

Solvent-free Suzuki and Stille cross-coupling reactions of 4- and 5-halo-1,2,3-triazoles

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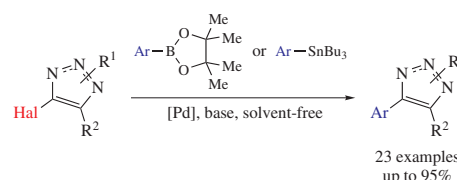
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An environmentally friendly and efficient synthesis of fully substituted 1,2,3-triazoles comprises solvent-free palladium-catalyzed Suzuki cross-coupling of halo-1,2,3-triazoles with pinacol arylboronates. The efficiencies of Stille and Suzuki reactions with halotriazoles under solvent-free conditions were compared.



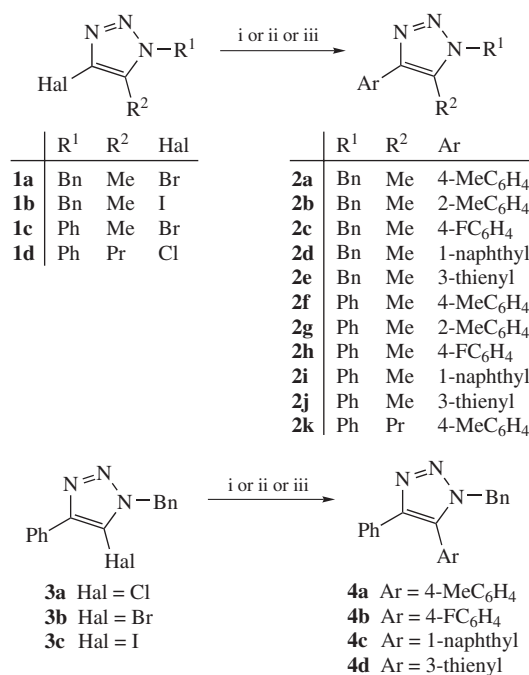
1,2,3-Triazoles are extensively used as medicines,¹ functional coatings,² find application in supramolecular chemistry,³ organic synthesis,⁴ transition metal catalysis⁵ and can be employed as sensing materials.⁶ Therefore, development of new universal syntheses of 1,2,3-triazoles is topical.⁷ 1,4,5-Trisubstituted 1,2,3-triazoles and their derivatives comprise an important and intensively studied chemotype of compounds,^{1(a),8} however they are not readily accessible *via* classical click reactions⁹ and cross-coupling of relevant halotriazoles. Notably, 5-halotriazoles were poorly available until recently.¹⁰ Therefore, the development of a new reliable versatile procedure for the synthesis of fully substituted 1,2,3-triazoles is of importance.

A number of procedures for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles *via* the Suzuki^{7,9(b),11} and Stille¹² cross-coupling reactions have been documented. Recently, we reported a general highly efficient 'green' synthesis of 1,4,5-trisubstituted 1,2,3-triazoles¹³ in water through the Suzuki reaction of 4- and 5-halo-1,2,3-triazoles¹⁰ advantageous by low catalyst loadings, avoidance of organic solvents in favor of water, and tolerance to various functional groups. We were the first to show that 4- and 5-chloro-1,2,3-triazoles could be used as the coupling partners.

One of the main directions of our research is the development of solvent-free copper,¹⁴ gold,¹⁵ and palladium¹⁶ mediated reactions. Here, we report on a 'greener' solvent-free synthetic procedure providing fully substituted 1,2,3-triazoles.

Initially, we compared performances of the Suzuki and Stille reactions of model 1-benzyl-4-bromo-5-methyl-1,2,3-triazole **1a** under solvent-free conditions (Scheme 1).[†] In the Suzuki

coupling, pinacol arylboronates ArBPIn were chosen as the counterparts since they can be readily accessed using the borylation^{16(c),17,18} methods, are easy to handle and are stable in air.¹⁹ In addition, pinacol arylboronates are often liquid at room temperature and readily soluble in aprotic solvents, which makes their use in solvent-free cross-coupling reactions beneficial.^{16(a),(c)}



Scheme 1 Reagents and conditions: i, procedure A, halotriazole (0.5 mmol), ArBPIn (0.525 mmol), Pd(OAc)₂ (0.005 mmol, 1 mol%), SPhos (0.01 mmol, 2 mol%), KOH (0.85 mmol), neat, 110 °C, 24 h; ii, procedure B, halotriazole (0.5 mmol), ArBPIn (0.525 mmol), Pd(PPh₃)₂Cl₂ (0.005 mmol, 1 mol%), KOH (0.85 mmol), neat, 110 °C, 24 h; iii, procedure C, halotriazole (0.5 mmol), ArSnBu₃ (0.55 mmol), Pd(OAc)₂ (0.005 mmol, 1 mol%), PCy₃ (0.01 mmol, 2 mol%), CsF (0.75 mmol), neat, 110 °C, 24 h.

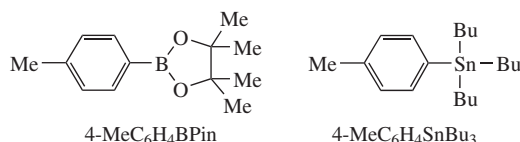
[†] Solvent-free preparation of 1,4,5-trisubstituted 1,2,3-triazoles.

General procedure A based on the Suzuki–Miyaura cross-coupling. A screw cap vial equipped with a magnetic stirring bar was charged with the corresponding 4- or 5-halo-1,2,3-triazole (0.5 mmol, 1.0 equiv.), ArBPIn (0.525 mmol, 1.05 equiv.), Pd(OAc)₂ (0.005 mmol, 0.01 equiv.), SPhos (0.01 mmol, 0.02 equiv.), and powdered 85% KOH (0.85 mmol, 1.7 equiv.). All the components were thoroughly mixed together. The vial was placed into a preheated oil bath (110 °C). After 24 h, the reaction

Table 1 Solvent-free Suzuki and Stille cross-coupling of halotriazoles **1**, **3**.

Entry	Halo-triazole	Organoelement counterpart		Procedure	Product	Yield (%)
		Ar	Leaving group			
1	1a	4-MeC ₆ H ₄	BPin	A	2a	94
2	1a	4-MeC ₆ H ₄	SnBu ₃	C	2a	46
3	1b	4-MeC ₆ H ₄	BPin	B	2a	73
4	1a	2-MeC ₆ H ₄	BPin	A	2b	71
5	1a	4-FC ₆ H ₄	BPin	A	2c	70
6	1a	1-naphthyl	BPin	A	2d	82
7	1a	3-thienyl	BPin	A	2e	74
8	1c	4-MeC ₆ H ₄	BPin	A	2f	71
9	1c	2-MeC ₆ H ₄	BPin	A	2g	78
10	1c	4-FC ₆ H ₄	BPin	A	2h	60
11	1c	1-naphthyl	BPin	A	2i	82
12	1c	3-thienyl	BPin	A	2j	65
13	1d	4-MeC ₆ H ₄	BPin	A	2k	37
14	1d	4-MeC ₆ H ₄	SnBu ₃	C	2k	25
15	3a	4-MeC ₆ H ₄	BPin	A	4a	52
16	3a	4-MeC ₆ H ₄	SnBu ₃	C	4a	65
17	3b	4-MeC ₆ H ₄	BPin	A	4a	37
18	3b	4-MeC ₆ H ₄	SnBu ₃	C	4a	35
19	3c	4-MeC ₆ H ₄	BPin	B	4a	96
20	3c	4-MeC ₆ H ₄	SnBu ₃	C	4a	62
21	3c	4-FC ₆ H ₄	BPin	B	4b	95
22	3c	1-naphthyl	BPin	B	4c	50
23	3c	3-thienyl	BPin	B	4d	68

The coupling of either 4-MeC₆H₄BPin or 4-MeC₆H₄SnBu₃ with bromotriazole **1a** upon 24 h heating afforded the same product **2a** (see Scheme 1, Table 1). For the catalytic systems, special Suzuki [Pd(OAc)₂/SPhos, KOH]^{16(a)} and Stille [Pd(OAc)₂/PCy₃, CsF]^{16(f)} versions were chosen since they are known to be suitable for the solvent-free procedures. The product **2a** was isolated by flash chromatography in 94% yield in case of Suzuki reaction and 46% in case of Stille reaction (Table 1, entries 1 and 2).



Since the Stille method provided only moderate yield of product **2a** in the model experiments, the further studies of the scope and limitations of solvent-free coupling of 4(5)-chloro/bromo/iodo-substituted 1,2,3-triazoles were performed based on the Suzuki coupling (Table 1). Target 1,4,5-trisubstituted 1,2,3-triazoles **2** and **4** were obtained in good-to-excellent yields from 4- and 5-halotriazoles **1**, **3** containing aryl (see Table 1,

mixture was cooled and treated with CH₂Cl₂–H₂O (1:1) mixture, the organic phase was separated and the solvent was evaporated *in vacuo*. The pure product was isolated by silica gel chromatography using hexane–EtOAc (10:1) mixture as eluent.

General procedure B based on the Suzuki–Miyaura cross-coupling. A mixture of 4- or 5-halo-1,2,3-triazole (0.5 mmol, 1.0 equiv.), ArBPin (0.525 mmol, 1.05 equiv.), Pd(PPh₃)₂Cl₂ (0.005 mmol, 0.01 equiv.) and powdered 85% KOH (0.85 mmol, 1.7 equiv.) was treated as in General Procedure A.

General procedure C based on the Stille cross-coupling. A mixture of 4- or 5-halo-1,2,3-triazole (0.5 mmol, 1.0 equiv.), tributyl(4-methylphenyl)-stannane (0.55 mmol, 1.1 equiv.), Pd(OAc)₂ (0.005 mmol, 0.01 equiv.), tricyclohexylphosphine (0.01 mmol, 0.02 equiv.), and anhydrous CsF (0.75 mmol, 1.5 equiv.) was treated as in General Procedure A.

entries 8–14) and benzyl (entries 1–7 and 15–23) substituents at the nitrogen atom. Various pinacol arylboronates bearing electron donating (entries 1, 3, 4, 8, 9), electron withdrawing (entries 5, 10, 21) and sterically hindered (entries 6, 11, 22) substituents in the aryl group can be efficiently used as coupling partners. Also, we used reaction with 3-thienylboronic acid pinacol ester (entries 7, 12, 23) to exemplify the reactivity of pinacol hetero-arylboronates in the cross-coupling.

Notably, in couplings of chloro- and bromo-1,2,3-triazoles we used a well-recognized Buchwald catalytic system Pd(OAc)₂/SPhos.²⁰ In cases of more active iodo-1,2,3-triazoles **2a** and **4a–d**, employment of a conventional catalyst Pd(PPh₃)₂Cl₂^{16(a)} was sufficient to reach good-to-excellent yields of the target compounds (see Table 1, entries 3, 19–23).

Couplings of 3-thienylboronic acid pinacol esters **2e,j** and **4d** proceed in yields below 75% (see Table 1, entries 7, 12, 23), which may be attributed to catalyst poisoning. It was documented previously²¹ that admixtures of thiols and organic sulfides usually contaminate the title organosulfur compounds. High affinity of such impurities to palladium can be the cause of catalyst deactivation.

In 5-iodo-1,2,3-triazole **3c**, 1- and 4-positioned substituents introduce steric encumbrance around 5-position, which might hinder the cross-coupling. In fact, the coupling of this iodo-hetarene with arylboronic esters of different electronic nature proceeded very efficiently to provide products **4a,b** in yields as high as 96 and 95%, respectively (see Table 1, entries 19, 21). Meanwhile, with bulky 1-naphthylboronic ester product **4c** was obtained in only 50% yield (entry 22). Therefore, 5-iodo-1,2,3-triazoles are less sensitive to electronic nature of pinacol arylboronates than to their steric properties.

In cases when the Suzuki coupling provided yields below 60% (see Table 1, entries 13, 15, 17), we additionally tested the performance of Stille reaction. Regularly, on moving to the Stille method the yields were even lower. However, in case of using chloro derivative **3a** some increase in the yield of product **4a** from 52% (Suzuki) to 65% (Stille) was observed (entries 15 and 16).

In conclusion, a comparison between performances of the Suzuki and Stille coupling reactions of 4- and 5-halo-1,2,3-triazoles under solvent-free conditions revealed the preference of the Suzuki method. The Buchwald catalytic system Pd(OAc)₂/SPhos is well suitable for the coupling of 4- and 5-bromo-1,2,3-triazoles, whereas more active iodotriazoles react efficiently under catalysis by conventional complex Pd(PPh₃)₂Cl₂. The elaborated procedure meets the requirements of ‘green’ chemistry for the following reasons: (i) no use of solvents; (ii) aerobic conditions; (iii) low catalyst loadings; and (iv) easily available, environmentally benign KOH as a base. Notably, we have previously shown that the Suzuki coupling of aryl halides can be efficiently performed under solvent-free conditions.^{16(a)} Herein, we have demonstrated that this methodology can be extended to heteroaromatic halides, particularly, challenging 4- and 5-halo-1,2,3-triazoles. This contribution presents no more than the second example of their Suzuki cross-coupling.¹³

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.009.

References

- (a) S. G. Agalave, S. R. Maujan and V. S. Pore, *Chem. Asian J.*, 2011, **6**, 2696; (b) H. C. Kolb and K. B. Sharpless, *Drug Discov. Today*, 2003, **8**, 1128.
- S. Kantheti, R. Narayan and K. V. S. N. Raju, *RSC Adv.*, 2015, **5**, 3687.
- (a) J. D. Crowley and P. H. Bandeen, *Dalton Trans.*, 2010, **39**, 612; (b) B. Schulze and U. S. Schubert, *Chem. Soc. Rev.*, 2014, **43**, 2522; (c) X. Wang, B. Huang, X. Liu and P. Zhan, *Drug Discov. Today*, 2016, **21**, 118.
- (a) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone and A. M. Almerico, *Eur. J. Org. Chem.*, 2014, 3289; (b) D. Pasini, *Molecules*, 2013, **18**, 9512.
- D. S. Huang, P. X. Zhao and D. Astruc, *Coord. Chem. Rev.*, 2014, **272**, 145.
- Y. H. Lau, P. J. Rutledge, M. Watkinson and M. H. Todd, *Chem. Soc. Rev.*, 2011, **40**, 2848.
- J. Deng, Y.-M. Wu and Q.-Y. Chen, *Synthesis*, 2005, 2730.
- (a) S. K. Maurya, D. R. Gollapalli, S. Kirubakaran, M. Zhang, C. R. Johnson, N. N. Benjamin, L. Hedstrom and G. D. Cuny, *J. Med. Chem.*, 2009, **52**, 4623; (b) H. F. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov and X. D. Shi, *J. Am. Chem. Soc.*, 2009, **131**, 12100; (c) J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302; (d) B. Chattopadhyay and V. Gevorgyan, *Angew. Chem. Int. Ed.*, 2012, **51**, 862; (e) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905; (f) M. A. Azagarsamy and K. S. Anseth, *ACS Macro Lett.*, 2013, **2**, 5; (g) A. V. Gulevich and V. Gevorgyan, *Angew. Chem. Int. Ed.*, 2013, **52**, 1371; (h) Q. Gu, H. H. Al Mamari, K. Graczyk, E. Diers and L. Ackermann, *Angew. Chem. Int. Ed.*, 2014, **53**, 3868.
- (a) L. Zhang, X. G. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. C. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998; (b) J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2009, **48**, 8018; (c) B. T. Worrell, S. P. Ellery and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2013, **52**, 13037; (d) S. T. Ding, G. C. Jia and J. W. Sun, *Angew. Chem. Int. Ed.*, 2014, **53**, 1877.
- P. S. Gribanov, M. A. Topchiy, I. V. Karsakova, G. A. Chesnokov, A. Y. Smirnov, L. I. Minaeva, A. F. Asachenko and M. S. Nechaev, *Eur. J. Org. Chem.*, 2017, 5225.
- (a) J. Huang, S. J. F. Macdonald and J. P. A. Harrity, *Chem. Commun.*, 2009, 436; (b) X.-J. Wang, K. Sidhu, L. Zhang, S. Campbell, N. Haddad, D. C. Reeves, D. Krishnamurthy and C. H. Senanayake, *Org. Lett.*, 2009, **11**, 5490; (c) X.-J. Wang, L. Zhang, D. Krishnamurthy, C. H. Senanayake and P. Wipf, *Org. Lett.*, 2010, **12**, 4632; (d) Z. Shan, M. Peng, H. Fan, Q. Lu, P. Lu, C. Zhao and Y. Chen, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1731; (e) R. De Simone, M. G. Chini, I. Bruno, R. Riccio, D. Mueller, O. Werz and G. Bifulco, *J. Med. Chem.*, 2011, **54**, 1565; (f) L. Zhang, Z. Li, X.-J. Wang, N. Yee and C. H. Senanayake, *Synlett*, 2012, 1052; (g) M. Kavitha, B. Mahipal, P. S. Mainkar and S. Chandrasekhar, *Comb. Chem. High Throughput Screen.*, 2013, **16**, 657; (h) X. Cao, Z. Sun, Y. Cao, R. Wang, T. Cai, W. Chu, W. Hu and Y. Yang, *J. Med. Chem.*, 2014, **57**, 3687; (i) D. Goyard, A. S. Chajistamatiou, A. I. Sotiropoulou, E. D. Chrysina, J.-P. Praly and S. Vidal, *Chem. Eur. J.*, 2014, **20**, 5423; (j) J. S. Oakdale, R. K. Sit and V. V. Fokin, *Chem. Eur. J.*, 2014, **20**, 11101; (k) N. Ahmed, N. K. Konduru, S. Ahmad and M. Owais, *Eur. J. Med. Chem.*, 2014, **82**, 552; (l) D. Wang, S. Chen and B. Chen, *Tetrahedron Lett.*, 2014, **55**, 7026; (m) K. Fehér, A. Gömöry and R. Skoda-Földes, *Monatsh. Chem.*, 2015, **146**, 1455.
- (a) V. Malnuit, M. Duca, A. Manout, K. Bougrin and R. Benhida, *Synlett*, 2009, 2123; (b) E. Thiery, V. You, A.-S. Mora and M. Abarbri, *Eur. J. Org. Chem.*, 2016, 529; (c) F. Wei, T. Zhou, Y. Ma, C.-H. Tung and Z. Xu, *Org. Lett.*, 2017, **19**, 2098; (d) H. Amdouni, G. Robert, M. Driowya, N. Furstoss, C. Métier, A. Dubois, M. Dufies, M. Zerhouni, F. Orange, S. Lacas-Gervais, K. Bougrin, A. R. Martin, P. Auberger and R. Benhida, *J. Med. Chem.*, 2017, **60**, 1523; (e) M. Yamada, M. Matsumura, M. Kawahata, Y. Murata, N. Kakusawa, K. Yamaguchi and S. Yasuie, *J. Organomet. Chem.*, 2017, **834**, 83.
- P. S. Gribanov, G. A. Chesnokov, M. A. Topchiy, A. F. Asachenko and M. S. Nechaev, *Org. Biomol. Chem.*, 2017, **15**, 9575.
- G. A. Chesnokov, M. A. Topchiy, P. B. Dzhevakov, P. S. Gribanov, A. A. Tukov, V. N. Khrustalev, A. F. Asachenko and M. S. Nechaev, *Dalton Trans.*, 2017, **46**, 4331.
- O. S. Morozov, P. S. Gribanov, A. F. Asachenko, P. V. Dorovatovskii, V. N. Khrustalev, V. B. Rybakov and M. S. Nechaev, *Adv. Synth. Catal.*, 2016, **358**, 1463.
- (a) A. F. Asachenko, K. R. Sorochkina, P. B. Dzhevakov, M. A. Topchiy and M. S. Nechaev, *Adv. Synth. Catal.*, 2013, **355**, 3553; (b) M. A. Topchiy, A. F. Asachenko and M. S. Nechaev, *Eur. J. Org. Chem.*, 2014, 3319; (c) P. B. Dzhevakov, M. A. Topchiy, D. A. Zharkova, O. S. Morozov, A. F. Asachenko and M. S. Nechaev, *Adv. Synth. Catal.*, 2016, **358**, 977; (d) M. A. Topchiy, P. B. Dzhevakov, M. S. Rubina, O. S. Morozov, A. F. Asachenko and M. S. Nechaev, *Eur. J. Org. Chem.*, 2016, 1908; (e) G. A. Chesnokov, P. S. Gribanov, M. A. Topchiy, L. I. Minaeva, A. F. Asachenko, M. S. Nechaev, E. V. Bermesheva and M. V. Bermeshev, *Mendeleev Commun.*, 2017, **27**, 618; (f) P. S. Gribanov, Y. D. Golenko, M. A. Topchiy, L. I. Minaeva, A. F. Asachenko and M. S. Nechaev, *Eur. J. Org. Chem.*, 2018, 120; (g) P. S. Gribanov, Yu. D. Golenko, M. A. Topchiy, A. N. Philippova, N. Yu. Kirilenko, N. V. Krivoshchapov, G. K. Sterligov, A. F. Asachenko, M. V. Bermeshev and M. S. Nechaev, *Mendeleev Commun.*, 2018, **28**, 323.
- (a) H. Ji, J. Cai, N. Gan, Z. Wang, L. Wu, G. Li and T. Yi, *Chem. Cent. J.*, 2018, **12**, 136; (b) J. Dong, H. Guo and Q.-S. Hu, *Eur. J. Org. Chem.*, 2017, 7087.
- (a) G. Yan, D. Huang and X. Wu, *Adv. Synth. Catal.*, 2018, **360**, 1040; (b) X. Qi, L.-B. Jiang, C. Zhou, J.-B. Peng and X.-F. Wu, *ChemistryOpen*, 2017, **6**, 345; (c) Y. Cheng, C. Mück-Lichtenfeld and A. Studer, *Angew. Chem. Int. Ed.*, 2018, **57**, 16832; (d) Y. Xu, X. Yang and H. Fang, *J. Org. Chem.*, 2018, **83**, 12831; (e) X. Qi, H.-P. Li, J.-B. Peng and X.-F. Wu, *Tetrahedron Lett.*, 2017, **58**, 3851.
- Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005.
- T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685.
- Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, eds. J. J. Li and G. Gribble, 2nd edn, Elsevier, Amsterdam, 2007.

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