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ORIGINAL PAPER

Palladium-catalyzed carbonylative Sonogashira cross-coupling for the synthesis of alkynones with formic acid as the CO source

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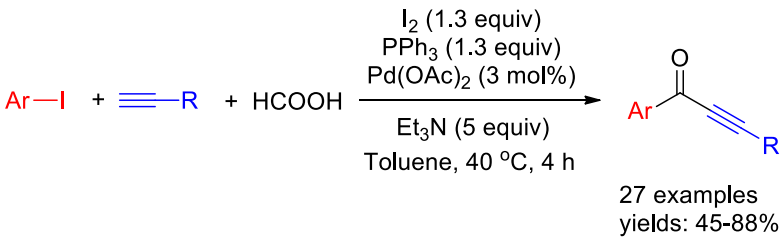
Abstract

A practical and efficient palladium-catalyzed carbonylative Sonogashira cross-coupling reaction for the synthesis of alkynones from aryl iodides, alkynes, and formic acid as the CO source has been described. Under the assistance of PPh_3/I_2, formic acid can be used as the CO source for synthesis of alkynones in moderate–good yields. Furthermore, it is also successfully applied for the modification of natural products, such as vindoline and tabersonin, to obtain the corresponding products.

Graphical abstract



Keywords Sonogashira cross-coupling · Aryl iodide · Alkyne · Palladium · Alkynones

Introduction

Alkynones are not only indispensable building blocks for constructing biologically active molecules [1, 2], natural products (e.g., anthrapyran metabolites, azaspiracid, and calystegine B_2) [3–5], agrochemicals and pharmaceutical materials [6], but also serve as versatile synthetic intermediates in the preparations of heterocycles such as pyrimidines [2, 7], quinolones [8], furans [9], pyrazoles [10, 11], pyrroles [12, 13], flavones [14], and benzodiazepines [15]. Hence, the synthesis of alkynones has gained considerable attention because of their wide application.

The classical preparative approach of alkynones relies on cross-coupling reactions of carboxylic acid chlorides with terminal alkynes or alkynyl organometallic reagents in the presence of transition metal catalysts [16–20]. However, the stability and functional group tolerance of the acid chlorides have hindered extended applications of this methodology. Since Kobayashi first reported palladium-catalyzed Sonogashira-type carbonylation in 1981 [21], many enhancements

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and various modifications of this transformation have been established [21–34], which can directly convert aryl halides and terminal alkynes into alkynones in the presence of CO atmosphere. However, these procedures suffer from the limitations with regard to high pressure and toxicity of CO.

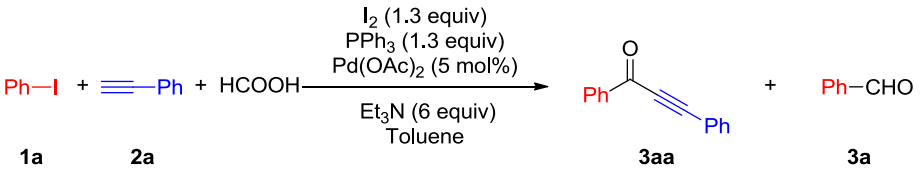
Consequently, great attention has been paid to develop CO surrogates. In our previous work, we applied $CHCl_3$ as CO precursor in the presence of $CsOH{\cdot}H_2O$ to produce alkynones in good yields [35]. Additionally, other CO surrogates, such as methyldiphenylsilane-carboxylic acid [36, 37], phenyl formate [38], 9-methyl-9*H*-fluorene-9-carbonyl chloride [39, 40], formamides [41–44], and formic acid [45–59], have been explored in this transformation as well. However, they also have some drawbacks such as high costs, low yields and harsh reaction conditions. Therefore, it is necessary to search for an efficient, mild and non-toxic agent as the CO surrogate. Herein, we developed a palladium–catalyzed carbonylative Sonogashira cross–coupling reaction of aryl iodide, alkynes, and formic acid as the CO source under the assistance of PPh_3/I_2. The results revealed that formic acid could release CO quickly and efficiently in the presence of PPh_3/I_2 under mild conditions.

Results and discussion

Initially, we carried out the reaction of iodobenzene (**1a**), phenyl acetylene (**2a**), formic acid, PPh_3/I_2, $Pd(OAc)_2$ as catalyst, and Et_3N as base in toluene. The mixture was stirred at 60 °C for 8 h, and the desired product **3aa** was formed in 68% yield determined by LC–MS. Encouraged by this result, we carried out a series of optimization experiments with model reaction and the results are summarized in Table 1.

First, we carried out the model reaction at different temperatures, finding that temperature had a significant impact on the yields of **3aa**. As shown in Table 1, **3aa** was obtained without significant difference of the yields (65–68%) when the temperature ranged from 40 to 60 °C (Table 1, entries 3–5). Further increasing the temperature lowers the yields (Table 1, entries 1–2). The main reason for this phenomenon was that the main byproduct benzaldehyde **3a** was formed. The results also revealed that **3a** could not be formed if the reaction temperature was not higher than 40 °C. The desired product **3aa** could be obtained in good yields at 40 °C (Table 1, entry 9). Therefore, 40 °C was chosen as the optimal reaction temperature for all further reactions. Furthermore, screening of reaction time showed that 4 h was superior to the others at which **3aa** could be obtained in 80% yield (Table 1, entries 7–11).

Table 1 Optimization of the reaction conditions



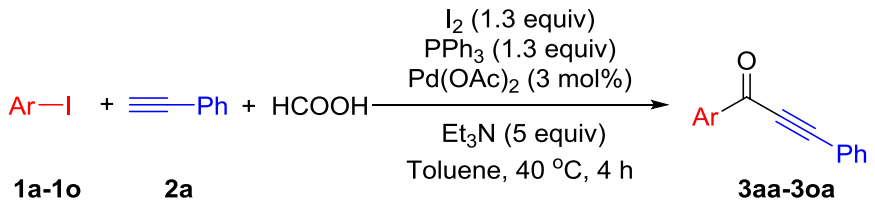
1a **2a** **3aa** **3a**

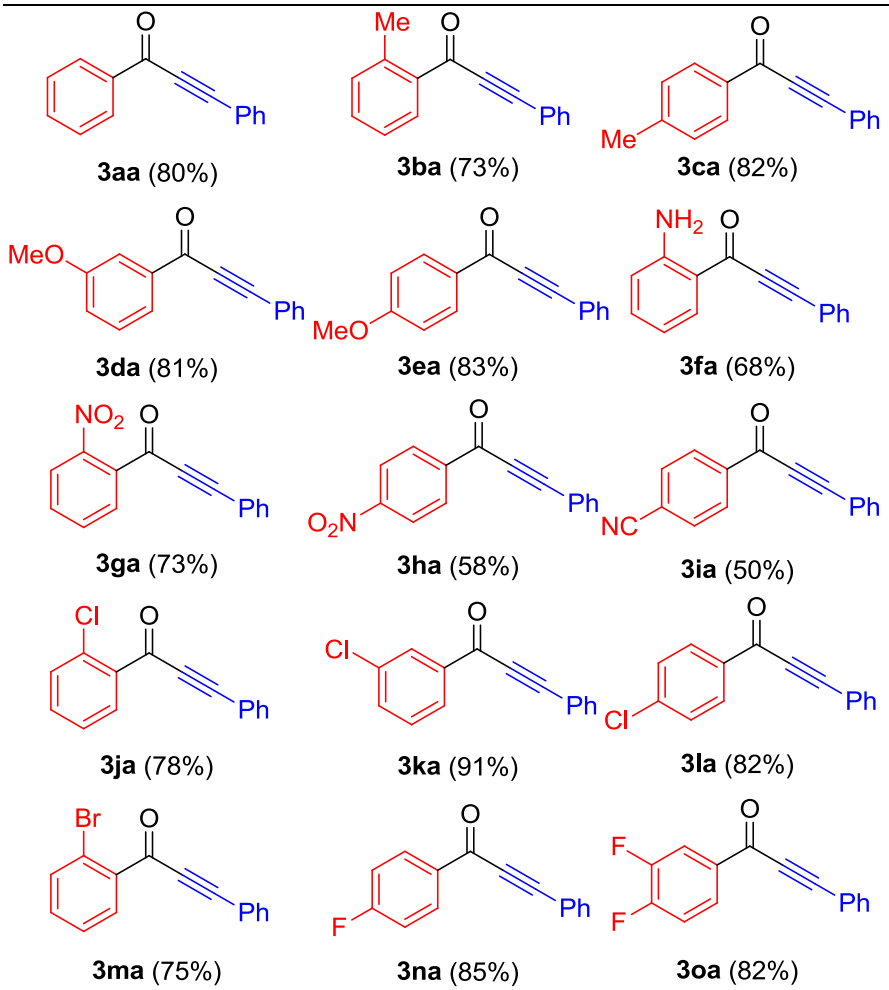
Entry	*T*/ °C	Time/h	Yield/%[a]	
			3aa	**3a**
1	80	8	5	55
2	70	8	48	37
3	60	8	68	7
4	50	8	67	3
5	40	8	65	0
6	30	8	33	0
7	40	6	70	0
8	40	5	72	0
9	40	4	80	0
10	40	3	73	0
11	40	2	61	0

Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol, 1.5 equiv), HCOOH (2 mmol, 2 equiv), I_2 (1.3 mmol, 1.3 equiv), PPh_3 (1.3 mmol, 1.3 equiv), $Pd(OAc)_2$ (5 mol%), Et_3N (6 mmol, 6 equiv), 4 cm^3 toluene

[a]Yields were determined by LC–MS

Table 2 Substrate scope of aryl iodides



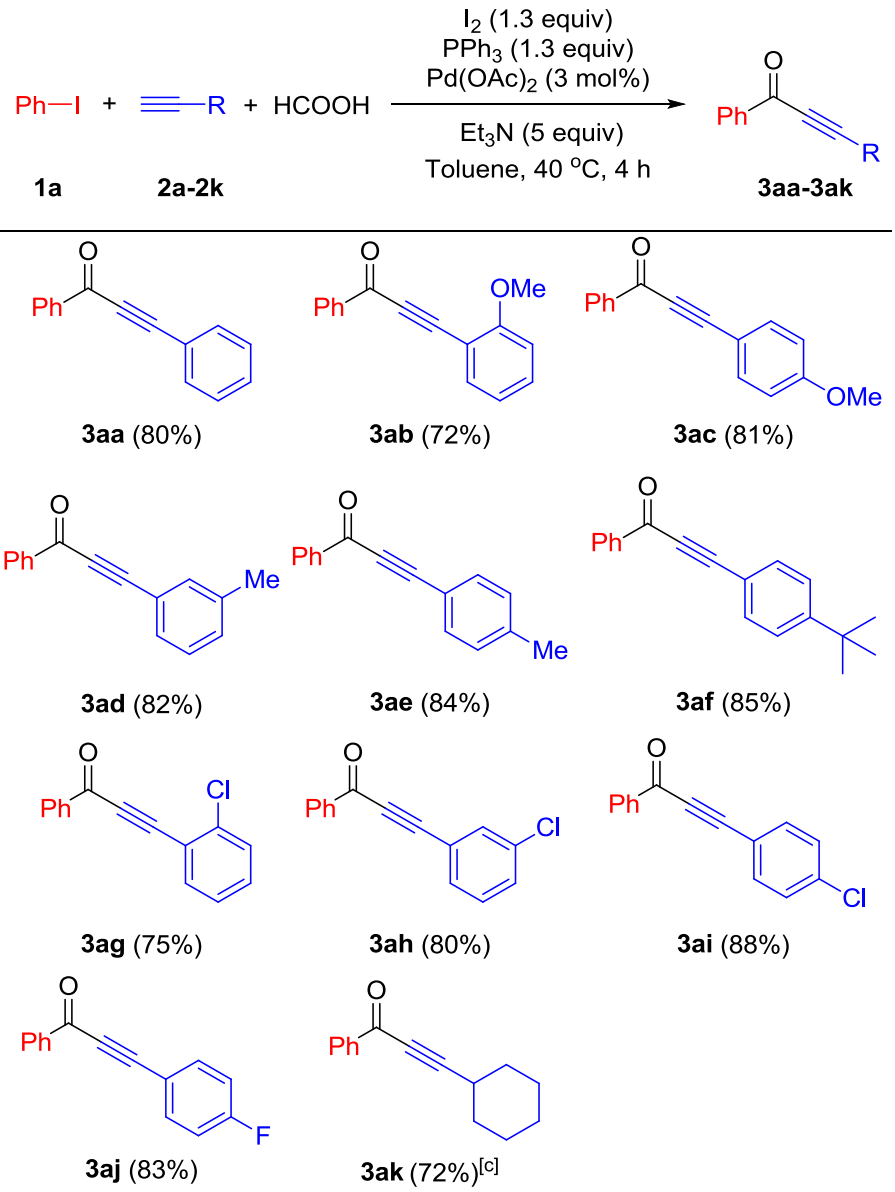


Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol, 1.5 equiv), HCOOH (2 mmol, 2 equiv), I_2 (1.3 mmol, 1.3 equiv), PPh_3 (1.3 mmol, 1.3 equiv), $Pd(OAc)_2$ (3 mol%), Et_3N (5 mmol, 5 equiv), 4 cm^3 toluene, 40 °C, 4 h; isolated yields

In addition, the other factors, such as amount of HCOOH, base, solvents, Pd cat, amount of I_2 and PPh_3, were also screened, and the results are provided in the Supplementary Material. After extensive experimentation, the optimal condition was established as HCOOH (2 equiv), $Pd(OAc)_2$ (3 mol%), I_2 (1.3 equiv), PPh_3 (1.3 equiv), Et_3N (5 equiv) in toluene at 40 °C for 4 h. Furthermore, we also tried different leaving groups in place of I-, such as Br-, Cl-, TsO-, and TfO-. However, the desired **3aa** was not observed in these cases (See the Supplementary Material, Table S8).

Under the optimized reaction conditions, the substrate scope of various aryl iodides and terminal alkynes were explored. As shown in Table 2, a series of aryl iodides was applied for this palladium-catalyzed carbonylative Sonogashira cross-coupling reaction. First, to examine the steric hindrance, *ortho*, *meta*, and *para* substituted substrates were selected for this cross-coupling reaction. The results showed that all the substrates reacted smoothly to obtain the desired products in moderated to good yields (50–85%). The yields ranged from 68 to 78% when the substrates contained *ortho* groups (Me^-, NH_2^-, NO_2^-, Cl^-, and Br^-). These results

Table 3 Substrate scope of alkynes



Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol, 1.5 equiv), HCOOH (2 mmol, 2 equiv), I_2 (1.3 mmol, 1.3 equiv), PPh_3 (1.3 mmol, 1.3 equiv), $Pd(OAc)_2$ (3 mol%), Et_3N (5 mmol, 5 equiv), 4 cm^3 toluene, 40 °C, 4 h; isolated yields

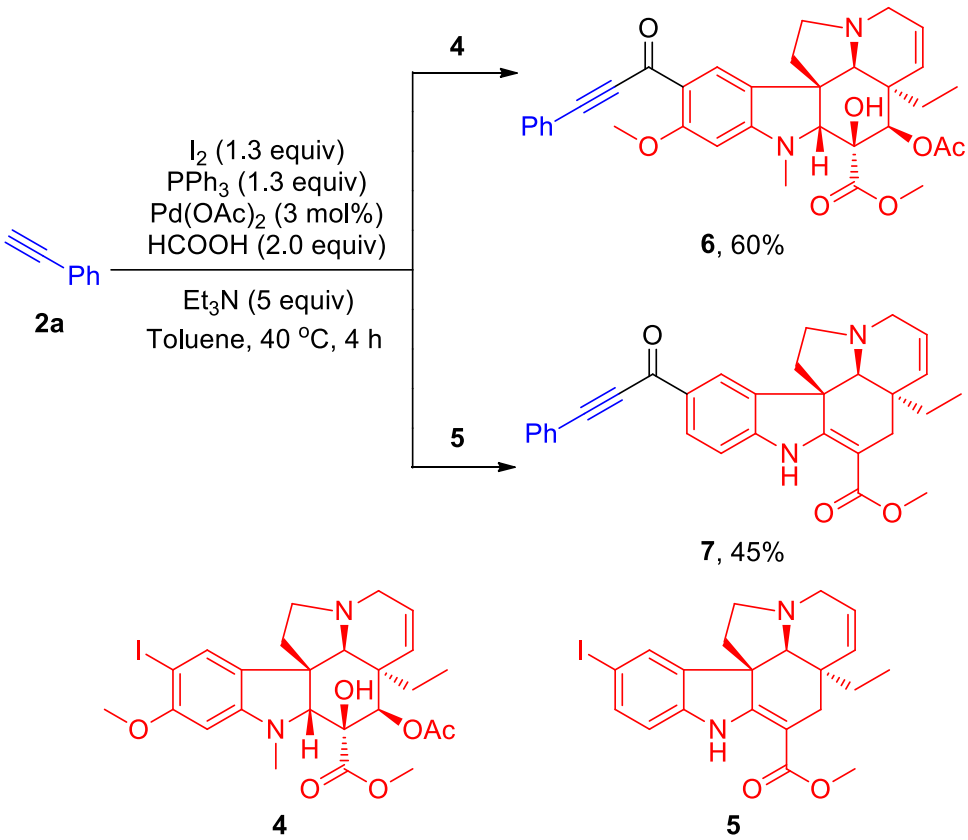
[a]This reaction proceeded for 8 h

clearly indicated that the steric hindrance of aryl iodides is without significant effect on this carbonylative Sonogashira coupling reaction. Moreover, the reaction also showed that aryl iodides including electron-donating or electron-withdrawing group could proceed smoothly to form the desired products. It should be noted that *para*-nitro and *para*-cyano iodobenzenes gave relatively lower yields than other substrates (Table 2, **3ha** and **3ia**). The main reason for these results was that aryl iodides with strong electron-withdrawing group were prone to form deiodination products under these reaction conditions.

Then, we turned our attention to test the generality of the alkyne coupling partner with various substituted terminal alkynes. As shown in Table 3, all of the substrates selected could react smoothly with the yields 72–88%. Moreover, the aliphatic alkyne was successively transformed into the desired product in good yield (**3ak**, 72%).

To further investigate the application of the Sonogashira cross-coupling reaction, two alkaloid natural products (vindoline and tabersonin) were examined (Scheme 1). The iodo-vindoline (**4**) and iodo-tabersonin (**5**) were synthesized according to the reported methods [60, 61]. Then,

Scheme 1



the reaction of **4** or **5** with phenylacetylene was carried out under standard conditions for 4 h. The corresponding products 15-alkynone-vindoline **6** and 10-alkynone-tabersonin **7** were obtained in 60% and 45% yields, respectively.

Based on the experimental results and previous reports, a plausible reaction mechanism is proposed (Scheme 2) [62]. Initially, I_2 and PPh_3 formed complex **A**, which promoted the release of CO from formic acid. Pd^{II} was reduced by PPh_3 to form Pd^0 complex **B** [62]. Through a oxidative addition process of aryl iodide to Pd^0 to form Pd^{II} complex **C**. Then, CO was captured by **C** to form **D**. After CO insertion, the benzoylpalladium halide **D** converted into arylpalladium alkyne complex **E** and released HI simultaneously under the action of base. Final reductive elimination is furnished to regenerate product alkynone and Pd^0 complex **B** that launched another catalytic cycle.

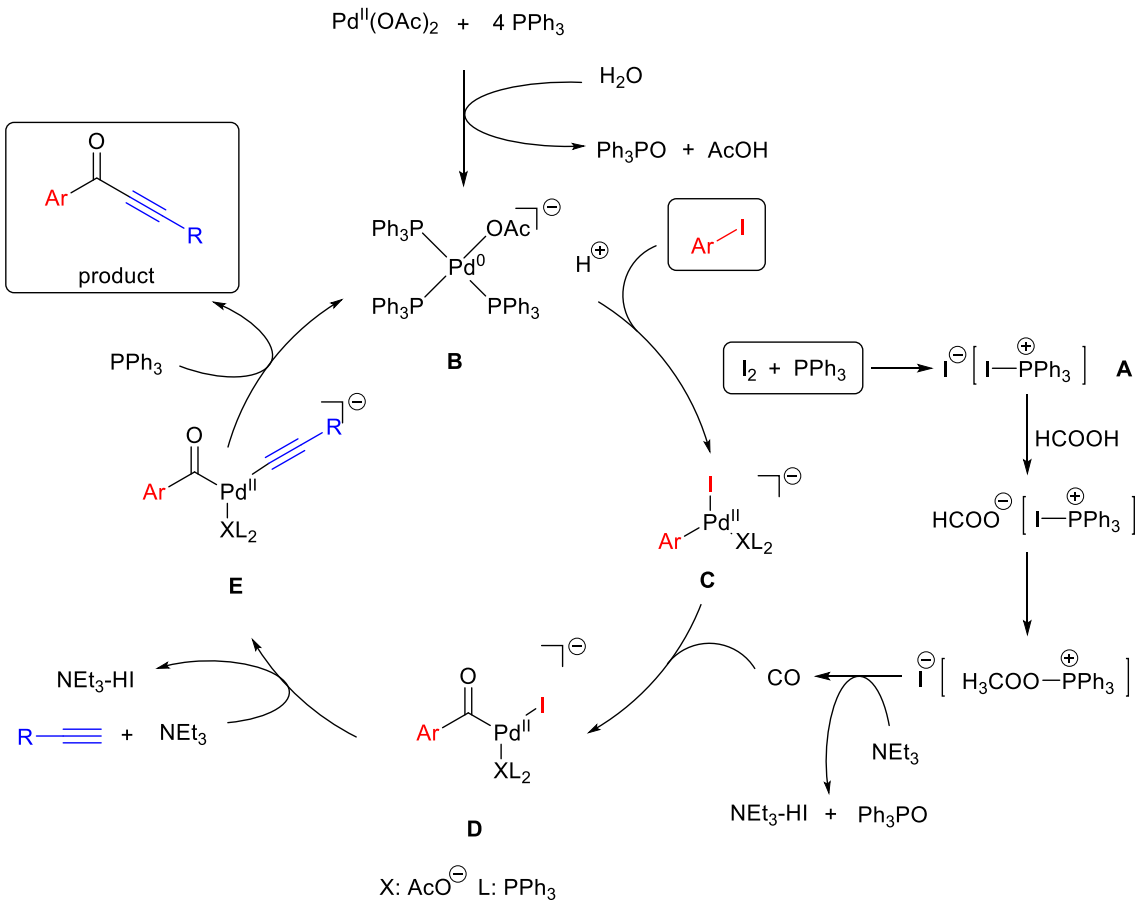
Conclusion

In conclusion, we have established a convenient and efficient palladium-catalyzed carbonylative Sonogashira cross-coupling reaction by employing formic acid as the CO source. The mild reaction conditions, short reaction times, good yields of the products, ease of work-up, and compatibility with various functional groups will make the present method a useful and important addition to the present methodologies for the synthesis of alkynones.

Experimental

Reactions were performed in flame-dried glassware using sealed tube. Liquids and solutions were transferred with syringes. All solvents and chemical reagents were obtained from commercial sources and used without further purifications. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal reference at 400 MHz and 101 MHz, respectively. Spectra were referenced to the residual solvent peak of $CDCl_3$ or DMSO-d_6 unless otherwise noted. High-resolution mass spectra (HRMS) were measured on a Micromass Q-Tof Global mass spectrometer and LCMS was run on Waters LCMS/SQD + UPLC H-class spectrometer. Flash column chromatography on silica gel (200–300 mesh) was used for the routine purification of reaction products. The column output was monitored by analytical thin-layer chromatography (TLC) on silica gel (100–200 mesh) precoated on glass plates (15 × 50 mm), and spots were visualized by ultraviolet light at 254 or 365 nm. Melting points were recorded on a WRS-1B melting point apparatus.

Scheme 2



Commercially available chemicals were obtained from Acros Organics, Strem Chemicals, Alfa Aesar, Adamas-beta, J&K, and TCI.

General procedure for the synthesis of compounds 3, 6, and 7

PPh_3 (1.3 mmol, 1.3 equiv), I_2 (1.3 mmol, 1.3 equiv) and 4 cm^3 toluene were added to a 20 cm^3 test tube equipped with a stir bar, which was stirred for 10 min at room temperature. Then, aryl iodide **1**, **4**, or **5** (1 mmol), alkyne **2** (1.5 mmol, 1.5 equiv), $Pd(OAc)_2$ (3 mol%), and Et_3N (5 mmol, 5 equiv) were added into the solution. At last, HCOOH (2 mmol, 2 equiv) was added, and the tube was immediately sealed and stirred at 40 °C for 4 h. After completion of the reaction, mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel to provide the corresponding products **3**, **6**, or **7**.

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References

1. Savarin CG, Murry JA, Dormer PG (2002) Org Lett 4:2071
2. Karpov AS, Müller TJJ (2003) Org Lett 5:3451
3. Forsyth CJ, Xu J, Nguyen ST, Samdal IA, Briggs LR, Rundberget T, Sandvik M, Miles CO (2006) J Am Chem Soc 128:15114
4. Marco-Contelles J, de Opazo E (2002) J Org Chem 67:3705
5. Tietze LF, Singidi RR, Gericke KM, Böckemeier H, Laatsch H (2007) Eur J Org Chem 35:5875
6. Chang KT, Choi SH, Kim SH, Yoon YJ, Lee WS (2002) J Chem Soc Perkin Trans 1:207
7. D'Souza DM, Müller TJJ (2008) Nat Protoc 3:1660
8. Abbiati G, Arcadi A, Marinelli F, Rossi E, Verdecchia M (2009) Eur J Org Chem 7:1027
9. Kel'in AV, Gevorgyan V (2002) J Org Chem 67:95
10. Grotjahn DB, Van S, Combs D, Lev DA, Schneider C, Rideout M, Meyer C, Hernandez G, Mejorado L (2002) J Org Chem 67:9200
11. Liu H-L, Jiang H-F, Zhang M, Yao W-J, Zhu Q-H, Tang Z (2008) Tetrahedron Lett 49:3805
12. Shen J-H, Cheng G-L, Cui X-L (2013) Chem Commun 49:10641

13. Kel'in AV, Sromek AW, Gevorgyan V (2001) J Am Chem Soc 123:2074
14. Sakamoto K, Honda E, Ono N, Uno H (2000) Tetrahedron Lett 41:1819
15. Willy B, Dallos T, Rominger F, Schönhaber J, Müller TJJ (2008) Eur J Org Chem 28:4796
16. Kalinin VN, Shostakovsky MV, Ponamaryov AB (1990) Tetrahedron Lett 31:4073
17. Delpech B, Calvo D, Lett R (1996) Tetrahedron Lett 37:1019
18. Dodero VI, Koll LC, Faraoni MB, Mitchell TN, Podestá JC (2003) J Org Chem 68:10087
19. Vong BG, Kim SH, Abraham S, Theodorakis EA (2004) Angew Chem Int Ed 43:3947
20. Trost BM, Ball ZT (2004) J Am Chem Soc 126:13942
21. Kobayashi T, Tanaka M (1981) J Chem Soc, Chem Commun 7:333
22. Ahmed MSM, Mori A (2003) Org Lett 5:3057
23. Liang B, Huang M, You Z, Xiong Z, Lu K, Fathi R, Chen J, Yang Z (2005) J Org Chem 70:6097
24. Sans V, Trzeciak AM, Luis S, Ziólkowski JJ (2006) Catal Lett 109:37
25. Liu J, Peng X, Sun W, Zhao Y, Xia C (2008) Org Lett 10:3933
26. Fusano A, Fukuyama T, Nishitani S, Inouye T, Ryu I (2010) Org Lett 12:2410
27. Wu X-F, Neumann H, Beller M (2010) Chem Eur J 16:12104
28. Wu X-F, Sundararaju B, Neumann H, Dixneuf PH, Beller M (2011) Chem Eur J 17:106
29. Wu X-F, Sundararaju B, Anbarasan P, Neumann H, Dixneuf PH, Beller M (2011) Chem Eur J 17:8014
30. Wu X-F, Neumann H, Beller M (2011) Org Biomol Chem 9:8003
31. Wu X-F, Neumann H, Beller M (2011) Angew Chem Int Ed 50:11142
32. Kim W, Park K, Park A, Choe J, Lee S (2013) Org Lett 15:1654
33. Natte K, Chen J, Neumann H, Beller M, Wu X-F (2014) Org Biomol Chem 12:5590
34. Li W, Wu X-F (2015) Org Biomol Chem 13:5090
35. Sun G, Lei M, Hu L (2016) RSC Adv 6:28442
36. Hu SD, Taaning RH, Lindhardt AT, Skrydstrup T (2011) J Am Chem Soc 133:18114
37. Lescot C, Nielsen DU, Makarov IS, Lindhardt AT, Daasbjerg K, Skrydstrup T (2014) J Am Chem Soc 136:6142
38. Chavan SP, Bhanage BM (2015) Eur J Org Chem 11:2405
39. Hermange P, Lindhardt AT, Taaning RH, Bjerglund K, Lupp D, Skrydstrup T (2011) J Am Chem Soc 133:6061
40. Friis SD, Skrydstrup T, Buchwald SL (2014) Org Lett 16:4296
41. Hosoi K, Nozaki K, Hiyama T (2002) Org Lett 4:2849
42. Wan Y, Alterman M, Larhed M, Hallberg A (2002) J Org Chem 67:6232
43. Ko S, Lee C, Choi MG, Na Y, Chang S (2003) J Org Chem 68:1607
44. Chen J, Feng J-B, Natte K, Wu X-F (2015) Chem Eur J 21:16370
45. Cacchi S, Fabrizi G, Goggiamani A (2003) Org Lett 5:4269
46. Cacchi S, Fabrizi G, Goggiamani A (2004) J Comb Chem 6:692
47. Korsager S, Taaning RH, Skrydstrup T (2013) J Am Chem Soc 135:2891
48. Hou J, Xie J-H, Zhou Q-L (2015) Angew Chem Int Ed 54:6302
49. Qi X, Jiang L-B, Li C-L, Li R, Wu X-F (2015) Chem Asian J 10:1870
50. Qi X, Jiang L-B, Li H-P, Wu X-F (2015) Chem Eur J 21:17650
51. Qi X, Li C-L, Jiang L-B, Zhang W-Q, Wu X-F (2016) Catal Sci Technol 6:3099
52. Qi X, Li C-L, Wu X-F (2016) Chem Eur J 22:5835
53. Jiang L-B, Li R, Li H-P, Qi X, Wu X-F (2016) ChemCatChem 8:1788
54. Qi X, Li H-P, Wu X-F (2016) Chem Asian J 11:2453
55. Qi X, Li R, Wu X-F (2016) RSC Adv 6:62810
56. Jiang L-B, Qi X, Wu X-F (2016) Tetrahedron Lett 57:3368
57. Ren W, Chang W, Dai J, Shi Y, Li J, Shi Y (2016) J Am Chem Soc 138:14864
58. Seo Y-S, Kim D-S, Jun C-H (2016) Chem Asian J 11:3508
59. Peng J-B, Qi X, Wu X-F (2017) Synlett 28:175
60. Johnson PD, Sohn JH, Rawal VH (2006) J Org Chem 71:7899
61. Lewin G, Rolland Y, Poisson J (1980) Heterocycles 14:1915
62. Amatore C, Jutand A (2000) Acc Chem Res 33:314