Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Pd-Catalyzed Ligand-Free C(5)–H Arylation of 1,4-disubstituted 1,2,3-triazoles Promoted by Microwave

Fen Zhao, Wen-Hai Tian, Fang Luo, Hui-Ling Cheng, Yu-Bo Jiang & Zhen Chen

To cite this article: Fen Zhao, Wen-Hai Tian, Fang Luo, Hui-Ling Cheng, Yu-Bo Jiang & Zhen Chen (2016): Pd-Catalyzed Ligand-Free C(5)–H Arylation of 1,4-disubstituted 1,2,3-triazoles Promoted by Microwave, Synthetic Communications

To link to this article: http://dx.doi.org/10.1080/00397911.2016.1222441

Pd-catalyzed ligand-free C(5)–H arylation of 1,4-disubstituted 1,2,3-triazoles promoted by microwave

Fen Zhao[1], Wen-Hai Tian[2], Fang Luo[1], Hui-Ling Cheng[1], Yu-Bo Jiang[1], Zhen Chen[1]

[1]Faculty of Science, Kunming University of Science and Technology, Kunming, China,[2]Department of Architectural Engineering, Huaibei Vocational and Technical College, Huaibei, China

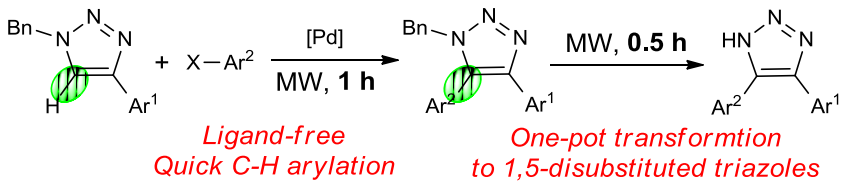
Address correspong Authors:
Yu-bo Jiang: Faculty of Science, Kunming University of Science and Technology, Kunming 650500, China. E-mail: ybjiang@kmust.edu.cn

Zhen Chen: Faculty of Science, Kunming University of Science and Technology, Kunming 650500, China. E-mail: chenzhen69@qq.com

Abstract

$Pd(OAc)_2$-catalyzed regioselective C(5)–H arylation of 1,4-disubstituted 1,2,3-triazoles was achieved without ligand under microwave conditions in 1 h, generating 1,4,5-trisubstituted 1,2,3-triazoles with good to excellent yields. The obtained molecules can be easily converted into 4,5-disubstituted 1,2,3-triazoles through the debenzylation process with one-pot manipulation.

Graphical Abstract



$Pd(OAc)_2$-catalyzed regioselective C–H arylation on the C-5 position of 1,4-disubstituted 1,2,3-triazoles was achieved without ligand under microwave conditions in 1 hour, generating 1,4,5-trisubstituted 1,2,3-triazoles with good to excellent yields. The obtained molecules can be converted into 4,5-disubstituted 1,2,3-triazoles facilely by debenzylation process in one pot.

KEYWORDS: Pd-catalyzed, ligand-free, C–H arylation, 1,2,3-triazoles, microwave

INTRODUCTION

With recent developments in the synthesis of various 1,2,3-triazole derivatives, these heterocycles have varied applications in many fields, including biological science as HIV protease inhibitors,[1,2] anticancer,[3,4] antituberculosis,[5–7] and antibacterial drugs,[8,9] as well as materials, such as energetic materials,[10,11] dyes,[12–14] ionic liquids,[15–17] liquid crystal,[18,19] and transition metal ligands.[20,21] The three types of 1,2,3-triazole derivatives mainly contain monosubstituted, disubstituted, and trisubstituted 1,2,3-triazoles. The monosubstituted and disubstituted 1,2,3-triazoles are prepared from azides and terminal alkynes catalyzed by Cu(I),[22–24] Ru(I),[25–27] and organic catalysts.[28,29] Three kinds of methodologies for the construction of trisubstituted 1,2,3-triazoles have been the focus of considerable attention in the past five years (Scheme 1). The first method employs the cycloaddition of organic azides with methylene ketones and internal alkynes and alkenes, using Cu, Fe, and organic catalysts (Scheme 1, a).[30–33] The second process employed to construct triazoles depends on

trapping the 5-Cu(I)-1,2,3-triazole intermediate in the CuAAC reaction by an exogenous electrophile (Scheme 1, b).[34–36] The third technique utilized to access this trisubstituted heterocycle involves the direct modification of 1,4-disubstituted 1,2,3-triazoles through Pd-catalyzed C–H functionalization, in which expensive phosphorous ligands are usually used (Scheme 1, c).[37,38] Some of aforementioned methods have high efficiency and good functional group compatibility. However, most of these methods have a long reaction time. In this study, we propose a microwave (10 W)-promoted efficient method to form 1,4,5-trisubstitued 1,2,3-triazoles from 1,4-disubstituted 1,2,3-triazoles, using $Pd(OAc)_2$ as the catalyst under ligand-free conditions for 1 h (Scheme 1, d).

RESULTS AND DISCUSSION

Our initial investigations focused on the model cross-coupling reaction of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **1a** with 1-iodo-4-methylbenzene **2a**, which was conducted under microwave conditions at 10 W for 1 h, generating the target molecule 1,4,5-trisubstituted 1,2,3-triazole **3a**. The C(5)–H bond of the triazole ring can be arylated, producing **3a** with 27% yield when the reaction was catalyzed by $Pd(PPh_3)_4$ (10%) under the influence of K_2CO_3 in solvent of H_2O (Table 1, entry 1). Further base screening indicated that Cs_2CO_3 favored the activation of the C(5)–H bond of 1,2,3-triazole, producing **3a** with 36% yield (Table 1, entry 2). When bases, such as ^{t}BuOK and Ag_2CO_3, were used, the product can be obtained, but with low yields (Table 1, entries 3 and 4). However, no target molecules of **3a** were detected when Na_2CO_3, K_3PO_4, or KH_2PO_3 was used as a base (Table 1, entries 5 to 7). When the reaction was performed with $Pd(OAc)_2$-PPh_3 as the catalyst system instead of $Pd(PPh_3)_4$, no expected

product was obtained (Table 1, entry 8). Further explorations indicate that the coupling was remarkably affected by the reaction medium. Aprotic organic solvents, such as DMSO, DMF, DMA, DCE, and DEA are favored for the construction of 1,4,5-trisubstituted 1,2,3-triazoles (Table 1, entries 9 to 13). A moderate yield of 58% was achieved when the reaction was conducted in DMA catalyzed by $Pd(OAc)_2$, using Cs_2CO_3 as the base (Table 1, entry 11). By contrast, no target molecules of **3a** were detected when PhMe or TFA was used as solvent (Table 1, entries 14 and 15). A better yield of 85% was obtained when PPh_3 was selected as a ligand for the aforementioned reaction (Table 1, entry 16). However, changing the ligand to S-Phos, X-Phos, or TCHP instead of PPh_3 resulted in lower yields (Table 1, entries 17 to 19). Notably, an excellent yield of 94% was achieved when the ligand of PPh_3 was replaced by trimethylacetic acid (^{t}BuCO$_2$H) (Table 1, entry 20). Trimethylacetic acid (^{t}BuCO$_2$H) may be used as cocatalyst in the basic reaction conditions.[39] Only a low yield of 46% was obtained when DMA-H_2O mixture (1:1 in volume) was applied as the solvent (Table 1, entry 21). Further explorations indicate that increasing or decreasing microwave power did not favor the reaction (Table 1, entries 22 to 23). If the amount of catalyst was decreased to 5%, then only a 72% yield of the product could be obtained (Table 1, entry 24). Conventional heating seems inefficient, as the yield reached only 55% when the reaction was conducted under 120 °C for 24 h (Table 1, entry 25). Thus, the optimized condition was achieved when the reaction of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **1a** (0.3 mmol) with 1-iodo-4-methylbenzene **2a** (0.36 mmol) was conducted in DMA catalyzed by $Pd(OAc)_2$ (0.03 mmol), using Cs_2CO_3 (0.6 mmol) as the base and ^{t}BuCO$_2$H (0.06 mmol) as the additive under 10 W microwave conditions for 1 h (Table 1, entry20).

The versatility and functional group tolerance of the C(5)–H arylation of triazoles **1** was investigated under the optimized reaction conditions. Table 2 shows that a variety of substituents, such as Me, OMe, F, Cl, and Br, on the substrates were tolerated and had no significant effect on the reactions, but obtained good to excellent yields in most cases. Halides and alkyl groups on *ortho*, *meta*, and *para* positions of aryl iodides were all suitable for this transformations. Notably, electron-rich iodides were observed to be more efficient for C–C coupling, producing higher yields than electron-poor iodides (Table 2, **3b**–**d** vs **3e**–**f**, **3h**–**i** vs **3j**, **3l**–**n** vs **3o**, and **3q**–**r** vs **3s**). The use of aryl bromides instead of iodides for this system were explored, and the reactions proceeded smoothly with excellent yields (as shown in parentheses in Table 2, **3a**–**c**, **3g**, and **3k**–**l**).

According to recent literature,[40] the proposed Pd(0)/Pd(II) catalytic cycle for the C(5)–H arylation of 1,4-disubstituted 1,2,3-triazoles to form 1,4,5-triazoles is shown in Scheme 2. The aryl palladium intermediate **A** is generated through oxidative addition of aryl iodide **1** to active species Pd(0), which was produced from the reduction of Pd(II) in situ. Then, the coordination of the base to intermediate **A** generates the Pd intermediate **B**, in which C–H bond activation will occur via the CMD pathway to yield the tricoordinated Pd intermediate **C**. Aryl triazole-4-yl palladium species **D** is formed through the release of a molecule of $CsHCO_3$. In the final step, reductive elimination of intermediate **D** yields the desired C–C coupling C(5) arylated product of 1,4,5-trisubstituted 1,2,3-triazole 3 through the release of the Pd(0) species to complete the catalytic cycle.

In addition, the applications of synthesized products were investigated. One of the most important processes is to transform the obtained trisubstituted molecules to 4,5-disubstituted 1,2,3-triazoles through the debenzylation process with one-pot manipulation. According to the reported methods,[41–43] we conducted some experiments by adding relevant reagents to the system for the next step of the debenzylation process under the same microwave conditions when C(5)–H arylation was completed. The ^{t}BuOK-DMSO combination is a good choice for this transformation. When the reaction for the synthesis of 1,4,5-triazoles is completed, 2 equiv of ^{t}BuOK and 1 mL of DMSO were added to the system for the subsequent debenzylation reaction. After the mixture was promoted under 10 W microwave for another 0.5 h, good to excellent yields of 4,5-disubstuted 1,2,3-triazoles **4** were obtained (Table 3).

CONCLUSION

In conclusion, we developed a highly efficient method for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles through C(5)–H activation of 1,4-disubstituted 1,2,3-triazoles under 10 W microwave conditions for 1 h catalyzed by $Pd(OAc)_2$. Moreover, the system can be easily used to prepare 4,5-disubstituted 1,2,3-triazoles through the debenzylation process with one-pot manipulation under similar conditions for another 0.5 h.

EXPERIMENTAL

All reactions were conducted using the CEM Discover-SP microwave instrument. ^{1}H and ^{13}C NMR spectra were recorded with a MercuryPlus 300 (300 MHz) or a Bruker ACF400 spectrometer (400 MHz) in d_6-DMSO or $CDCl_3$ with TMS as an internal standard. All reactions were monitored by TLC analysis with HuanghaiGF 254 silica gel-coated plates. Column chromatography was conducted using 300 to 400 mesh silica gel at medium pressure. Infrared spectra were recorded on the Bruker Vertex Series FTIR (KBr) and were reported in reciprocal centimeters (cm^{-1}). Melting points were obtained using the Büchi melting point apparatus and were uncorrected. HRMS spectra were recorded on the Waters Micromass Premier Q-TOF spectrometer.

General Procedures For The Synthesis Of Compound 3a

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole **1a** (0.3 mmol), iodobenzene **2a** (0.36 mmol, 1.2 equiv), $Pd(OAC)_2$ (7 mg, 0.03 mmol, 10 mol%), $^{t}BuCO_2H$ (6 mg, 0.06 mmol, 20 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 equiv), and DMA (2.0 mL) were added to a 5 mL microwave reaction tube. The mixture was promoted under 10 W microwave for 1 h. After consumption of the 1-benzyl-4-phenyl-1*H*-1,2,3-triazole monitored by TLC analysis, the mixture was added with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield a crude product. Purification by column

chromatography on silica gel yielded the desired 1-benzyl-4,5-diphenyl-1*H*-1,2,3-triazole **3a**.

Formation Of Compound 4a By The Debenzylation Process With One-Pot Manipulation

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole **1a** (0.3 mmol), 1-iodo-4-methylbenzene **2a** (0.36 mmol, 1.2 equiv), $Pd(OAC)_2$ (7 mg, 0.03 mmol, 10 mol%), $^tBuCO_2H$ (6 mg, 0.06 mmol, 20 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 2.0 equiv), and DMA (2.0 mL) were added to a 5 mL microwave reaction tube. The mixture was promoted under 10 W microwave for 1 h. After consumption of **1a** monitored by TLC analysis, the mixture was added with 2 equiv of ^{t}BuOK and 1 mL DMSO and promoted under 10 W microwave for another 0.5 h until the debenzylation process was completed. Then, the system was added with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield a crude product. Purification by column chromatography on silica gel yielded the desired 4-phenyl-5-(*p*-tolyl)-1*H*-1,2,3-triazole **4a**.

Spectral Data For The Selected Compounds

Compound **3f**: Brown solid; mp 89 °C to 91 °C; ^{1}H NMR (400 MHz, DMSO): δ = 7.59 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.48-7.39 (m, 3H), 7.36 to 7.23 (m, 7H),

6.98 (d, J = 5.1 Hz, 2H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ = 143.2, 134.9, 133.2, 132.0, 130.5, 129.9, 129.3, 129.1, 128.8, 128.3, 128.1, 128.1, 127.4, 126.7, 126.7, 125.8, 51.0; IR (KBr) = 3,418, 3,128, 2,308, 1,602, 1,568, 1,498, 1,349, 1,130, 1,096, 990, 814, 777, 693 cm^{-1}; HRMS calculated for $[C_{21}H_{16}ClN_3+H]^+$ = 346.1106, Found = 346.1108.

Compound **3i**: Light brown oil; ^{1}H NMR (400 MHz, DMSO): δ = 7.43 to 7.32 (m, 4H), 7.31 to 7.22 (m, 3H), 7.16 to 7.04 (m, 4H), 7.04 to 6.91 (m, 2H), 5.43 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ = 142.8, 138.0, 136.5, 135.2, 133.1, 129.8, 129.8, 128.6, 128.5, 128.4, 128.0, 127.5, 127.3, 126.7, 126.5, 125.6, 50.7, 20.3, 20.2; IR (KBr) = 3,419, 3,129, 1,610, 1,514, 1,000, 823, 731, 703, 687, 521 cm^{-1}; HRMS calculated for $[C_{23}H_{21}N_3+H]^+$ = 340.1808, Found = 340.1809.

Compound **3j**: Light brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 to 7.35 (m, 4H), 7.28 to 7.23 (m, 3H), 7.18 to 6.93 (m, 6H), 5.40 (s, 2H), 2.30 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 137.7, 135.8, 135.2, 132.2, 131.4, 129.4, 129.2, 128.7, 128.2, 127.6, 127.3, 126.6, 126.0, 52.0, 21.1; IR (KBr) = 3,419, 3,129, 1,621, 1,515, 1,480, 1,091, 984, 824, 734, 517 cm^{-1}; HRMS calculated for $[C_{22}H_{18}ClN_3+H]^+$ = 360.1262, Found = 360.1260.

Compound **3m**: Light yellow solid; mp 108 °C to 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 to 7.44 (m, 2H), 7.32 to 7.22 (m, 5H), 7.07 to 6.99 (m, 2H), 6.94 (d, J = 7.1 Hz, 1H), 6.87 (s, 1H), 6.84 to 6.72 (m, 2H), 5.37 (s, 2H), 3.76 (s, 3H), 2.29 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 159.1, 144.2, 138.8, 135.5, 133.2, 130.6, 130.2, 128.9, 128.5, 128.0, 127.8, 127.8, 127.5, 127.1, 123.6, 113.8, 55.1, 52.0, 21.2; IR (KBr) = 3,419, 3,131, 2,956, 2,835, 1,614, 1,562, 1,455, 1,352, 1,175, 1,109, 1,038, 996, 841, 815, 794, 705, 675, 594, 576 cm^{-1}; HRMS calculated for $[C_{23}H_{21}N_3O+H]^+$ = 356.1757, Found = 356.1755.

FUNDING

We are grateful for the financial support provided by the National Natural Science Foundation of China (Grant No. 51464021) and the Science and Technology Planning Project of Yunnan Province (Grant No. KKSY201307056).

SUPPORTING INFORMATION

Full experimental detail, ^1H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

REFERENCES

1. Massarotti, A.; Aprile, S.; Mercalli, V.; Del Grosso, E.; Grosa, G.; Sorba, G.; Tron, G. *Chem Med Chem.* **2014**, *9*, 2497-2508.

2. Fang, Z.; Kang, D.; Zhang, L.; Huang, B.; Liu, H.; Pannecouque, C.; De Clercq, E.; Zhan, P.; Liu, X. *Chem. Biol. Drug Des.* **2015**, *86*, 614-618.

3. Zhao, L.; Mao, L.; Hong, G.; Yang, X.; Liu, T. *Bioorg. Med. Chem. Lett.* **2015**, *25* 2540-2544.

4. Ferreira, J.; Garcia, M. X.; Caamano, O.; Brea, J. M.; Loza, M. I. *Eur. J. Med. Chem.* **2015**, *98*, 212-220.

5. Keri, R. S.; Patil, S. A.; Budagumpi, S.; Nagaraja, B. M. *Chem. Biol. Drug Des.* **2015**, *86*, 410-423.

6. Menendez, C.; Rodriguez, F.; Ribeiro, A. L.; Zara, F.; Frongia, C.; Lobjois, V.; Saffon, N.; Pasca, M. R.; Lherbet, C.; Baltas, M. *Eur. J. Med. Chem.* **2013**, *69* 167-173.

7. Gon-zaga, D. T. G.; da Rocha, D. R.; da Silva, F. C.; Ferreira, V. F. *Curr. Top. Med. Chem.* **2013**, *13*, 2850-2865.

8. Pyta, K.; Klich, K.; Domagalska, J.; Przybylski, P. *Eur. J. Med. Chem.* **2014**, *84*, 651-676.

9. Zhang, H.; Wei, J.; Kumar, K. V.; Rasheed, S.; Zhou, C. *Med. Chem. Res.* **2015**, *24*, 182-196.

10. Kumar, A. S.; Ghule, V. D.; Subrahmanyam, S.; Sahoo, A. K. *Chem. Eur. J.* **2013**, *19*, 509-518.

11. He, C.; Shreeve, J. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6260-6264.

12. Padalkar, V. S.; Lanke, S. K.; Chemate, S. B.; Sekar, N. *J. Fluoresc.* **2015**, *25*, 985-996.

13. Duan, T.; Fan, K.; Li, K.; Cao, W.; Zhong, C.; Chen, X.; Peng, T.; Qin, J. *Dyes Pigments* **2015**, *117*, 108-115.

14. Qin, J.; Zhang, S.; Du, D.; Shen, P.; Bao, S.; Lan, Y.; Su, Z. *Chem. Eur. J.* **2014**, *20*,5625-5630.

15. Jeong, Y.; Ryu, J. *J. Org. Chem.* **2010**, *75*, 4183-4191.

16. Bolje, A.; Kosmrlj, J. *Org. Lett.* **2013**, *15*, 5084-5087.

17. Obadia, M.; Colliat-Dangus, G.; Debuigne, A.; Serghei, A.; Detrembleur, C.; Drockenmuller, E. *Chem. Commun.* **2015**, *51*, 3332-3335.

18. Krikorian, M.; Liu, S.; Swager, T. M. *J. Am. Chem. Soc.* **2014**, *136*, 2952-2955.

19. Beltran, E.; Serrano, J. L.; Sierra, T.; Gimenez, R. *J. Mater. Chem.* **2012**, *22*, 7797-7805.

20. Wang, D.; Etienne, L.; Echeverria, M.; Moya, S.; Astruc, D. *Chem. Eur. J.* **2014**, *20*, 4047-4054.

21. Ozkal, E.; Llanes, P.; Bravo, F.; Ferrali, A.; Pericas, M. A. *Adv. Synth. Catal.* **2014**, *356*, 857-869.

22. Hansen, S. G.; Jensen, H. H. *Synlett* **2009**, 3275-3278.

23. Wu, L.; Xie, Y.; Chen, Z.; Niu, Y.; Liang, Y. *Synlett* **2009**, 1453-1456.

24. Albadi, J.; Keshavarz, M.; Abedini, M.; Vafaie-nezhad, M. *Chin. Chem. Lett.* **2012**, *23*, 797-800.

25. Bai, H.; Cai, Z.; Wang, S.; Ji, S. *Org. Lett.* **2015**, *17*, 2898-2901.

26. Deraedt, C.; Pinaud, N.; Astruc, D. *J. Am. Chem. Soc.* **2014**, *136*, 12092-12098.

27. Johansson, J. R.; Lincoln, P.; Norden, B.; Kann, N. *J. Org. Chem.* **2011**, *76*, 2355-2359.

28. Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063-5073.

29. Yan, W.; Liao, T.; Tuguldur, O.; Zhong, C.; Petersen, J. L.; Shi, X. *Chem. Asian J.* **2011**, *6*, 2720-2724.

30. Wang, D.; Chen, S.; Chen, B. *Tetrahedron Lett.* **2014**, *55*, 7026-7028.

31. Xia, Y.; Chen, L.; Lv, S.; Sun, Z.; Wang, B. *J. Org. Chem.* **2014**, *79*, 9818-9825.

32. Bhaumik, A.; Samanta, S.; Pathak, T. *J. Org. Chem.* **2014**, *79*, 6895-6904.

33. Chen, Y.; Nie, G.; Zhang, Q.; Ma, S.; Li, H.; Hu, Q. *Org. Lett.* **2015**, *17*, 1118-1121.

34. Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237-1240.

35. Wu, Y.; Deng, J.; Li, Y.; Chen,Q. *Synthesis* **2005**, 1314-1318.

36. Wang, B.; Liu, N.; Chen, W.; Huang, D.; Wang, X.; Hu, Y. *Adv. Synth. Catal.* 2015, *357*, 401-407.

37. He, T.; Wang, M.; Li, P.; Wang, L. *Chin. J. Chem.* **2012**, *30*, 979-984.

38. Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333-2336.

39. Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008,** *10*, 2299-2302.

40. Yamajala, K. D. B.; Patil, M.; Banerjee, S. *J. Org. Chem.* **2015**, *80*, 3003-3011.

41. Koguchi, S.; Kazuki, I. *Synthesis.* **2012**, *44*, 3603-3608.

42. Papudippu, M.; Shu, H.; Izenwasser, S.; Wade, D.; Gulasey, G.; Fournet, S.; Stevens, E. D.; Lomenzo, S. A.; Trudell, M. L. *Med. Chem. Res.* **2012**, *21*, 4473-4484.

43. Farooq, T.; Sydnes, L. K.; Tornroos, K. W.; Haug, B. E. *Synthesis.* **2012**, *44*, 2070-2078.

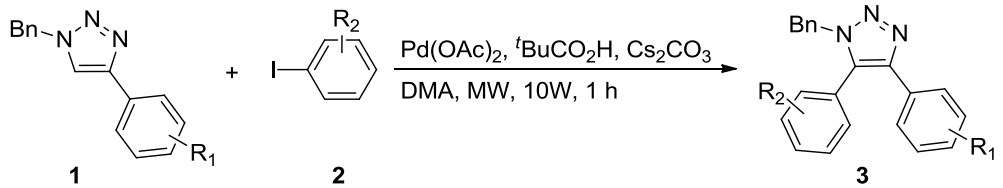
Table 1 Optimization of the reaction conditions.[a]

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

Entry	Cat.	Additive	Base	Solvent	**3a** (%)[b]
1	$Pd(PPh_3)_4$	–	K_2CO_3	H_2O	27
2	$Pd(PPh_3)_4$	–	Cs_2CO_3	H_2O	36
3	$Pd(PPh_3)_4$	–	^tBuOK	H_2O	22
4	$Pd(PPh_3)_4$	–	Ag_2CO_3	H_2O	15
5	$Pd(PPh_3)_4$	–	Na_2CO_3	H_2O	0
6	$Pd(PPh_3)_4$	–	K_3PO_4	H_2O	0
7	$Pd(PPh_3)_4$	–	KH_2PO_4	H_2O	0
8	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	H_2O	0
9	$Pd(OAc)_2$	–	Cs_2CO_3	DMSO	42
10	$Pd(OAc)_2$	–	Cs_2CO_3	DMF	48
11	$Pd(OAc)_2$	–	Cs_2CO_3	DMA	58
12	$Pd(OAc)_2$	–	Cs_2CO_3	DCE	32
13	$Pd(OAc)_2$	–	Cs_2CO_3	DEA	30
14	$Pd(OAc)_2$	–	Cs_2CO_3	PhMe	0
15	$Pd(OAc)_2$	–	Cs_2CO_3	TFA	0
16	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMA	85
17	$Pd(OAc)_2$	TCHP	Cs_2CO_3	DMA	34
18	$Pd(OAc)_2$	X-Phps	Cs_2CO_3	DMA	45
19	$Pd(OAc)_2$	S-Phps	Cs_2CO_3	DMA	32
20	**$Pd(OAc)_2$**	**$^tBuCO_2H$**	**Cs_2CO_3**	**DMA**	**94**
21	$Pd(OAc)_2$	$^tBuCO_2H$	Cs_2CO_3	DMA-H_2O	46
22[c]	$Pd(OAc)_2$	$^tBuCO_2H$	Cs_2CO_3	DMA	68
23[d]	$Pd(OAc)_2$	$^tBuCO_2H$	Cs_2CO_3	DMA	70
24[e]	$Pd(OAc)_2$	$^tBuCO_2H$	Cs_2CO_3	DMA	72
25[f]	$Pd(OAc)_2$	$^tBuCO_2H$	Cs_2CO_3	DMA	55

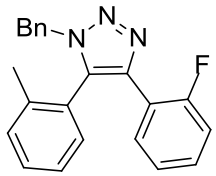
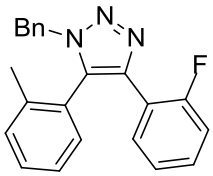
[a]Reaction conditions unless noted: 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **1a** (0.3 mmol), 1-iodo-4-methylbenzene **2a** (0.36 mmol), palladium catalyst (0.03 mmol), additive (0.06 mmol), and base (0.6 mmol) were added to 2 mL of solvent and the reaction was conducted under 10 W microwave conditions for 1 h.
[b]Isolated yields.
[c]Microwave 5 W used.
[d]Microwave 10 W used.
[e]5% $Pd(OAc)_2$ was used.
[f]Conducted under120 °C by conventional heating for 20 h.

Table 2 Synthesis of 1,4-disubstituted 1,2,3-triazoles **3** by expanding aromatic nitrocompounds.[a,b]



1 **2** **3**

3a 91% (80%)[c]	**3b** 94% (90%)[c]	**3c** 95% (89%)[c]	**3d** 92%
3e 62%	**3f** 79%	**3g** 82% (79%)[c]	**3h** 91%
3i 93%	**3j** 93%	**3k** 95% (83%)[c]	**3l** 96% (92%)[c]
3m 92%	**3n** 89%	**3o** 65%	**3p** 94%
3q 77%	**3r** 68%	**3s** 60%	**3t** 76% (63%)[c]

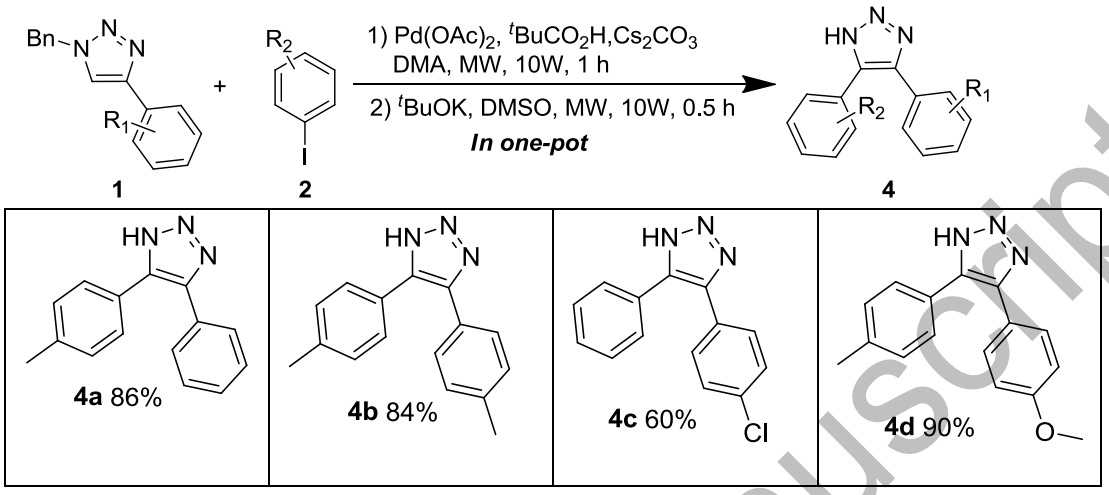
 **3u** 90%	 **3v** 60%		

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (0.03 mol), $^tBuCO_2H$ (0.06 mmol), and Cs_2CO_3 (0.6 mmol) were added to 2 mL of DMA and the reaction was conducted under 10 W microwave for 1 h.

[b]Yield of isolated product after column chromatography.

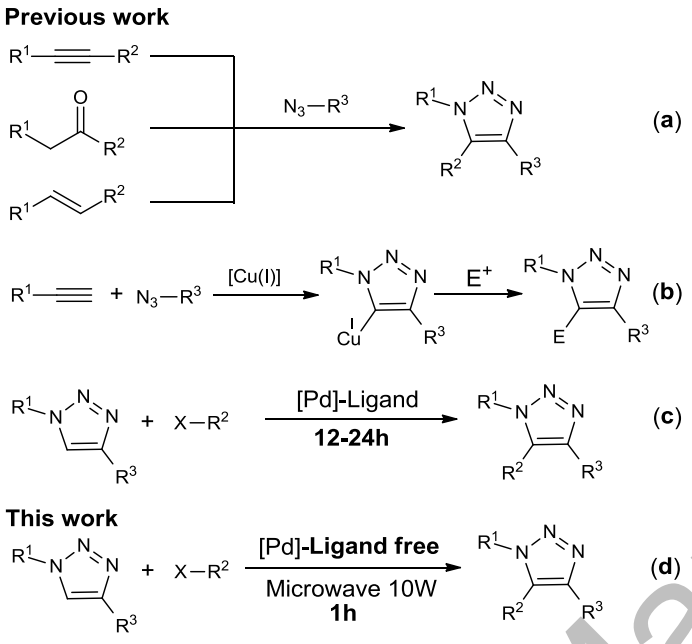
[c]Isolated yields using aryl bromides instead of aryl iodides.

Table 3 Formation of 4,5-disubstuted 1,2,3-triazoles through the debenzylation process with one-pot manipulation.[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $Pd(OAC)_2$ (0.03 mmol), $^tBuCO_2H$ (0.06 mmol), and Cs_2CO_3 (0.6 mmol) were added to 2 mL of DMA and the reaction was conducted under 10 W microwave for 1 h. Then, the system was added with 2 equiv of ^{t}BuOK and 1 mL of DMSO and the reaction was conducted under 10 W microwave for another 0.5 h.
[b]Isolated yields.

Scheme 1. Methods employed to construct trisubstituted 1,2,3-triazoles



Scheme 2. Proposed mechanism