Synthetic Methods

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Highly N^2-Selective Palladium-Catalyzed Arylation of 1,2,3-Triazoles**

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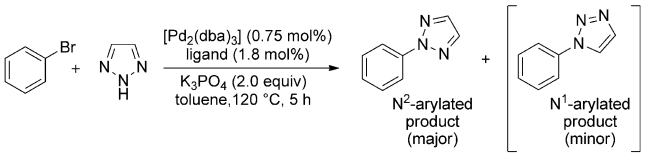
N-Substituted 1,2,3-triazoles have found widespread applications in material science and medicinal chemistry.[1,2] Because of the importance of this structural motif, many practical synthetic methods have been developed. Among them, the Huisgen azide–alkyne dipolar cycloaddition (AAC) is perhaps the most commonly utilized method for the synthesis of N^1-substituted 1,2,3-triazoles.[3] In particular, recent developments in copper-[4] and ruthenium-catalyzed[5] AAC reactions have provided a general and regioselective access to 1,4- and 1,5-substituted 1,2,3-triazoles, respectively. In contrast, regioselective synthesis of N^2-substituted 1,2,3-triazoles remains a challenging issue. A particularly interesting subset of these compounds are N^2-aryl-1,2,3-triazoles, which are found in biologically active compounds including an orexin receptor antagonist (MK4305),[2a,b] JAK kinase inhibitors,[2c] and 2,3-oxidosqualene cyclase inhibitors.[2d] Ideally, the most direct route to N^2-aryl-1,2,3-triazoles involves N arylation of 1,2,3-triazoles.[2a–c,6,7] However, S_NAr and copper-catalyzed arylation reactions of simple 1,2,3-triazoles generally give mixtures of regioisomers with poor to moderate N^2 selectivity.[8] Recently, Shi and co-workers[9] and Wang and co-workers[10] reported the highly N^2-selective S_NAr and copper-catalyzed arylation reactions using 4,5-disubstituted 1,2,3-triazoles, where C^4- and C^5-substituents prevent substitution on the N^1- and N^3-position by steric hindrance.[11] Despite these advances, a highly (>90%) N^2-selective arylation method of 4-substituted and 4,5-unsubstituted 1,2,3-triazoles is still lacking. Herein, we report that exceptional levels of N^2 selectivity can be obtained in the palladium-catalyzed N arylation of simple 1,2,3-triazoles by the use of the very bulky biaryl phosphine ligand **L1**. This method enabled the first highly N^2-selective arylation of 4-substituted and 4,5-unsubstituted 1,2,3-triazoles with aryl bromides, chlorides, and triflates.

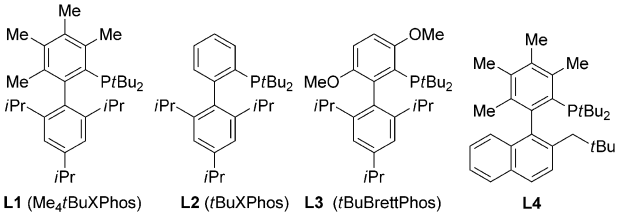
We initiated our study by examining the N arylation of 1,2,3-triazole with bromobenzene in the presence of [Pd_2(dba)$_3$] (0.75 mol%) with a series of biaryl phosphine ligands (**L1**–**L4**; 1.8 mol%). Gratifyingly, the palladium-catalyzed reaction of 1,2,3-triazole using **L1** furnished the N^2-arylated product in 90% yield with excellent N^2 selectivity (N^2/N^1 = 97:3; Table 1, entry 1).[12] To the best of our knowledge, this is the first palladium-catalyzed and highly N^2-selective arylation of 4,5-unsubstituted 1,2,3-triazoles. It was important to preheat a solution of [Pd_2(dba)$_3$] and **L1** before they were exposed to the 1,2,3-triazole, bromobenzene, and K_3PO_4. The reaction was significantly less efficient without catalyst preheating (entry 2), which is presumably a result of the inhibitory effect of 1,2,3-triazole on the in situ formation of the catalytically active Pd^0/ligand complex. The use of less sterically hindered biaryl phosphines **L2**–**L4** provided, at best, a 16% yield of the N-arylated product (entries 3–5). These low yields suggest that the nature of the both upper-ring substituents and lower-ring isopropyl groups of **L1** are crucial to the present catalyst system.

Table 1: Ligand effects on the palladium-catalyzed N arylation of 1,2,3-triazole.[a]



Entry	Ligand	Conversion [%][b]	Yield of N^2-arylated product [%][b]	N^2/N^1[c]
1	**L1**	100	93 (90)[d]	97:3
2[e]	**L1**	9	7	n.d.
3	**L2**	<5	<5	n.d.
4	**L3**	20	<16	96:4
5	**L4**	<5	<5	n.d.

[a] Reaction conditions: bromobenzene (1 mmol), 1,2,3-triazole (1.2 mmol), K_3PO_4 (2 mmol), [Pd_2(dba)$_3$] (0.75 mol%), ligand (1.8 mol%), toluene (1 mL), 120°C, 5 h. [Pd_2(dba)$_3$] and ligand were premixed in toluene (0.5 mL) at 120°C for 3 min. [b] Determined by GC analysis of crude reaction mixture. [c] N^2 to N^1 ratio was determined by GC analysis. [d] Yield of the isolated product. [e] Reaction was performed without premixing [Pd_2(dba)$_3$] and **L1**. dba = dibeynzylideneacetone, n.d. = not determined.



We also examined the substrate scope of the N arylation of 1,2,3-triazole (Table 2). A variety of aryl bromides, chlorides, and triflates with ester, ketone, aldehyde, acetal, nitro, and cyano groups could be employed in the N-arylation reactions. While slightly decreased N^2 selectivity was observed for the reactions of aryl chlorides with *para*-electron-withdrawing groups (entries 9 and 10), excellent N^2 selectivity (>95% N^2 selective) was observed in all other substrates examined.

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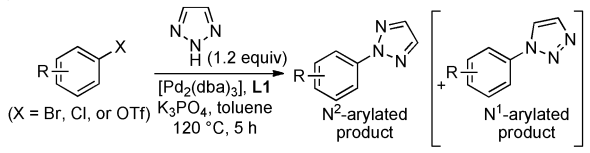
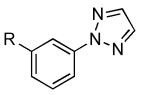
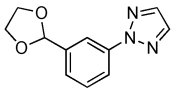
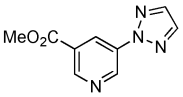
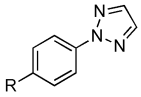
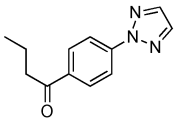
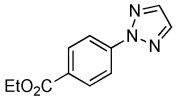
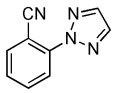
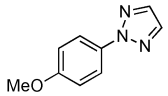
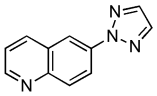
Table 2: Substrate scope of N^2-selective arylation of 4,5-unsubstituted 1,2,3-triazole.[a]



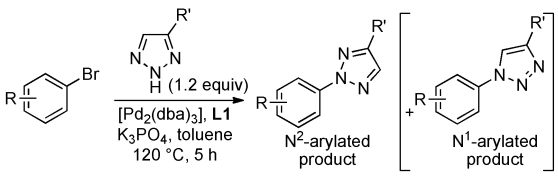
Entry	Major product			Pd [mol%]	Yield [%][b]	N^2/N^1[c]
1		R = CN	X = Br	1.0	89	97:3
2		R = OBn	X = Br	1.0	90	99:1
3		R = NO_2	X = Br	0.5	87	98:2
4		R = Cl	X = Br	0.5	91	97:3
5		–	X = Br	1.0	87	97:3
6		–	X = Br	1.0	83	97:3
7		R = CHO	X = Br	1.0	79	97:3
8		R = Cy	X = Br	1.5	78	96:4
9		–	X = Cl	0.5	84	95:5
10		–	X = Cl	0.7	83	95:5
11		–	X = Cl	2.0	46	99:1
12		–	X = OTf	1.5	90	98:2
13		–	X = OTf	0.5	91	98:2

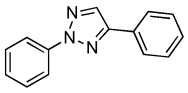
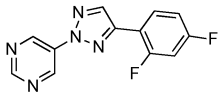
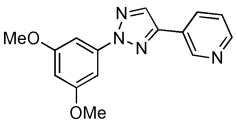
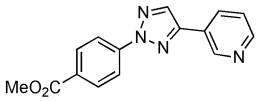
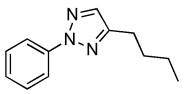
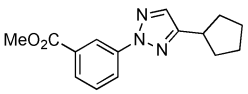
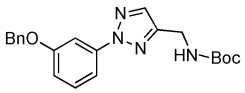
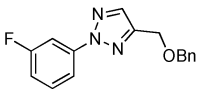
[a] Reaction conditions: ArX (1 mmol), 1,2,3-triazole (1.2 mmol), K_3PO_4 (2 mmol), $[Pd_2(dba)_3]$ (0.25–0.75 mol%), **L1** (0.5–1.8 mol%), toluene (1 mL), 120°C, 5 h. [b] Yields are those for the isolated N^2-arylated product (average of two runs). [c] Determined by GC analysis of the crude reaction mixture. Cy = cyclohexyl, Tf = trifluoromethanesulfonyl.

The yield was diminished when the aryl halide bearing an *ortho* substituent was employed (entry 11), probably because of unfavorable steric interactions between the bulky ligand and the *ortho* substituent (entry 11). Lower (0.3–0.7 mol%) palladium loadings could be employed for the electron-deficient aryl halides and triflate (entries 3, 4, 9, 10, and 13).

To expand the generality of this process, we examined the N arylation of 4-substituted 1,2,3-triazoles (Table 3). The N arylation of 4-phenyl-1,2,3-triazole with bromobenzene gave excellent N^2/N^1 selectivity; the N^3-arylated product was not detected by GC/MS or ^1H NMR analysis of the crude reaction mixture (entry 1). Similarly, N arylation of other

Table 3: Substrate scope of N^2-selective arylation of 4-substituted 1,2,3-triazoles.[a]



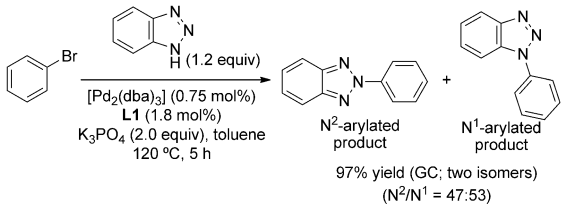
Entry	Major product	Pd [mol%]	Yield [%][b]	N^2/N^1[c]
1		1.5	90	97:3
2		1.0	90	98:2
3		1.5	86	98:2
4		0.5	85	96:4
5		1.5	91	98:2
6		1.0	93	99:1
7		1.5	91	99:1
8		1.5	94	99:1

[a] Reaction conditions: ArX (1 mmol), 4-substituted 1,2,3-triazole (1.2 mmol), K_3PO_4 (2 mmol), $[Pd_2(dba)_3]$ (0.5–0.75 mol%), **L1** (1.0–1.8 mol%), toluene (1 mL), 120°C, 5 h. [b] Yields are of the isolated N^2-arylated product (average of two runs). [c] Determined by GC analysis of the crude reaction mixture. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

4-aryl-substituted 1,2,3-triazoles gave products with 98% N^2 selectivity (entries 2–3). These N^2 selectivities are higher than those reported for copper-catalyzed N arylations ($N^2/N^1 = 4:1$) and S_NAr reactions ($N^2/N^1 = 1.6:1$) of 4-aryl-1,2,3-triazoles.[7a] Reactions of primary alkyl, functionalized primary-alkyl- and secondary-alkyl-substituted 1,2,3-triazoles also showed excellent N^2 selectivities (entries 4–7).

While excellent N^2 selectivity was observed for the reactions of 4,5-unsubstituted and 4-substituted 1,2,3-triazoles, we obtained a near 1:1 mixture of N^1- and N^2-aryl isomers for the reaction of benzotriazole with bromobenzene (Scheme 1).

To gain insight into the origin of regioselectivity, we performed DFT calculations of the presumed intermediates. For the N arylations of benzotriazole and 1,2,3-triazole with bromobenzene, transmetallation of the triazolate to the [**L1**Pd(Ph)(Br)] complex could provide tautomeric species



Scheme 1. Palladium-catalyzed N arylation of benzotriazole.

A/ **A′**, and **B**/**B′**, respectively (Figure 1).[13–14] The relative energies of the key intermediates and the transition states (TSs) are shown in Figure 1. In the benzotriazole case, a small energetic preference ($\Delta G = 1.6$ kcal mol^{-1}) for the N^2-benzotriazolate complex **A** over the N^1-benzotriazolate **A′** was observed. Comparison of the two isomeric transition states for the reductive elimination from the benzotriazolate complexes **A** and **A′** showed that only an insignificant energetic preference existed between the **A**-TS and **A′**-TS ($\Delta\Delta G^{\ddagger} = 0.1$ kcal mol^{-1}). The poor regioselectivity (N^2/N^1 = 47:53) observed for the benzotriazole system can be explained by the close relative energies of the **A**-TS and **A′**-TS. In the 1,2,3-triazole system, the transition states for the reductive elimination (**B**-TS and **B′**-TS) are significantly different ($\Delta\Delta G^{\ddagger} = 3.3$ kcal mol^{-1}) in favor of the transition state leading to the N^2-arylated product, which is in agreement with the observed regioselectivity.

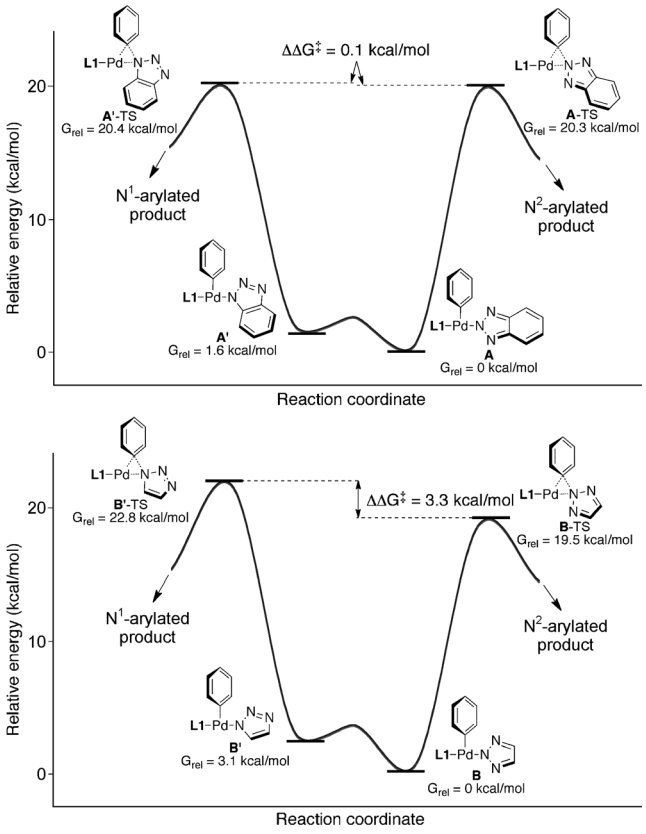


Figure 1. Energy diagrams for the reductive elimination of benzotriazolate/Pd and 1,2,3-triazolate/Pd complexes.

In summary, we have established a highly N^2-selective palladium-catalyzed arylation of 4,5-unsubstituted and 4-substituted 1,2,3-triazoles with aryl bromides, chlorides, and triflates. Theoretical calculations suggested that highly N^2-selective arylation of 1,2,3-triazoles is due to rapid reductive elimination from N^2-1,2,3-triazolate/Pd complex **B**. Together with the well-established copper- and ruthenium-catalyzed AAC, the present palladium-catalyzed system allows straightforward and regioselective preparation of N-aryl 1,2,3-triazoles.

Experimental Section

General procedure: An oven-dried vial was equipped with a magnetic stir bar and charged with [Pd$_2$(dba)$_3$] and **L1**. The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). Toluene (0.5 mL) was added to the vial via syringe. The resulting dark-purple mixture was stirred at 120 °C for 3 min, at this point the color of the mixture turned to dark brown. A second oven-dried vial, which was equipped with a stir bar, was charged with K_3PO_4 (424 mg, 2.0 mmol; aryl halides and 1,2,3-triazoles that were solid at room temperature were added at this point). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). The 1,2,3-triazole (1.2 mmol) and aryl halide (1.0 mmol) were then added via syringe, as well as the premixed catalyst solution and toluene (0.5 mL; total 1.0 mL toluene). The reaction mixture was heated at 120 °C for 5 h. The reaction was cooled to room temperature, diluted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel to give pure products.

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[1] Reviews for N^1-substituted 1,2,3-triazoles, see: a) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128–1137; b) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249–1262.

[2] Recent applications of N^2-aryl-1,2,3-triazoles, see: a) C. D. Cox, M. J. Breslin, D. B. Whitman, J. D. Schreier, G. B. McGaughey, M. J. Bogusky, A. J. Roecker, S. P. Mercer, R. A. Bednar, W. Lemaire, J. G. Bruno, D. R. Reiss, C. Meacham Harrell, K. L. Murphy, S. L. Garson, S. M. Doran, T. Prueksaritanont, W. B. Anderson, C. Tang, S. Roller, T. D. Cabalu, D. Cui, G. D. Hartman, S. D. Young, K. S. Koblan, C. J. Winrow, J. J. Renger, P. J. Coleman, *J. Med. Chem.* **2010**, *53*, 5320–5332; b) C. A. Baxter, E. Cleator, K. M. J. Brands, J. S. Edwards, R. A. Reamer, F. J. Sheen, G. W. Stewart, N. A. Strotman, D. J. Wallace, *Org. Process Res. Dev.* **2011**, *15*, 367–375; c) Z. J. Jia, C. Venkataramani, W. Huang, M. Mehrotra, Y. Song, Q. Xu, S. M. Bauer, A. Pandey, WO2009136995, **2009**; d) T. Watanabe, Y. Umezawa, Y. Takahashi, Y. Akamatsu, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5807–5810.

[3] R. Huisgen in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 1–176.

[4] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.

[5] a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998 – 15999; b) M. M. Majireck, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 8680 – 8683.

[6] M. Taillefer, N. Xia, A. Ouali, *Angew. Chem.* **2007**, *119*, 952 – 954; *Angew. Chem. Int. Ed.* **2007**, *46*, 934 – 936.

[7] For synthesis of 2-aryl-1,2,3-triazoles by oxidative cyclization of bisphenylhydrazone, see: K. S. Balachandran, I. Hiryakkanavar, M. V. George, *Tetrahedron* **1975**, *31*, 1171 – 1177.

[8] $N^2/N^1 = 1$–4.3:1 was reported for the S_NAr and copper-catalyzed N arylation of 4-substituted and 4,5,-unsubstituted 1,2,3-triazole; see Ref. [2b], [2c], [6], and [7a].

[9] Y. Liu, W. Yan, Y. Chen, J. L. Petersen, X. Shi, *Org. Lett.* **2008**, *10*, 5389 – 5392.

[10] X.-J. Wang, L. Zhang, H. Lee, N. Haddad, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2009**, *11*, 5026 – 5028.

[11] For N^2-selective alkylation of 4,5-disubstituted 1,2,3-triazoles, see: a) Y. Chen, Y. Liu, J. L. Petersen, X. Shi, *Chem. Commun.* **2008**, 3254 – 3256; b) X.-J. Wang, K. Sidhu, L. Zhang, S. Campbell, N. Haddad, D. C. Reeves, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2009**, *11*, 5490 – 5493; c) X.-J. Wang, L. Zhang, D. Krishnamurthy, C. H. Senanayake, P. Wipf, *Org. Lett.* **2009**, *11*, 4632 – 4635; for N^2-selective allylation of 4-substituted 1,2,3-triazoles, see: d) S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 7786 – 7787; e) S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 2386 – 2393; for N^2-selective hydroxymethylation of 4-substituted 1,2,3-triazoles, see: J. Kalisiak, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2008**, *10*, 3171 – 3174.

[12] C-Arylated products were not observed under these conditions. For C arylation of N^1-substituted 1,2,3-triazoles, see: S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333 – 2336.

[13] Since 1,2,3-triazole has a pK_a value of 9.26, it could be deprotonated in the presence K_3PO_4. L. D. Hansen, B. D. West, E. J. Baca, C. L. Blank, *J. Am. Chem. Soc.* **1968**, *90*, 6588 – 6592.

[14] The possibility that the triazolate first binds to the Pd^0/**L1** complex followed by oxidative addition of PhBr to produce **A**/**A′** and **B**/**B′** cannot be ruled out.

