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

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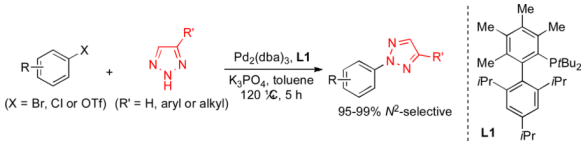
Abstract



Highly N^2-selective arylation of 4,5-unsubstituted and 4-substituted 1,2,3-triazoles was achieved for the first time by Pd/**L1** catalyst system. A wide range of N^2-aryl-1,2,3-triazoles were prepared from aryl bromides, chlorides and triflates with excellent (95–99%) N^2-selectivity. DFT calculations suggest that formation of N^2-arylated 1,2,3-triazoles is favored kinetically.

Keywords

palladium; homogeneous catalysis; C-N coupling; 1,2,3-triazole; *N*-arylation

N-Substituted-1,2,3-triazoles have found widespread applications in material science and medicinal chemistry.[1–2] Due to 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 Cu-[4] and Ru-catalyzed[5] AAC reactions have provided a general and regioselective access to 1,4- and 1,5-substituted 1,2,3-triazoles, respectively. On the other hand, regioselective synthesis of N^2-substituted 1,2,3-triazoles remains a challenging issue. A particulary 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 Cu-catalyzed arylation reactions of simple 1,2,3-triazoles generally give mixtures of regioisomers with poor to moderate N^2-selectivity.[8] Recently, Shi[9] and Wang[10] reported

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

The substrate scope of the *N*-arylation of 1,2,3-triazole is shown in Scheme 1. 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. The yield was diminished when the aryl halide bearing an *ortho*-substituent was employed (46% yield, entry 11) probably due to unfavorable steric interaction between the bulky ligand and the *ortho*-substituent (entry 11). Lower (0.3–0.7 mol%) Pd 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 (Scheme 2). 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 ^{1}H NMR analysis of the crude reaction mixture (entry 1). Similarly, *N*-arylation of other 4-aryl-substituted 1,2,3-triazoles gave products with 98% N^2-selectivity (entries 2–3). These N^2-selectivity are higher than selectivity reported for Cu-catalyzed *N*-arylation (N^2:N^1=4:1) and S_NAr reaction (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-triazole also showed excellent N^2-selectivities (entries 4–7, 98–99% N^2-selective).

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

In order to gain insight into the origin of regioselectivity, we performed DFT calculation 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 **A/A'** and **B/B'** respectively.[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 (ΔG = 1.6 kcal/mol) 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 only an insignificant energetic preference exist between the **A**-TS and **A'**-TS ($\Delta\Delta G^{\ddagger}$ = 0.1 kcal/mol). 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) in favor of the transition state leading to the N^2-arylated product, which is in agreement with the observed regioselectivity.

In summary, we have established a highly N^2-selective Pd-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 Cu- and Ru-catalyzed AAC, present Pd-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) and then 1,2,3-triazole (1.2 mmol) and aryl halide (1.0 mmol) were added via syringe and the premixed catalyst solution and toluene (0.5 mL) was added by syringe to the second vial (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 via flash chromatography to give pure products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Brands KMJ, Edwards JS, Reamer RA, Sheen FJ, Stewart GW, Strotman NA, Wallace DJ. Org. Process Res. Dev. 2011; 15:367–375. Jia ZJ, Venkataramani C, Huang W, Mehrotra M, Song Y, Xu Q, Bauer SM, Pandey A. WO2009136995. 2009 Watanabe T, Umezawa Y, Takahashi Y, Akamatsu Y. Bioorg. Med. Chem. Lett. 2010; 20:5807–5810. [PubMed: 20728352] .

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12. *C*-Arylated products were not observed under these conditions. For *C*-arylation of N^1-substituted 1,2,3-triazoles, see; Chuprakov S, Chernyak N, Dudnik AS, Gevorgyan V. Org. Lett. 2007; 9:2333–2336. [PubMed: 17489598] .
13. Since 1,2,3-triazole has a pKa of 9.26, it could be deprotonated in the presence K_3PO_4. Hansen LD, West BD, Baca EJ, Blank CL. 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.

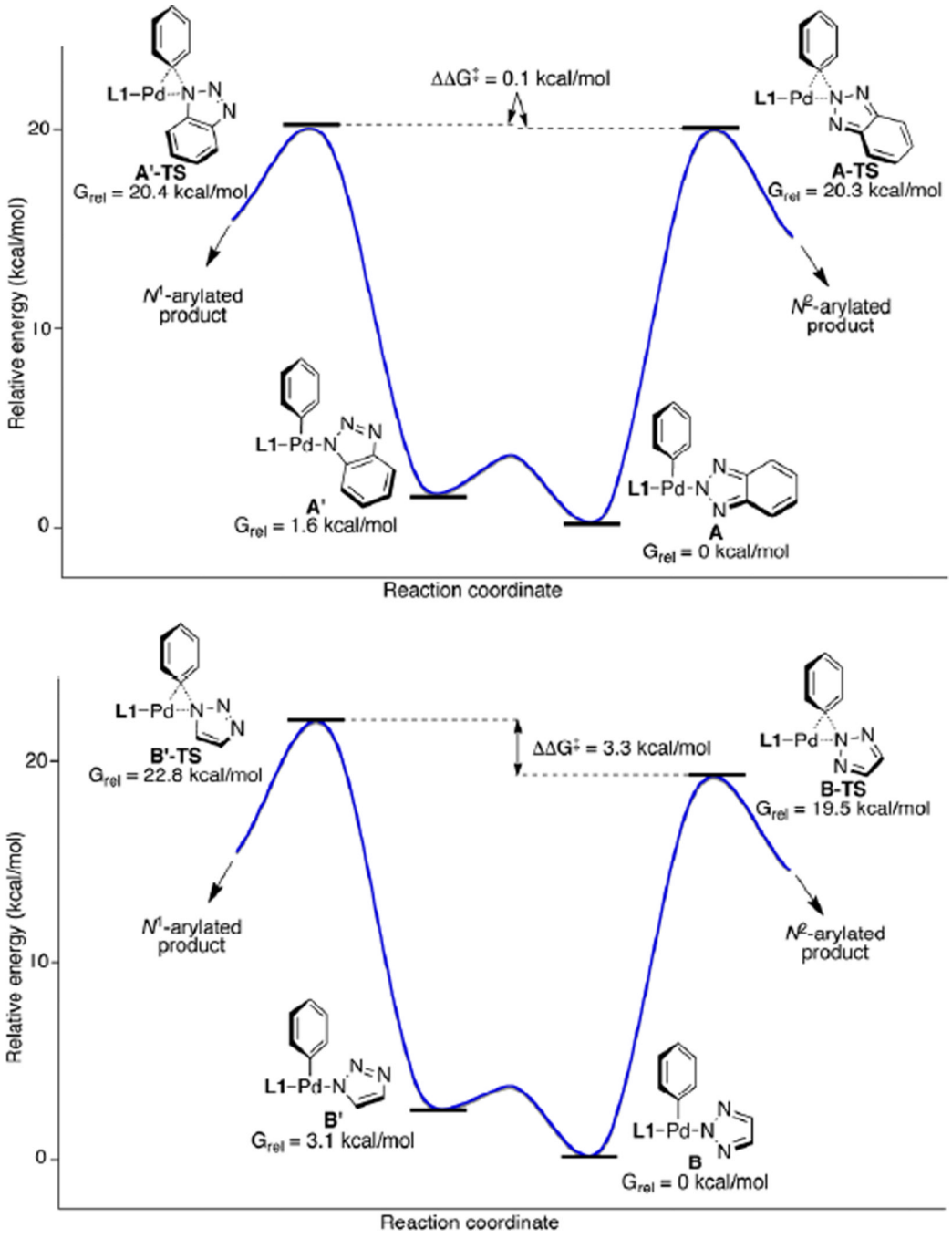
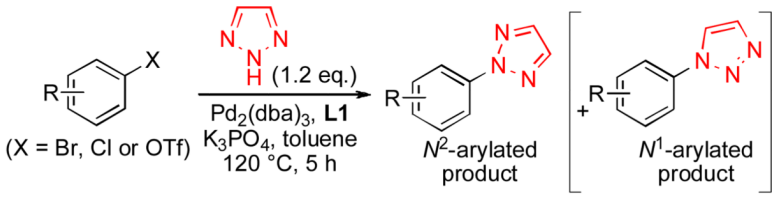


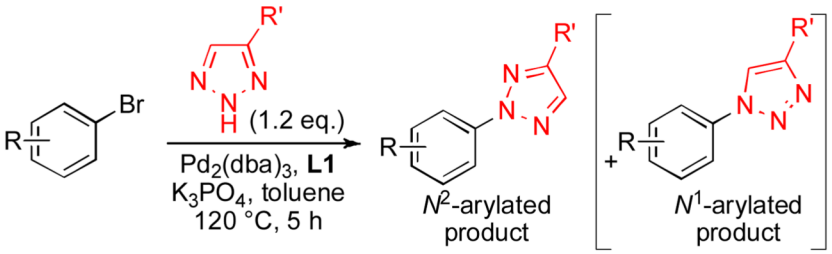
Figure 1.
Energy diagrams for the reductive elimination of benzotriazolate-Pd and 1,2,3-triazolate-Pd complexes

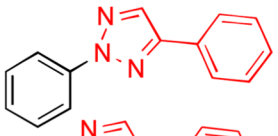
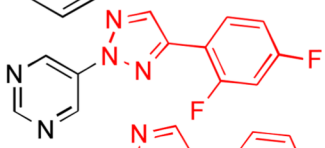
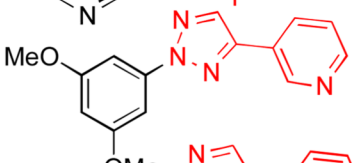
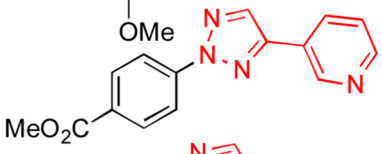
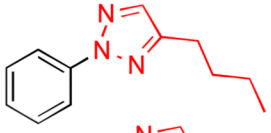
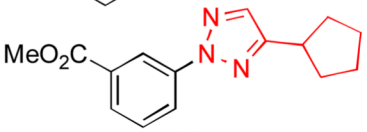
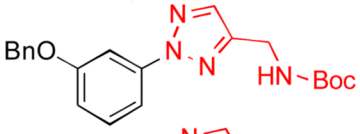
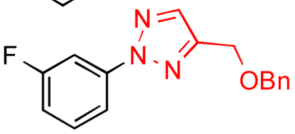


entry	major product	Pd (mol%)	yield (%)	N^2:N^1 [a]
1	R = CN	1.0	89	97:3
2	R = OBn	1.0	90	99:1
3	R = NO_2	0.5	87	98:2
4	R = Cl	0.5	91	97:3
5	(X = Br)	1.0	87	97:3
6	(X = Br)	1.0	83	97:3
7	R = CHO	1.0	79	97:3
8	R = Cy	1.5	78	96:4
9	(X = Br)	0.5	84	95:5
10	(X = Cl)	0.7	83	95:5
11	(X = Cl)	2.0	46	99:1
12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

Scheme 1.

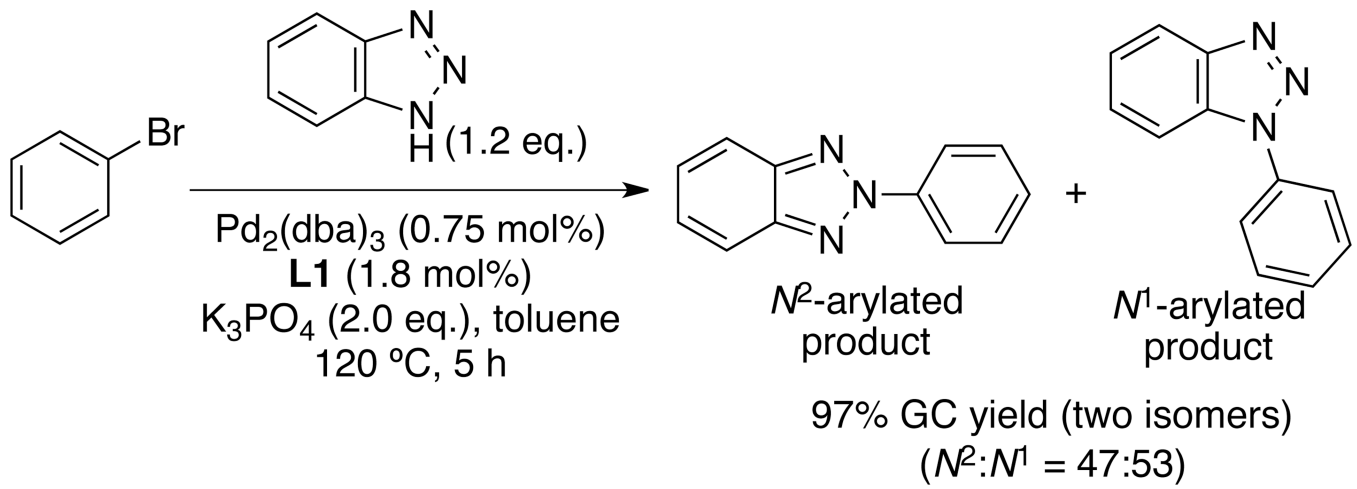
Substrate scope of N^2-selective arylation of 4,5-unsubstituted 1,2,3-triazole; Ar-X (1 mmol), 1,2,3-triazole (1.2 mmol), K_3PO_4 (2 mmol), $Pd_2(dba)_3$ (0.25–0.75 mol%), **L1** (0.5–1.8 mol %), toluene (1 mL), 120 °C, 5 h. Yields are isolated yield of N^2-arylated product (average of two runs). [a] Determined by GC analysis.



entry	major product	Pd (mol%)	yield (%)	N^2:N^1 [a]
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

Scheme 2.

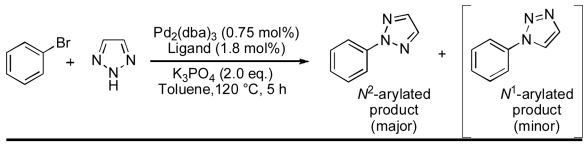
Substrate scope of N^2-selective arylation of 4-substituted 1,2,3-triazoles; Ar-X (1 mmol), 4-substituted 1,2,3-triazole (1.2 mmol), K_3PO_4 (2 mmol), $Pd_2(dba)_3$ (0.5–0.75 mol%), **L1** (1.0–1.8 mol%), toluene (1 mL), 120 °C, 5 h. Yields are isolated yield of N^2-arylated product (average of two runs). [a] Determined by GC analysis.



Scheme 3.
Pd-catalyzed *N*-arylation of benzotriazole

Table 1

Ligand effects on the Pd-catalyzed *N*-arylation of 1,2,3-triazole [a]



entry	ligand	GC conv. (%)	GC yield of N^2-arylated product (%)	N^2:N^1 [b]
1	**L1**	100	93 (90)[c]	97:3
2[d]	**L1**	9	7	N.D. [e]
3	**L2**	<5	<5	N.D.
4	**L3**	20	16	96:4
5	**L4**	<5	<5	N.D.

[a] 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] N^2-N^1 ratio was determined by GC.

[c] Isolated yield.

[d] Reaction was performed without premixing $Pd_2(dba)_3$ and **L1**.

[e] Not determined.