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Direct Pd-Catalyzed Arylation of 1,2,3-Triazoles†

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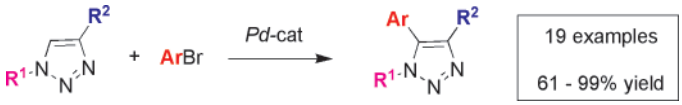
ABSTRACT



A highly efficient method for the synthesis of multisubstituted 1,2,3-triazoles via a direct Pd-catalyzed C-5 arylation has been developed.

1,2,3-Triazoles, due to their unique chemical and structural properties, have received much attention over the past decades and found wide application in medicinal chemistry and material science.[1] The importance of 1,2,3-triazoles has resulted in the development of several synthetic methods for their construction.[2] One of the most important and useful approaches to the synthesis of 1,2,3-triazoles utilizes Huisgen's 1,3-dipolar [3+2]-cycloaddition of azides and alkynes.[3] However, this methodology, in most cases, leads to the formation of a mixture of regioisomeric products and requires the presence of a strong electron-withdrawing substitutent at the alkyne.[1a,4] Recently, Fokin and Sharpless reported Cu(I)-catalyzed regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles,[5] and later, in collaboration with Jia, the Ru(II)-catalyzed approach toward complimentary regioisomers, the 1,5-disubstituted 1,2,3-triazoles.[6]

Known methods for the regioselective synthesis of fully substituted 1,2,3-triazoles include reactions of azides with active methylene compounds[7] or bromo-magnesium acetylides, with subsequent addition of electrophile;[8] metalation of the existing triazole ring followed by reaction with electrophile;[9] and cross-coupling reactions of 5-halo-1,2,3-triazoles.[10] However, these methods have certain limitations, as they require employment of organometallic reagents or halotriazoles. An alternative approach may involve direct transition metal-catalyzed arylation and heteroarylation, which has been recently shown to be a powerful synthetic tool for functionalization of aromatic heterocycles.[11] Recently, Daugulis demonstrated an efficient Pd-catalyzed

† Dedicated to Prof. Ivars Kalvins on occasion of his 60th birthday.

(1) (a) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, UK, 1996; Vol. 4, pp 1−126. (b) Whiting, M.; Muldoon, J.; Lin, Y.-C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1435. (c) Bourne, Y.; Kolb, H. C.; Radić, Z.; Sharpless, K. B.; Taylor, P.; Marchot, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 1449. (d) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radić, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053. (e) Alvarez, R.; Velazques, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlesson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.

(2) For recent reviews, see: (a) Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339. (b) Tome, A. C. Product class 13: 1,2,3-triazoles. In *Science of Synthesis*; Stor, R., Gilchrist, T., Eds.; Thieme: New York, 2004; Vol. 13, pp 415−601.

(3) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176.

(4) (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 4, pp 1069−1109.

(5) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) See also: Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(6) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

(7) L'Abbè, G. *Ind. Chim. Belge* **1969**, *34*, 519 and references therein.

(8) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237.

(9) (a) Holzer, W.; Ruso, K. *J. Heterocycl. Chem.* **1992**, *29*, 1203. (b) Ohta, S.; Kawasaki, I.; Uemura, T.; Yamashita, M.; Yoshioka, T.; Yamaguchi, S. *Chem. Pharm. Bull.* **1997**, *45*, 1140. (c) Uhlmann, P.; Felding, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1997**, *62*, 9177. (d) Felding, J.; Uhlmann, P.; Kristensen, J.; Vedsø, P.; Begtrup, M. *Synthesis* **1998**, 1181.

(10) Deng, J.; Wu, Y.-M.; Chen, Q.-Y. *Synthesis* **2005**, 2730.

(11) For recent reviews, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, DOI: 10.1039/b606984n. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

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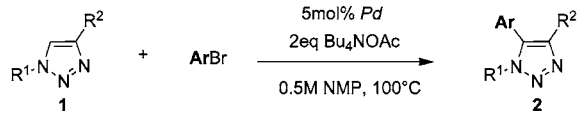
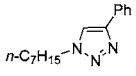
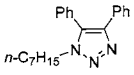
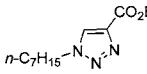
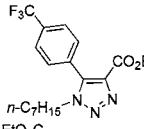
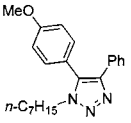
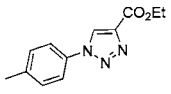
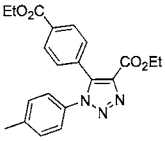
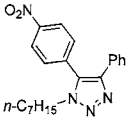
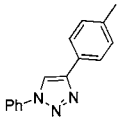
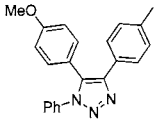
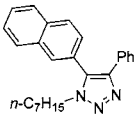
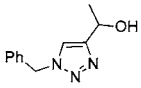
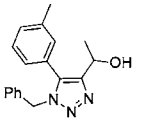
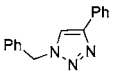
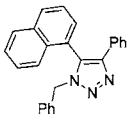
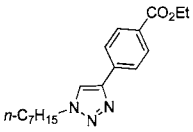
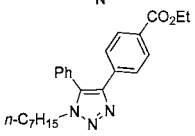
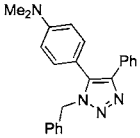
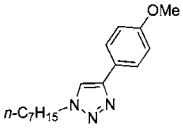
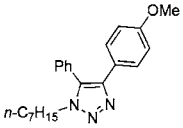
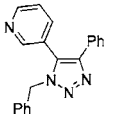
Table 1. C-5 Arylation of 1,4-Disubstituted 1,2,3-Triazoles



#	Triazole		Time, h	Product		Yield, %[a]	#	Triazole		Time, h	Product		Yield, %[a]
1		**1a**	2		**2a**	96[b]	8		**1c**	10		**2h**	78[d]
2	〃	〃	2		**2b**	97[b]	9		**1d**	6		**2i**	84[c]
3	〃	〃	18		**2c**	74[b]	10		**1e**	18		**2j**	90[b]
4	〃	〃	3		**2d**	>99[c]	11		**1f**	24		**2k**	61[c]
5		**1b**	3		**2e**	66[c]	12		**1g**	24		**2l**	81[b]
6	〃	〃	10		**2f**	90[c]	13		**1h**	24		**2m**	89[b]
7	〃	〃	10		**2g**	77[d]							

[a] Isolated yield; 0.5 mmol scale. [b] $Pd(PPh_3)_2Cl_2$ was used as the catalyst. [c] $Pd(OAc)_2$ was used as the catalyst. [d] $Pd_2(dba)_3 \cdot CHCl_3$ was used as the catalyst.

arylation of 1,2,4-triazole.[12] However, to the best of our knowledge, arylation of 1,2,3-triazoles has not been reported to date.[13]

Motivated by the importance of developing new general methods toward multisubstituted 1,2,3-triazoles, we examined the feasibility of a direct Pd-catalyzed arylation reaction with aryl bromides: a method proved efficient in the highly regioselective C-3 arylation of indolizines.[14] It was found that C-5 arylation of 1,4-disubstituted 1,2,3-triazoles **1a**−**h** in the presence of Pd catalyst and tetrabutylammonium acetate in NMP proceeded smoothly to provide C-5 arylated triazoles **2a**−**m** in good to excellent yields (Table 1).[15] It was found that this methodology allows for efficient introduction of both electron-deficient and electron-rich aryl groups at the C-5 position of a triazole ring. Thus, a variety of 1,4-disubstituted 1,2,3-triazoles, containing electron-withdrawing aryl- (entry 12) or carbethoxy groups (entries 8 and 9), electron-donating aryl groups (entries 10 and 13), as well as secondary aliphatic alcohol (entry 11), at the C-4 position and alkyl, aryl, and benzyl groups at nitrogen, were shown to undergo C-5 arylation successfully. It was also demonstrated that a variety of functional groups such as methoxy (entries 2, 10, and 13), carbethoxy (entries 8, 9, and 12), nitro (entry 3), hydroxy (entry 11), *N*,*N*-dialkylamino (entry 6), and trifluoromethyl (entry 8) were perfectly tolerated under these reaction conditions. Notably, aryl bromides bearing 2-naphthyl (entry 4), bulky 1-naphthyl

(12) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.

(13) For intramolecular Heck-type vinylation of 1,2,3-triazole, see: Chen, W.-L.; Su, C.-L.; Huang, X. *Synlett* **2006**, 1446.

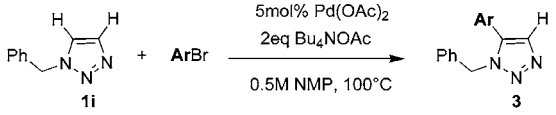
(14) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.

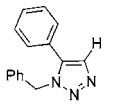
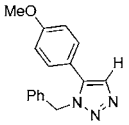
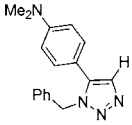
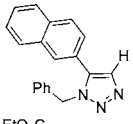
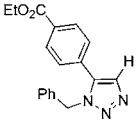
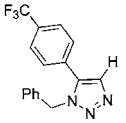
(15) Notably, we did not observe triazole-directed arylation of *N*-aryl or *N*-benzyl substitutents under these reaction conditions. For amide- and heterocycle-directed arylation of arenes via C−H activation, see, for example: (a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (b) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

(entry 5), and *m*-tolyl (entry 11) groups and an electron-deficient heteroaromatic 3-pyridyl moiety (entry 7) can also be employed in this reaction.

Encouraged by these results, we next examined the arylation of the 4,5-unsubstituted 1,2,3-triazole core. To our delight, a direct Pd-catalyzed arylation of *N*-monosubstituted triazole **1i** with phenyl bromide proceeded highly regioselectively producing C-5 arylated triazole **3a** as a single regioisomer[16] (entry 1, Table 2). Although 1,5-disubstituted

Table 2. Regioselective C-5 Arylation of 1-Benzyl-1,2,3-triazole



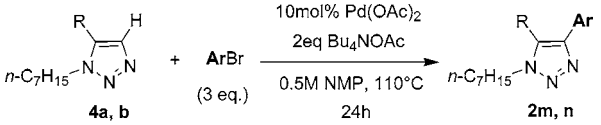
#	ArBr	Product		Yield, %[a]
1	Ph		**3a**	80[b]
2	MeO–Br		**3b**	71[b]
3	Me_2N–Br		**3c**	83
4	Br		**3d**	77[b]
5	EtO_2C–Br		**3e**	64
6	F_3C–Br		**3f**	67

[a] Isolated yield; 0.5 mmol scale. [b] A trace amount of bisarylated product was detected by GC/MS analysis of the crude reaction mixture.

1,2,3-triazoles can be accessed regioselectively from organic azides and terminal acetylenes[6] or bromomagnesium acetylides,[8] only syntheses of 1,2,3-triazoles employing an electron-withdrawing or a simple phenyl group at alkyne were demonstrated by these methods. Thus, we were interested in the development of an alternative regioselective approach toward 1,5-disubstituted 1,2,3-triazoles with an orthogonal substitution pattern at C-5. Gratifyingly, we have found that C-5 arylation of *N*-monosubstituted 1,2,3-triazoles with aryl bromides bearing electron-donating functional groups such as methoxy (entry 2) and *N*,*N*-dialkylamino (entry 3) afforded triazoles **3b** and **3c** regioselectively in good yields. Moreover, this direct arylation approach allows for efficient and regioselective introduction of electron-withdrawing aryl substitutents at C-5 (entries 5−7), thus revealing good generality of this methodology and extending the scope of the existing methods toward 1,5-disubstituted 1,2,3-triazoles.

As shown above, only trace amounts, if any, of bisarylated products were detected in the arylation of 1-monosubstituted triazole **1i** (entries 1, 2, and 4, Table 2). To verify whether efficient C-4 arylation of 1,5-disubstituted 1,2,3-triazoles is possible, we examined arylation of triazoles **4a** and **4b** under standard conditions. It was found that arylation at C-4 is extremely sluggish compared to that for C-5, providing only moderate yields of products **2m** and **2n** even upon prolonged heating with 10 mol % of Pd catalyst and 3 equiv of aryl bromide (Scheme 1).

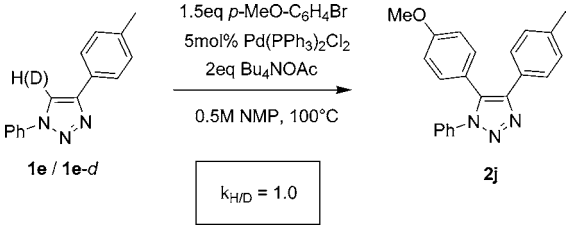
Scheme 1. C-4 Arylation of 1,5-Disubstituted 1,2,3-Triazoles



	R	Ar	
a	Ph	*n*-MeO-C_6H_4	36%
b	*n*-Bu	Ph	60%

Naturally, we were interested in elucidating the mechanism for this Pd-catalyzed arylation reaction. Thus, our kinetic isotope effect studies (Scheme 2) revealed no isotope effect

Scheme 2. Kinetic Isotope Effect Studies



($k_{H/D}$ = 1.0). Additionally, no deuterium scrambling for **1e**-*d* was observed under these reaction conditions. These data, in combination with the lack of an observed change in reaction rates in the presence of Cu-salts[17] and failure when performing reactions in the presence of hydride sources,[17] are not supportive for the possible involvement of C−H activation,[18] cross-coupling,[19] and Heck-type[20] mechanisms

(16) Fundamental differences in C-5 and C-4 reactivity of 1,2,3-triazoles are also observed during lithiation reactions. See, for example: (a) Grimmett, M. R.; Iddon, B. *Heterocycles* **1995**, *41*, 1525. (b) Raap, R. *Can. J. Chem.* **1971**, *49*, 1792. (c) Ghose, S.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 775.

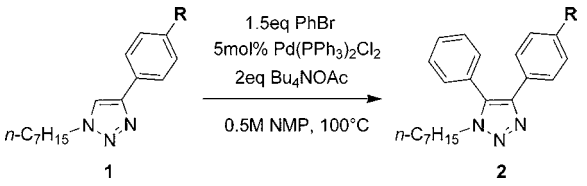
(17) See the Supporting Information for details.

(18) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

(19) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

earlier proposed for arylation of certain heterocycles.[21] The observed higher reactivity in arylation of electron-rich triazole **1h** during competitive kinetic studies provided certain support for an electrophilic mechanism for this reaction (Table 3).[22,23]

Table 3. Kinetic Studies



	R	k_R/k_H
h	MeO	1.3
a	H	1.0
g	CO_2Et	1.0

Finally, we performed DFT calculations (B3LYP/6-311+G**) of electrostatic potential charges at C-4 and C-5 positions of model triazole **5** (Figure 1). Development of substantial negative charge at C-5 and positive charge at C-4 in **5** provided additional support for an electrophilic mechanism and explained the origins of the observed high regioselectivity in the C-5 arylation of *N*-monosubstituted 1,2,3-triazoles as well as deminished reactivity in C-4 arylation (Scheme 1). It is believed that the combination of

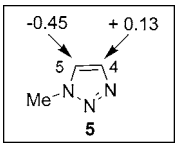
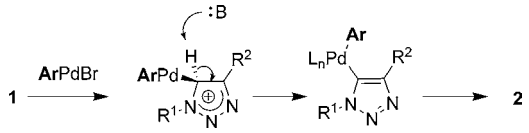


Figure 1. Electrostatic potential charges at C-4 and C-5.

experimental and computational data presented above strongly supports involvement of an electrophilic mechanism[22] as the most probable pathway for the Pd-catalyzed C-5 arylation of 1,2,3-triazoles (Scheme 3).

Scheme 3. Proposed Mechanism for Arylation of 1,2,3-Triazoles



In summary, we have shown that a variety of unsymmetrically substituted 1,2,3-triazoles can be easily synthesized via a direct Pd-catalyzed arylation of 1,4-disubstituted triazoles, compounds readily accessible via "click" chemistry. We have also found that 1,5-disubstituted 1,2,3-triazoles can be efficiently synthesized via a highly regioselective C-5 arylation of *N*-monosubstituted triazoles. Experimental and computational studies strongly support the electrophilic nature for this transformation.

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Supporting Information Available: Preparative procedures and analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070697U

(20) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. *Org. Lett.* **2003**, *5*, 301.

(21) For a detailed discussion of these mechanisms, see refs 11a and 14. See also: Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

(22) For a discussion on the electrophilic mechanism in the arylation of heterocycles, see refs 19, 21, and 12.

(23) Although nearly equal reactivity of **1a** vs **1g** is not clearly understood, a similar trend was observed in cationic Heck reactions in the styrene series (k_{rel} *p*-OMe:H:*p*-CO_2Me = 1.21:1.00:0.96), see: Fristrup, P.; Le Quement, S.; Tanner, D.; Norrby, P.-O. *Organometallics* **2004**, *23*, 6160.