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Multicatalytic synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates via a tandem four-component reaction

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ABSTRACT

A tandem four-component reaction of 2-bromobenzaldehyde, alkyne, amine, and diethyl phosphite catalyzed by the combination of palladium and copper salts provides a facile and efficient route to 1,2-dihydroisoquinolin-1-ylphosphonate. A cascade Sonogashira-intramolecular cyclization-nucleophilic addition may be involved in the reaction process.

Tandem C–C bond formations are powerful methods for molecular complexity generation from relatively simple starting materials in a convergent way.[1–3] These transformations are usually operated in one pot without the need for intermediate workups or purifications. 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. Recently, the multicatalytic processes have attracted growing interest in the filed of tandem reactions.[4,5] One or more catalysts are involved in the reaction and promote two or more distinct chemical transformations in a single flask. We have also developed multicatalytic system for the generation of 1,2-dihydroisoquinolines.[6] For instance, silver triflate and proline catalysis were found highly effective in the three-component reactions of 2-alkynylbenzaldehydes, amines, and ketones.[6a] The combination of $Mg(ClO_4)_2/Cu(OTf)_2$ shows high efficiency as well in the one-pot reaction of 2-alkynylbenzaldehydes, amines, zinc, and allylic bromide or benzyl bromide. As part of a continuing effort in our laboratory toward developing highly efficient strategies for accessing privileged organic architectures,[7] we became interested in exploring the new multicatalytic processes to facilitate the natural product-like compounds generation.

The importance of 1,2-dihydroisoquinolines has been recognized since many natural products and pharmaceuticals containing this scaffold show remarkable biological activities.[8] Effort for development of new 1,2-dihydroisoquinoline-based structures and novel methods for their construction continues to be given.[9–11] Recently, we also have developed efficient methods for 1,2-dihydroisoquinoline synthesis via tandem reactions.[6,7g,11] Among the compounds constructed, the 1,2-dihydroisoquinolin-1-ylphosphonates showed promising activity as PTP1B (protein tyrosine phosphatase) inhibitor in the subsequent biological assays. With expectation to search for better inhibitor, we need to develop efficient and rapid syntheses and evaluations of analogous structures. Since the multicatalytic processes offer the potential to significantly advance the field of synthesis, herein we would like to disclose our recent efforts for the synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates via a multicatalytic system in a four-component reaction starting from 2-bromobenzaldehyde, alkyne, amine, and diethyl phosphite.

Encouraged by the advancement of Sonogashira coupling reaction[12,13] as well as the intramolecular electrophilic cyclization,[14,15] we conceived that during the reaction process, 2-alkynylbenzaldehyde would be formed via coupling reaction of 2-bromobenzaldehyde with alkyne in the presence of palladium catalyst. Following condensation with amine would generate the *o*-alkynylarylaldimine, which then undergo the intramolecular electrophilic cyclization in the presence of suitable Lewis acid. Subsequent nucleophilic addition of diethyl phosphite would afford the desired 1,2-dihydroisoquinolin-1-ylphosphonates. To verify the practicability of this projected route, we started to investigate the possibility for multicatalytic one-pot four-component reaction of 2-bromobenzaldehyde, alkyne, amine, and diethyl phosphite.

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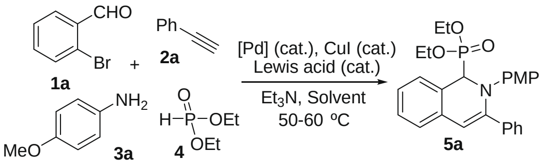
At the outset, our studies commenced with the reaction of 2-bromobenzaldehyde **1a**, phenyl acetylene **2a**, *p*-anisidine **3a**, and diethyl phosphite **4** (Table 1). Initially, the reaction occurred in the presence of different palladium catalyst and copper(I) iodide. We reasoned that the presence of palladium and copper catalyst would facilitate both the Sonogashira coupling reaction and cyclization-nucleophilic addition process. However, only trace amount of desired 1,2-dihydroisoquinoline **5a** was detected when the reaction was catalyzed by $PdCl_2$ (5 mol %) and CuI (5 mol %) in the presence of Et_3N as base in THF at 60 °C (Table 1, entry 1). Most of the product generated was the Sonogashira coupling adduct 2-alkynylbenzaldehyde. Similar results were observed when other palladium catalysts (such as $Pd(PhCN)_2Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, and $Pd(dppf)Cl_2$) were employed in the reaction (Table 1, entries 2–5). We conceived that the palladium catalyst might be deactivated in the subsequent transformation. Thus, different Lewis acids were screened, including AgOTf, $Sc(OTf)_3$, $Cu(OTf)_2$, $In(OTf)_3$, or $Zn(OTf)_2$ (Table 1, entries 6–10). To our delight, 60% yield of product **5a** was generated when $Cu(OTf)_2$ was used as co-catalyst in the above reaction (Table 1, entry 7). Solvent screening identified THF was the best choice (Table 1, entries 11–14). Finally, we found that the yield could be increased to 80% in the presence of molecular sieves (Table 1, entry 15). Decreasing the reaction temperature diminished the product yield with prolonged reaction time (data not shown in Table 1). Screening the ratio of catalysts revealed that the reaction occurred efficiently as well catalyzed by the combination of $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (1 mol %), and $Cu(OTf)_2$ (10 mol %) (Table 1, entry 16).

Having demonstrated the viability of this catalytic strategy we next investigated the scope of the transformation under the optimized conditions [$PdCl_2(PPh_3)_2$ (2 mol %), CuI (1 mol %), $Cu(OTf)_2$ (10 mol %), Et_3N, 4A molecular sieves, THF, 50–60 °C]. The results are summarized in Table 2. For all cases, this four-component tandem reaction proceeded smoothly, leading to the corresponding products **5** in moderate to good yields. For instance, reaction of 2-bromobenzaldehyde **1a** with phenyl acetylene **2a**, *p*-toluidine **3b**, and diethyl phosphite **4** under the standard conditions gave rise to the desired product **5b** in 63% yield (Table 2, entry 2). When 3,5-dimethylaniline **3c** was utilized as a replacement, the desired product **5c** could be afforded in 50% yield (Table 2, entry 3). Similar yield was obtained when aniline **3d** was utilized as a coupling partner (Table 2, entry 4, 50% yield). When aniline with electron-withdrawing group attached on the aromatic ring (such as 4-fluoroaniline **3e**) was employed in the reaction, the expected product **5e** was afforded in 60% yield (Table 2, entry 5). Other alkynes were used in the multi-component reactions of 2-bromobenzaldehyde **1a** as well. Moderate yields were observed when ethynylcyclopropane **2b** reacted with 2-bromobenzaldehyde **1a**, aniline **3a** or **3d** with diethyl phosphite **4** (Table 2, entries 6 and 7). Higher yields were displayed when 4-methoxyphenyl acetylene **2c** was utilized in the reaction of 2-bromobenzaldehyde **1a** (Table 2, entries 8–10). We also tested other substrates, such as 2-bromo-5-fluorobenzaldehyde **1b** and 6-bromopiperonal **1c** in this multicatalytic system. As expected, the four-component reactions worked well to give rise to the corresponding product **5** in reasonable yields (Table 2, entries 11–15).

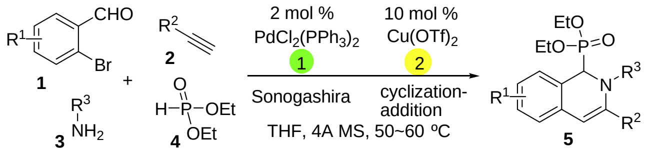
Table 1
Initial studies for the multicatalytic one-pot four-component reaction

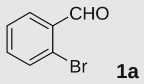
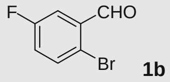
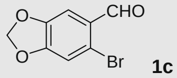


Entry	[Pd] (5 mol %)/CuI (5 mol %)	Lewis acid (10 mol %)	Solvent	Yield[a] (%)
1	$PdCl_2$/CuI	None	THF	Trace
2	$Pd(PhCN)_2Cl_2$/CuI	None	THF	Trace
3	$Pd(PPh_3)_2Cl_2$/CuI	None	THF	Trace
4	$Pd(OAc)_2$/CuI	None	THF	Trace
5	$Pd(dppf)Cl_2$/CuI	None	THF	Trace
6	$Pd(PPh_3)_2Cl_2$/CuI	AgOTf	THF	43
7	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	THF	60
8	$Pd(PPh_3)_2Cl_2$/CuI	$In(OTf)_3$	THF	20
9	$Pd(PPh_3)_2Cl_2$/CuI	$Zn(OTf)_2$	THF	21
10	$Pd(PPh_3)_2Cl_2$/CuI	$Sc(OTf)_3$	THF	28
11	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	DCE	33
12	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	Toluene	42
13	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	DMF	28
14	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	EtOH	45
15[b]	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	THF	80
16[c]	$Pd(PPh_3)_2Cl_2$/CuI	$Cu(OTf)_2$	THF	80

[a] Isolated yield based on 2-bromobenzaldehyde **1**.
[b] In the presence of molecular sieves.
[c] [Pd] (2 mol %), CuI (1 mol %), in the presence of molecular sieves.

Table 2
Multicatalytic one-pot four-component reaction of 2-bromobenzaldehyde **1**, alkyne **2**, amine **3**, and diethyl phosphite **4**[16]



Entry	Substrate **1**	R^2	R^3	Yield[a] (%)
1	 **1a**	C_6H_5 (**2a**)	$4\text{-}MeOC_6H_4$ (**3a**)	80 (**5a**)
2	**1a**	C_6H_5 (**2a**)	$4\text{-}MeC_6H_4$ (**3b**)	63 (**5b**)
3	**1a**	C_6H_5 (**2a**)	$3,5\text{-}Me_2C_6H_3$ (**3c**)	50 (**5c**)
4	**1a**	C_6H_5 (**2a**)	C_6H_5 (**3d**)	50 (**5d**)
5	**1a**	C_6H_5 (**2a**)	$4\text{-}FC_6H_4$ (**3e**)	60 (**5e**)
6	**1a**	Cyclopropyl (**2b**)	$4\text{-}MeOC_6H_4$ (**3a**)	42 (**5f**)
7	**1a**	Cyclopropyl (**2b**)	C_6H_5 (**3d**)	40 (**5g**)
8	**1a**	$4\text{-}MeOC_6H_4$ (**2c**)	$4\text{-}MeC_6H_4$ (**3b**)	62 (**5h**)
9	**1a**	$4\text{-}MeOC_6H_4$ (**2c**)	C_6H_5 (**3d**)	70 (**5i**)
10	**1a**	$4\text{-}MeOC_6H_4$ (**2c**)	$4\text{-}FC_6H_4$ (**3e**)	64 (**5j**)
11	 **1b**	C_6H_5 (**2a**)	$4\text{-}MeOC_6H_4$ (**3a**)	55 (**5k**)
12	**1b**	C_6H_5 (**2a**)	$4\text{-}MeC_6H_4$ (**3b**)	44 (**5l**)
13	**1b**	Cyclopropyl (**2b**)	$4\text{-}MeOC_6H_4$ (**3a**)	42 (**5m**)
14	 **1c**	C_6H_5 (**2a**)	$4\text{-}MeOC_6H_4$ (**3a**)	52 (**5n**)
15	**1c**	C_6H_5 (**2a**)	$4\text{-}MeC_6H_4$ (**3b**)	50 (**5o**)

[a] Isolated yield based on 2-bromobenzaldehyde **1**.

In conclusion, we have described an efficient route for generation of 1,2-dihydroisoquinolin-1-ylphosphonate via a tandem four-component reaction of 2-bromobenzaldehyde, alkyne, amine, and diethyl phosphite under multicatalytic conditions. We believe that the operational simplicity of the present process combined with the efficiency of this method will make it potentially attractive for further library construction.

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16. *General procedure for the multicatalytic one-pot four-component reaction of 2-bromobenzaldehyde* **1**, *alkyne* **2**, *amine* **3**, *and diethyl phosphite* **4**: A mixture of 2-bromobenzaldehyde **1** (0.5 mmol), alkyne **2** (1.0 mmol, 2.0 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (1 mol %), and Et_3N (1.5 mmol, 3.0 equiv) in THF was stirred at 50 °C. After consumption of 2-bromobenzaldehyde **1** as indicated by TLC, amine **3** (0.5 mmol, 1.0 equiv), diethyl phosphite **4** (0.6 mmol, 1.2 equiv), $Cu(OTf)_2$ (10 mol %), and 4A molecular sieves (100 mg) were added. After completion of the reaction, the 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 **5**. Selected example: diethyl 2-(4-methoxyphenyl)-3-phenyl-1,2-dihydroiso-quinolin-1-ylphosphonate (**5a**), 80% yield. yellow liquid. ^1H 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; HRMS calcd for $C_{26}H_{28}NO_4P$: 449.1756, found: 449.1752.