A one-pot method for the synthesis of phenylalkynyl-substituted terminal alkynes by deprotection/stannylation followed by a Migita–Kosugi–Stille coupling

Li-fen Peng[a], Bing-hao Wang[a], Ming Wang[a], Zi-long Tang[a]*, Yan-zi Jiang[a], Yin-chun Jiao[a] and Xin-hua Xu[b]

[a]*Key Laboratory of Theoretical Organic Chemistry and Functional Molecule of Ministry of Education, Hunan Provincial Key Laboratory of Controllable Preparation and Functional Application of Fine Polymers, School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, P.R. China*

[b]*State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P.R. China*

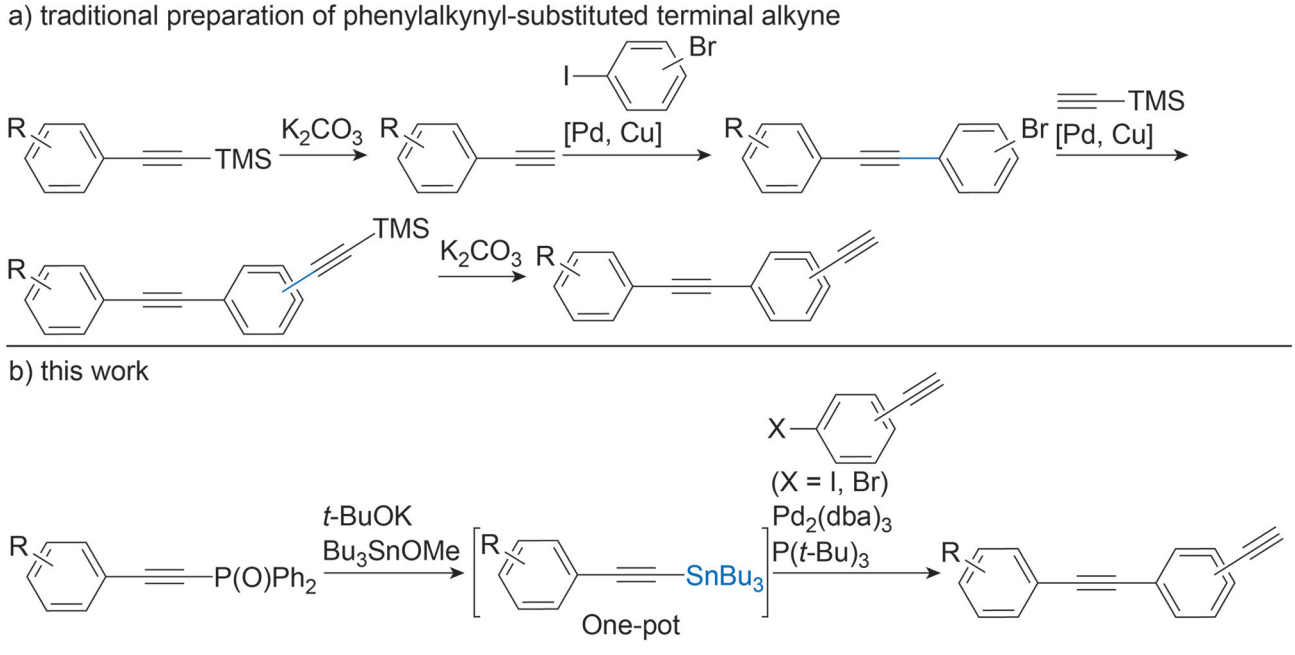
A practical one-pot approach for the synthesis of arylalkynyl-substituted terminal alkynes has been developed through a deprotection/stannylation of a phenylethynyl phosphine oxide followed by Migita–Kosugi–Stille coupling, avoiding the longer synthetic route involving repeated deprotection/Sonogashira coupling. Other features of this approach include mild reaction conditions, excellent yields, facile isolation of products and wide functional group tolerance.

Keywords: one-pot synthesis, alkynes, deprotection, Migita–Kosugi–Stille coupling, terminal alkynes

Alkynes are versatile building blocks for the synthesis of natural product analogues and hybrid structures.[1] For example, the hydrophobic, rigid and linear attributes of acetylenes produce derivatives with interesting physical properties and biological activity such as antibacterial,[2] antifungal,[3] pesticidal[4] and antitumour[5] activity. Aromatic acetylenes have structures with unique electronic properties due to their rigid skeleta and rich π electron density. The conjugated system of an aryl-ethynyl moiety produces important organic materials, such as organic field-effect transistors,[6] organic light-emitting diodes[7] and dye-sensitised solar cells.[8]

Phenylalkynyl-substituted terminal alkynes are important intermediates to prepare these conjugated aryl-ethynyl organic materials. The conventional synthesis of these phenylalkynyl-substituted terminal alkynes involves the Sonogashira coupling of aryl halides with alkynes protected with a trialkylsilyl group such as trimethylsilyl (TMS) and *t*-butyldimethylsilyl.[9] This traditional synthesis, though powerful, frequently suffers from some severe drawbacks, such as difficult isolation of the product with a similar R_f value to that of the starting material and by-products, low total yields and longer synthetic steps involving repeated deprotection/Sonogashira coupling (Scheme 1a).[10] Thus, the development of a practical procedure for the preparation of phenylalkynyl-substituted terminal alkynes with higher total yields, short synthetic steps and easy purification is required. Recently, we developed a new protecting group, $Ph_2P(O)$, which enabled the easy isolation of the Sonogashira coupling product because of its high polarity. We exemplified the usefulness of this protecting group in the synthesis of phenylalkynes.[11]

To overcome the drawbacks of the traditional synthesis of phenylalkynyl-substituted terminal alkynes, we have expanded the use of the $Ph_2P(O)$ protecting group to a one-pot synthesis of phenylalkynyl-substituted terminal alkynes through a deprotection/stannylation sequence followed by a Migita–Kosugi–Stille coupling (Scheme 1b).



Scheme 1 General methods for synthesis of phenylalkynyl-substituted terminal alkynes.

* Correspondent. E-mail: 1060137@hnust.edu.cn

Results and discussion

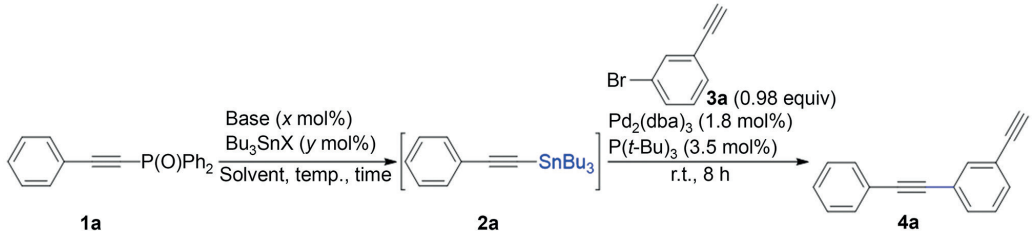
We began our studies with the deprotection/stannylation of diphenyl(phenylethynyl)phosphine oxide **1a** in the presence of MeOK and Bu_3SnCl followed by Migita–Kosugi–Stille coupling with 1-bromo-3-ethynylbenzene **3a** in the presence of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$. In our experiments, MeOK (20 mol%) and Bu_3SnCl (100 mol%) were added to a solution of **1a** (1.0 mmol) in acetone (5.0 mL) at room temperature, under nitrogen, and stirred for 6 h. Then 1-bromo-3-ethynylbenzene **3a** (0.98 equiv.), $Pd_2(dba)_3$ (1.8 mol%) and P(*t*-Bu)$_3$ (3.5 mol%) were added to the reaction mixture and stirred at room temperature for another 4 h. The desired product **4a** was obtained in 8% yield (Table 1, entry 1). The yield was improved to 33% by increasing the temperature to 50 °C (Table 1, entry 2). The yield was not improved significantly by increasing the amount of Bu_3SnCl and MeOK (Table 1, entries 3 and 4). The yield was improved to 58% when 50 mol% *t*-BuOK was used instead of MeOK (Table 1, entry 6). When Bu_3SnOMe was used as the stannylation reagent instead of Bu_3SnCl, product **4a** was obtained in 66% yield (Table 1, entry 8). Then we explored the effect of solvents, such as acetone, THF and toluene, on the reaction (Table 1, entries 8–10). We found that THF was the most suitable solvent for the deprotection/stannylation of **1a**. We also examined the temperature required to promote the reaction (Table 1, entries 10–13). The results showed that refluxing significantly improved the reaction and by extending the reaction time to 4.5 h, the product was obtained in 88% yield (Table 1, entry 13). Thus, after carefully analysing the reaction conditions, the optimum conditions are 1.0 mmol of **1a**, 50 mol% of *t*-BuOK and 100 mol% of Bu_3SnOMe in THF at reflux under nitrogen for 4.5 h, followed by addition of **3a** (0.98 equiv.), $Pd_2(dba)_3$ (1.8 mol%) and P(*t*-Bu)$_3$ (3.5 mol%) to the reaction mixture at room temperature under nitrogen with stirring for 8 h.

In the above reaction, only the stannylethyne **2a** reacted with the phenyl bromide portion of **3a**, and the terminal ethyne moiety of **3a** remained untouched.[10] The polarity of $Ph_2P(O)$ facilitated the isolation of the product **4a** from the remaining starting material **1a** by column chromatography on silica gel: R_f = 0.38 for **4a** and R_f = 0 for **1a** in hexane.

To demonstrate the efficiency of this reaction, we explored the generality of our method with various substrates, and the results are summarised in Table 2. This showed that the reaction worked well with various substrates **1** and **3**. The presence of both electron-withdrawing (*e.g.* Cl, F, CN, NO_2, Table 2, entries 4–7, 75–87%) and electron-donating (*e.g.* Me, MeO, Table 2, entries 8 and 9, 79–83%) functional groups in the phenyl ring of the phenyl phosphine oxide **1** gave the desired products in good yields. Both alkynyl-substituted phenyl bromides (Table 2, entries 2, 3, 6, 7 and 9, 78–85%) and iodides (Table 2, entries 1, 4, 5 and 8, 83–91%) gave the corresponding products in good to excellent yields. The presence of the alkynyl group at the *m*, *p* or *o* positions of the alkynyl-substituted phenylhalides **3** gave the desired products in excellent yields (Table 2, entries 1–3, 82–91%). However, the Migita–Kosugi–Stille coupling of alkynyl-substituted phenyl chloride did not give the desired product because of the low reactivity of the chloride (Table 2, entry 10, 0%).

In conclusion, we have developed a practical method for the synthesis of phenylalkynyl-substituted terminal alkynes from ethynylphosphine oxide and alkynyl-substituted phenylhalides through deprotection/stannylation followed by Migita–Kosugi–Stille coupling. A broad range of ethynylphosphine oxide and alkynyl-substituted phenylhalides were tolerated by this method, and all the phenylalkynyl-substituted terminal alkynes were obtained in good to excellent yields. Because of the mild reaction conditions, the short synthetic route, the easy isolation of the products and the excellent yields, this work provides a convenient way to prepare these important phenylalkynyl-substituted terminal alkynes.

Table 1 Optimisation of the reaction conditions[a]



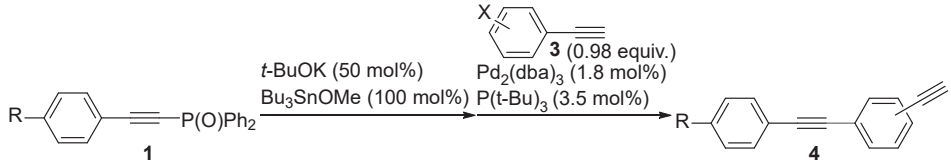
1a **2a** **4a**

Entry	Base (*x*, mol%)	Bu_3SnX (*y*, mol%)	Solvent	Temperature (°C)	Time (h)	Yield of **4a** (%)[b]
1	MeOK (20)	Bu_3SnCl (100)	Acetone	r.t.	6	8
2	MeOK (20)	Bu_3SnCl (100)	Acetone	50	6	33
3	MeOK (20)	Bu_3SnCl (150)	Acetone	50	6	35
4	MeOK (50)	Bu_3SnCl (150)	Acetone	50	6	34
5	*t*-BuOK (20)	Bu_3SnCl (100)	Acetone	50	6	45
6	*t*-BuOK (50)	Bu_3SnCl (100)	Acetone	50	6	58
7	*t*-BuOK (80)	Bu_3SnCl (100)	Acetone	50	6	57
8	*t*-BuOK (50)	Bu_3SnOMe (100)	Acetone	50	6	66
9	*t*-BuOK (50)	Bu_3SnOMe (100)	THF	50	6	69
10	*t*-BuOK (50)	Bu_3SnOMe (100)	Toluene	50	6	42
11	*t*-BuOK (50)	Bu_3SnOMe (100)	THF	50	6	73
12	*t*-BuOK (50)	Bu_3SnOMe (100)	THF	Reflux	6	87
13	*t*-BuOK (50)	Bu_3SnOMe (100)	THF	Reflux	4.5	88

[a]Reaction conditions: diphenyl(phenylethynyl)phosphine oxide **1a** (1 mmol), solvent (5.0 mL).

[b]Isolated yields.

Table 2 Deprotection/stannylation and Migita–Kosugi–Stille coupling of various ethynylphosphine oxide **1** with alkynyl-substituted phenylhalides **3**



Entry	**1** (R)	**3** (X)	**4** (R; C≡CH)	Yield (%)[a]
1	**1a** (H)	**3b** (*m*-I)	**4a** (H; *m*-C≡CH)	91
2	**1a** (H)	**3c** (*p*-Br)	**4b** (H; *p*-C≡CH)	82
3	**1a** (H)	**3d** (*o*-Br)	**4c** (H; *o*-C≡CH)	85
4	**1b** (Cl)	**3e** (*o*-I)	**4d** (Cl; *o*-C≡CH)	87
5	**1c** (F)	**3e** (*o*-I)	**4e** (F; *o*-C≡CH)	85
6	**1d** (CN)	**3d** (*o*-Br)	**4f** (CN; *o*-C≡CH)	78
7	**1e** (NO_2)	**3d** (*o*-Br)	**4g** (NO_2; *o*-C≡CH)	75
8	**1f** (Me)	**3e** (*o*-I)	**4h** (Me; *o*-C≡CH)	83
9	**1g** (OMe)	**3d** (*o*-Br)	**4i** (OMe; *o*-C≡CH)	79
10	**1g** (OMe)	**3d** (*o*-Cl)	**4i** (OMe; *o*-C≡CH)	0

[a]Isolated yields.

Experimental

Dry solvents, reagents and catalysts were purchased as analytical grade and used without further purification. Ethynylphosphine oxide **1** and alkynyl-substituted phenylhalides **3** were synthesised according to literature procedures.[12] Analytical TLCs were performed with silica gel 60 F254 plates. Column chromatography was carried out using silica gel 60 (200–300 mesh). Melting points were measured on a SGW X-4 (INESA) melting point apparatus and are uncorrected. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Tetramethylsilane (TMS) was used as internal reference for ^{1}H and ^{13}C chemical shifts and $CDCl_3$ was used as solvent.

Synthesis of arylalkynyl-substituted terminal alkynes **4a**–**i***; general procedure*

A THF solution (5.0 mL) of **1** (1.0 mmol) was treated with Bu_3SnOMe (1.0 mmol) and *t*-BuOK (0.5 mmol). The mixture was stirred for 4.5 h under nitrogen at reflux. The reaction mixture was then treated with **3** (207.1 mg, 0.98 mmol), P(*t*-Bu)$_3$ (0.035 mmol) and $Pd_2(dba)_3$ (0.018 mmol) at room temperature, and the mixture was stirred under nitrogen at room temperature for 8 h. After workup with diethyl ether (3 × 10.0 mL)/NH_4F_{aq} (10%, 10.0 mL), the organic layer was dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel to afford **4a**–**i**. **4a**,[13] **4b**,[10] **4c**,[14] **4d**,[14] **4e**,[14] **4f**,[14] **4g**,[15] **4h**[14] and **4i**[14] are known compounds and were identified by their previously reported spectroscopic data.

4a: Colourless oil (lit.[13] colourless oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (s, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.35–7.36 (m, 3H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.50–7.54 (m, 3H), 7.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.82, 82.73, 88.27, 90.04, 122.39, 122.84, 123.58, 128.36, 128.41, 128.48, 131.61, 131.75, 131.81, 135.05.

4b: White powder; m.p. 90–91 °C (lit.[16] 91.6–92.1 °C,); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (s, 1H), 7.35–7.37 (m, 3H), 7.46–7.51 (m, 4H), 7.53–7.54 (m,2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.86, 83.24, 88.79, 91.33, 121.79, 122.85, 123.71, 128.38, 128.52, 131.44, 131.60, 132.04.

4c: Yellow oil (lit.[14] light yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (s, 1H), 7.29 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.36 (m, 3H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 81.10, 82.18, 87.84, 93.54, 123.15, 124.63, 126.32, 127.89, 128.32, 128.48, 128.52, 131.76, 132.57.

4d: Pale yellow powder (lit.[14] clear solid); m.p. 113–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.36 (s, 1H), 7.31 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 3H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 81.18, 82.09, 88.77, 92.32, 121.64, 124.65, 125.94, 128.12, 128.56, 128.68, 131.74, 132.62, 132.94, 134.53.

4e: Pale yellow powder (lit.[14] light yellow solid); m.p. 102–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 1H), 7.18 (tt, *J* = 8.9, 2.3 Hz, 2H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.45 (td, *J* = 7.5, 1.5 Hz, 1H), 7.59 (dd, **J** = 7.8, 1.2 Hz, 2H), 7.62 (dd, *J* = 8.9, 5.4 Hz, 2H); ^{13}C NMR (125 MHz, CD_3CN): δ 83.06, 83.53, 88.72, 93.44, 117.36 (d, *J* = 22.0 Hz), 120.45 (d, *J* = 3.2 Hz), 125.73, 127.01, 129.97, 130.43, 133.14, 133.99, 135.12 (d, *J* = 8.8 Hz), 164.18 (d, *J* = 247.5 Hz).

4f: Yellow oil (lit.[14] light yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39 (s, 1H), 7.33 (m, 2H), 7.55 (m, 2H), 7.62 (d, *J* = 1.8 Hz, 2H), 7.64 (d, *J* = 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 81.53, 81.80, 91.54, 92.03, 111.57, 118.45, 124.86, 125.09, 127.95, 128.62, 128.75, 131.88, 131.96, 132.12, 132.67.

4g: Pale yellow powder (lit.[15] yellow solid); m.p. 98–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41 (s, 1 H), 7.32–7.42 (m, 2 H), 7.55–7.61 (m, 2 H), 7.67–7.73 (m, 2 H), 8.21–8.27 (m, 2 H).

4h: Yellow oil (lit.[14] light yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.39 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.54 (dd, *J* = 7.7, 2.2 Hz, 2H).

4i: Red solid; m.p. 110–111 °C (lit.[17] 112–114 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (s, 1H), 3.83 (s, 3H), 6.89 (dd, *J* = 8.9, 4.6 Hz, 2H), 7.27 (td, *J* = 7.6, 1.4 Hz, 1H), 7.33 (td, *J* = 7.6, 1.5 Hz, 1H), 7.53 (m, 4H).

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