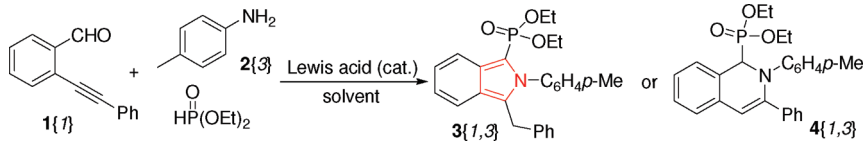
Scheme 1. Initial Studies for the Reaction of 2-Alkynylbenzaldehyde **1**{*1*}, Aniline **2**{*3*}, and Diethyl Phosphite



nate was obtained when other metal salts were utilized (Kabachnik−Fields reaction).[10] The Kabachnik−Fields reaction (three-component reaction of aldehyde, amine, and phosphite) is well studied, and many Lewis acids have been successfully employed in such reaction. Since $FeCl_3$ was the most effective catalyst for α-amino (2-alkynylphenyl)methylphosphonate formation[10j] and the palladium catalyst worked efficiently for the subsequent 5-*exo*-cyclization,[2e] the above reactions were performed again in combination with 5 mol % of $PdCl_2$. To avoid the competitive pathway, this three-component reaction was performed in the presence of Lewis acid (5 mol %) for 30 min to facilitate the α-amino (2-alkynylphenyl)methylphosphonate formation. Next, 5 mol % of $PdCl_2$ was added in the mixture for the subsequent transformation. The desired product **3**{*1*,*3*} was isolated in 59% yield when the reaction was carried out in the presence of $FeCl_3$ (5 mol %) and $PdCl_2$ (5 mol %) in MeCN at 60 °C. Other combinations of $PdCl_2$ with Lewis acids gave inferior results. With these promising results, we started to screen solvents for the reaction. We found that the reaction worked most efficiently in DCE/MeCN (*v*/*v* 1:1) with 77% isolated yield. Reactions performed in other solvents led to inferior results with low yields and prolonged reaction time. No effects were observed for the concentration screening. The reaction was retarded when the temperature was decreased to 25 °C. Further, a reduction of the amount to 1 mol % diminished the progress of the reaction.

Using optimized conditions (5 mol % of $FeCl_3$, 5 mol % of $PdCl_2$, DCE/CH_3CN, 60 °C), we investigated the scope of this cocatalytic system with regard to tolerance of functional groups in case of different 2-alkynylbenzaldehydes

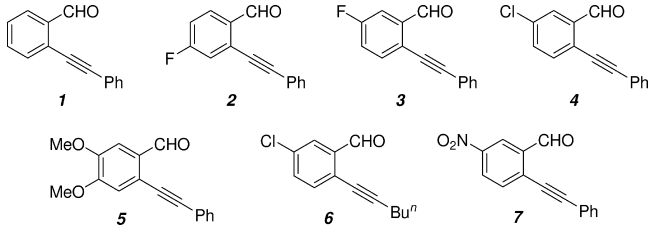


Figure 2. Diversity reagents **1**{*1*−*7*}.

1 and amines **2**. The diverse reagents are shown in Figures 2 and 3. This cocatalytic system proved to be highly efficient and we found a good general applicability of the protocol because of its remarkable functional group compatibility, which afforded the desired phosphonylated isoindoles **3** in good to excellent yields (Table 1). Moreover, the conditions proved to be useful for various anilines. As expected, both electron-rich and electron-poor anilines were suitable partners in this process. Different functional groups such as methyl, methoxy, hydroxy, acetyl, ester, cyano, nitro, halo, and trifluoromethyl groups were all tolerated under standard conditions. With respect to 2-alkynylbenzaldehyde **1**, it seemed that the R^2 group attached to the triple bond was crucial for the transformation. No desired product formation was observed when substrate **1**{*6*} was employed in the reaction with aniline **2**{*1*} and diethyl phosphite. We reasoned that the presence of aryl group (R^2) attached to the triple bond might facilitate its [1,5]-H shift after 5-*exo*-cyclization in the reaction process. When dimethoxy-substituted 2-alkynylbenzaldehyde **1**{*5*} was utilized in the reactions with aniline **2**{*1*} or **2**{*3*} with diethyl phosphite, the desired products were observed in low yields. The electron-donating groups attached to the aromatic ring of 2-alkynylbenzaldehyde proved to decrease the electrophilicity of the substrate. When nitro-substituted 2-alkynylbenzaldehyde **1**{*7*} was employed in the three-component reaction, the corresponding products were isolated in moderate yield (entries 52−55). This result indicated that the presence of strong electron-withdrawing nitro group in the aromatic ring might reduce the nucleophilicity of amine in the intermediate α-amino (2-alkynylphenyl)methylphosphonate.

Conclusion

In conclusion, we have described a facile and efficient route for the generation of diverse 2*H*-isoindol-1-ylphosphonates via a $FeCl_3$ and $PdCl_2$ cocatalyzed three-component reaction of 2-alkynylbenzaldehydes, anilines, and phosphite. The focused library was prepared based on parallel diversity-oriented synthesis. However, some limitations were observed for the substrate selection: Electron-donating groups attached

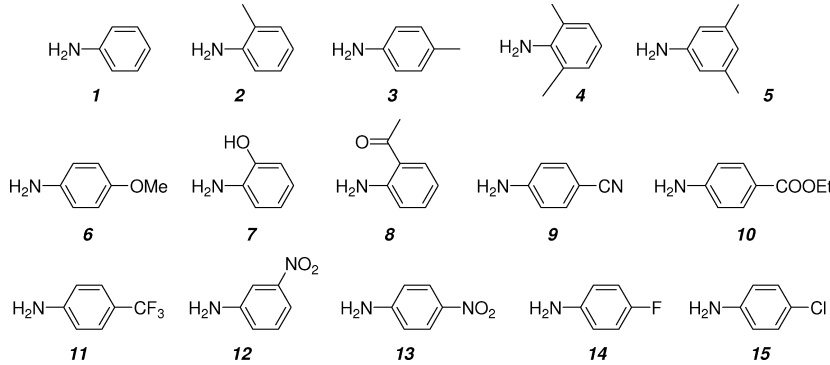
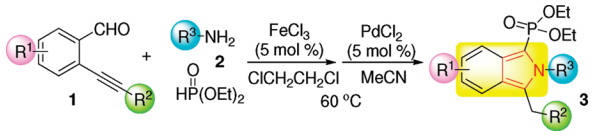


Figure 3. Aniline reagents **2**{*1*−*15*}.

Table 1. Generation of Diverse 2*H*-Isoindol-1-ylphosphonates via Three-Component Reaction of 2-Alkynylbenzaldehyde **1**, Aniline **2**, and Phosphite



entry	aldehyde **1**	amine **2**	product	yield (%)[a]	purity[d]
1	**1**{*1*}	**2**{*1*}	**3**{*1,1*}	76	>97%
2	**1**{*1*}	**2**{*2*}	**3**{*1,2*}	60	>97%
3	**1**{*1*}	**2**{*3*}	**3**{*1,3*}	77	>97%
4	**1**{*1*}	**2**{*5*}	**3**{*1,5*}	66	>97%
5	**1**{*1*}	**2**{*6*}	**3**{*1,6*}	80	>97%
6	**1**{*1*}	**2**{*11*}	**3**{*1,11*}	70	>97%
7	**1**{*1*}	**2**{*12*}	**3**{*1,12*}	70	>97%
8	**1**{*1*}	**2**{*14*}	**3**{*1,14*}	70	>97%
9	**1**{*1*}	**2**{*15*}	**3**{*1,15*}	71	>97%
10	**1**{*2*}	**2**{*1*}	**3**{*2,1*}	85	>97%
11	**1**{*2*}	**2**{*2*}	**3**{*2,2*}	70	>97%
12	**1**{*2*}	**2**{*3*}	**3**{*2,3*}	80	>97%
13	**1**{*2*}	**2**{*4*}	**3**{*2,4*}	63	>97%
14	**1**{*2*}	**2**{*5*}	**3**{*2,5*}	74	>97%
15	**1**{*2*}	**2**{*6*}	**3**{*2,6*}	66	>97%
16	**1**{*2*}	**2**{*7*}	**3**{*2,7*}	61	>97%
17	**1**{*2*}	**2**{*8*}	**3**{*2,8*}	66	>97%
18	**1**{*2*}	**2**{*9*}	**3**{*2,9*}	73	>97%
19	**1**{*2*}	**2**{*10*}	**3**{*2,10*}	76	>97%
20	**1**{*2*}	**2**{*11*}	**3**{*2,11*}	80	>97%
21	**1**{*2*}	**2**{*12*}	**3**{*2,12*}	72	>97%
22	**1**{*2*}	**2**{*13*}	**3**{*2,13*}	61	>97%
23	**1**{*2*}	**2**{*14*}	**3**{*2,14*}	88	>97%
24	**1**{*2*}	**2**{*15*}	**3**{*2,15*}	74	>97%
25	**1**{*3*}	**2**{*1*}	**3**{*3,1*}	76	>97%
26	**1**{*3*}	**2**{*2*}	**3**{*3,2*}	73	>97%
27	**1**{*3*}	**2**{*3*}	**3**{*3,3*}	81	>97%
28	**1**{*3*}	**2**{*5*}	**3**{*3,5*}	82	>97%
29	**1**{*3*}	**2**{*6*}	**3**{*3,6*}	78	>97%
30	**1**{*3*}	**2**{*7*}	**3**{*3,7*}	90	>97%
31	**1**{*3*}	**2**{*9*}	**3**{*3,9*}	91	>97%
32	**1**{*3*}	**2**{*10*}	**3**{*3,10*}	94	>97%
33	**1**{*3*}	**2**{*11*}	**3**{*3,11*}	76	>97%
34	**1**{*3*}	**2**{*12*}	**3**{*3,12*}	81	>97%
35	**1**{*3*}	**2**{*13*}	**3**{*3,13*}	84	>97%
36	**1**{*3*}	**2**{*14*}	**3**{*3,14*}	84	>97%
37	**1**{*3*}	**2**{*15*}	**3**{*3,15*}	86	>97%
38	**1**{*4*}	**2**{*1*}	**3**{*4,1*}	96	>97%
39	**1**{*4*}	**2**{*3*}	**3**{*4,3*}	91	>97%
40	**1**{*4*}	**2**{*5*}	**3**{*4,5*}	80	>97%
41	**1**{*4*}	**2**{*6*}	**3**{*4,6*}	94	>97%
42	**1**{*4*}	**2**{*9*}	**3**{*4,9*}	60	>97%
43	**1**{*4*}	**2**{*10*}	**3**{*4,10*}	96	>97%
44	**1**{*4*}	**2**{*11*}	**3**{*4,11*}	80	>97%
45	**1**{*4*}	**2**{*12*}	**3**{*4,12*}	70	>97%
46	**1**{*4*}	**2**{*13*}	**3**{*4,13*}	77	>97%
47	**1**{*4*}	**2**{*14*}	**3**{*4,14*}	90	>97%
48	**1**{*4*}	**2**{*15*}	**3**{*4,15*}	96	>97%
49	**1**{*5*}	**2**{*1*}	**3**{*5,1*}	<20[b]	
50	**1**{*5*}	**2**{*3*}	**3**{*5,3*}	<20[b]	
51	**1**{*6*}	**2**{*1*}	**3**{*6,1*}	*c*	
52	**1**{*7*}	**2**{*1*}	**3**{*7,1*}	54	>97%
53	**1**{*7*}	**2**{*3*}	**3**{*7,3*}	43	>97%
54	**1**{*7*}	**2**{*6*}	**3**{*7,6*}	44	>97%
55	**1**{*7*}	**2**{*11*}	**3**{*7,11*}	40	>97%

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**. [b] GC analysis. [c] No product formation was observed. [d] Determined by ^{1}H NMR.

to the aromatic core decrease the electrophilicity of the substrate; resulting in low yields of the desired isoindole. Additionally, aliphatic amines are not suitable for this transformation and only aryl substituted acetylene-benzaldehydes proved to be effective starting materials in this reaction. Nevertheless, biological screening of the small molecules generated here revealed their potential as HCT-116 inhibitors. Further investigations are ongoing and the results will be published in due time.

Experimental Section

General Experimental Procedure for $FeCl_3$ and $PdCl_2$ Co-catalyzed Three-Component Reaction of 2-Alkynylbenzaldehyde 1, Aniline 2, and Phosphite. Iron(III) chloride (0.015 mmol, 5 mol %) was added to a solution of 2-alkynylbenzaldehyde**1** (0.3 mmol), aniline **2** (0.3 mmol, 1.0 equiv), and diethyl phosphite (0.36 mmol, 1.2 equiv) in DCE (1.0 mL). The mixture was heated at 60 °C with vigorous stirring for 30 min. Next, palladium(II) chloride (0.015 mmol, 5 mol %) and MeCN (1.0 mL) were added to the solution. The reaction mixture was then vigorously stirred at 60 °C until completion of the reaction. After the solution was cooled to room temperature, the mixture was diluted with ethyl acetate (5.0 mL) and quenched with water (5.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (eluting with PE/EA = 3/1 to 1/1) to provide the desired product **3**.

Selected Examples. Diethyl 3-Benzyl-2-phenyl-2*H*-isoindol-1-ylphosphonate 3{*1,1*}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (t, J = 7.2 Hz, 6H), 3.79−3.85 (m, 2H), 3.90−3.96 (m, 2H), 4.13 (s, 2 H), 6.82 (t, J = 3.6 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 7.12−7.23 (m, 6H), 7.37 (t, J = 7.6 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 16.1, 31.1, 61.6, 107.7 (d, $^1J_{CP}$ = 234 Hz), 119.6, 120.6, 121.7, 123.3 (d, $^3J_{CP}$ = 13 Hz), 124.8, 126.2, 128.2, 128.3, 128.4, 128.5, 129.1, 131.5 (d, $^3J_{CP}$ = 9 Hz), 132.8 (d, $^2J_{CP}$ = 19 Hz), 138.1, 138.5. ^{31}P NMR (161 MHz, $CDCl_3$): δ 10.1. HRMS calcd for $C_{25}H_{26}NO_3P$: (M + H^+) 420.1729, found 420.1720.

Diethyl 3-Benzyl-2-*o*-tolyl-2*H*-isoindol-1-ylphosphonate 3{*1,2*}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (t, J = 7.3 Hz, 3H), 1.15 (t, J = 7.3 Hz, 3H), 1.66 (s, 3H), 3.81−3.96 (m, 4H), 3.95 (d, J = 16.0 Hz, 1H), 4.09 (d, J = 15.6 Hz, 1H), 6.80−6.82 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 7.05−7.12 (m, 4H), 7.17−7.23 (m, 3H), 7.37 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 16.1, 17.0, 31.3, 61.7, 107.1 (d, $^1J_{CP}$ = 236 Hz), 119.8, 120.6, 121.6, 123.3 (d, $^3J_{CP}$ = 13 Hz), 124.7, 125.8, 126.4, 128.3, 128.6, 128.7, 129.5, 130.4, 131.1 (d, $^3J_{CP}$ = 9 Hz), 132.7 (d, $^2J_{CP}$ = 18 Hz), 136.9, 137.3, 138.1. ^{31}P NMR (161 MHz, $CDCl_3$): δ 10.3. HRMS calcd for $C_{26}H_{28}NO_3P$: (M + H^+) 434.1885, found 434.1881.

Diethyl 3-Benzyl-2-*p*-tolyl-2*H*-isoindol-1-ylphosphonate 3{*1,3*}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (t, J = 7.2 Hz, 6H), 2.42 (s, 3H), 3.82−3.88 (m, 2H), 3.93−3.99 (m, 2 H), 4.12 (s, 2 H), 6.86 (d, J = 7.6 Hz, 2H), 7.01−7.07 (m, 3H), 7.13−7.25 (m, 6H), 7.54 (dd, J = 8.4, 0.8 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 21.3, 31.1, 61.5, 107.7 (d, $^1J_{CP}$ = 233 Hz), 119.7, 120.6, 121.5, 123.2 (d, $^3J_{CP}$ = 13 Hz), 124.7, 126.2, 128.0, 128.2, 128.3, 128.9, 131.5 (d, $^3J_{CP}$ = 9 Hz), 132.8 (d, $^2J_{CP}$ = 19 Hz), 135.5, 138.7, 139.1. ^{31}P NMR (161 MHz, $CDCl_3$) δ 10.3.

HRMS calcd for $C_{26}H_{28}NO_3P$: ($M + H^+$) 434.1885, found 434.1882; ($M + Na^+$) 456.1704, found 456.1697.

Diethyl 3-Benzyl-6-chloro-2-phenyl-2*H*-isoindol-1-ylphosphonate 3{*4,1*}. ^1H NMR (400 MHz, $CDCl_3$): 1.13 (t, $J =$ 7.0 Hz, 6H), 3.80−3.98 (m, 4H), 4.09 (s, 2 H), 6.78−6.80 (m, 2H), 6.97 (dd, $J = 9.2$, 1.8 Hz, 1H), 7.12−7.14 (m, 5H), 7.36−7.40 (m, 2H), 7.44−7.49 (m, 2H), 8.18−8.19 (m, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 16.2, 31.2, 61.8, 108.0 (d, $^1J_{CP} = 234$ Hz), 119.5, 121.3, 121.6 (d, $^3J_{CP} = 13$ Hz), 123.1, 126.5, 128.2, 128.3, 128.4, 128.5, 129.4, 130.9, 132.0 (d, $^3J_{CP} = 9$ Hz), 133.1 (d, $^2J_{CP} = 18$ Hz), 137.8, 138.2. ^{31}P NMR (161 MHz, $CDCl_3$): δ 9.8. HRMS calcd for $C_{25}H_{25}ClNO_3P$: ($M + H^+$) 454.1339, found 454.1325. (For details, please see Supporting Information.)

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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