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

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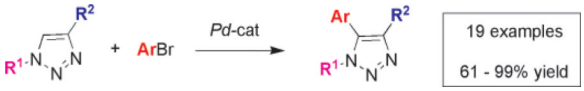
Abstract



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 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

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

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.

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 (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 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).

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 ($k_{H/D}$ = 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 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]

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 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).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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

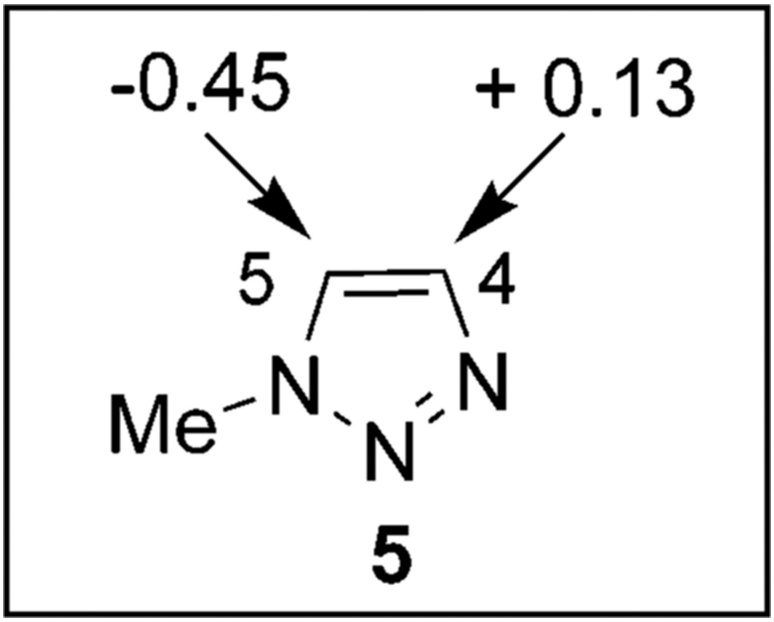
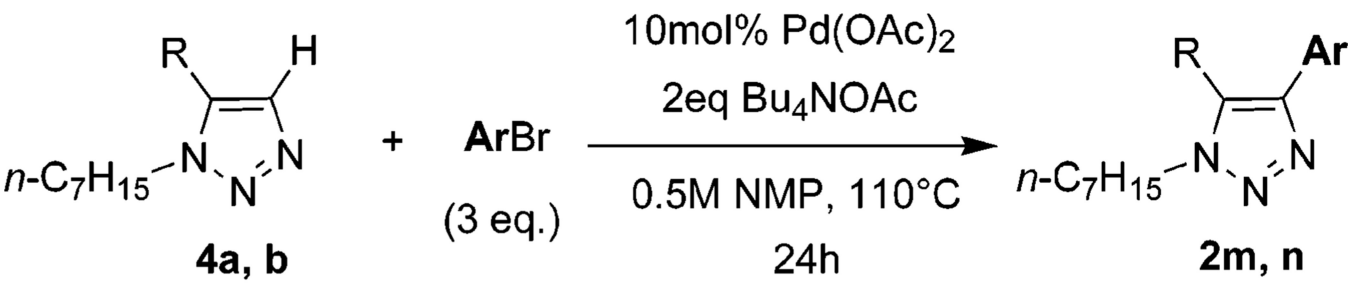
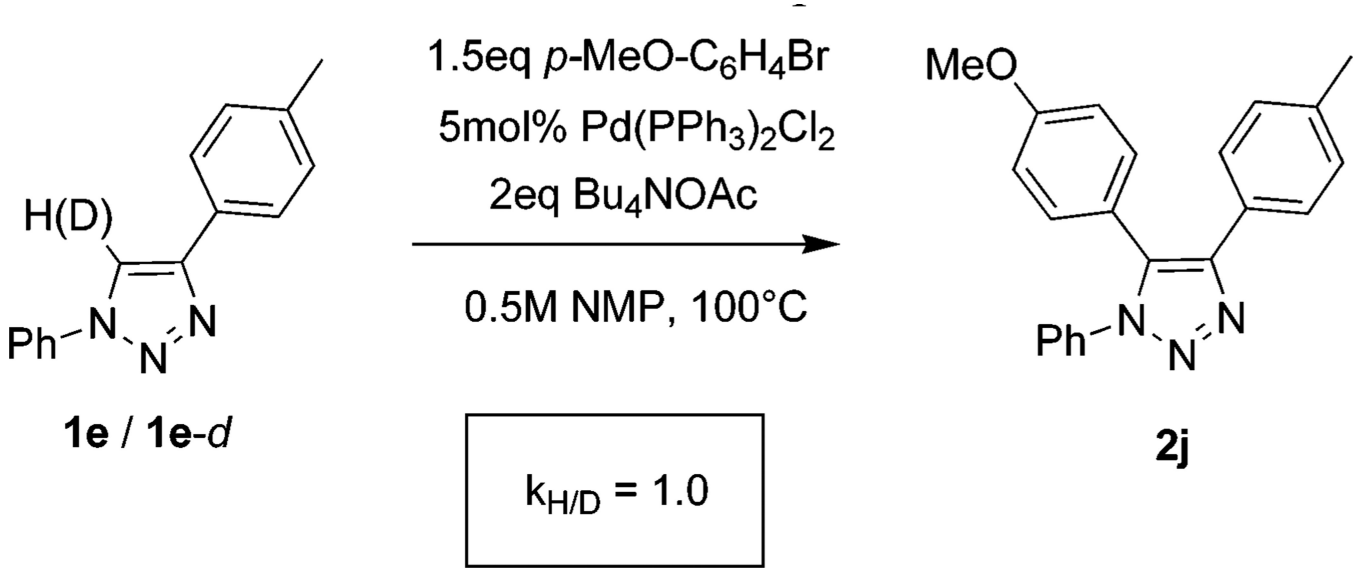


Figure 1.
Electrostatic potential charges at C-4 and C-5.

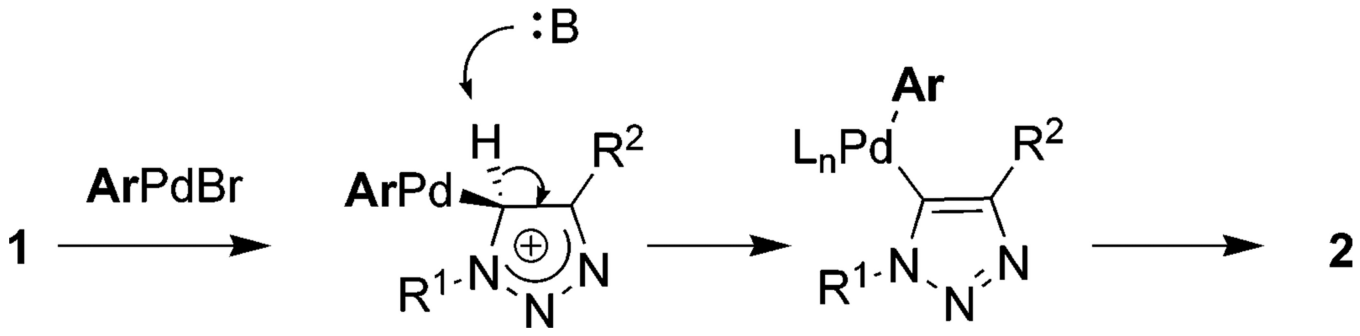


	R	Ar	
a	Ph	*n*-MeO-C_6H_4	36%
b	*n*-Bu	Ph	60%

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



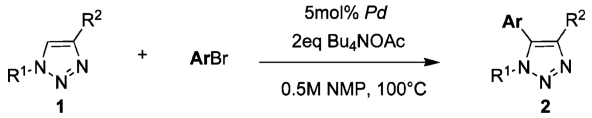
Scheme 2.
Kinetic Isotope Effect Studies

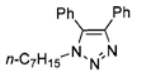
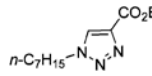
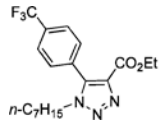
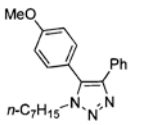
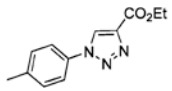
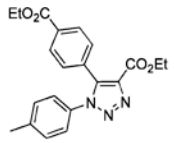
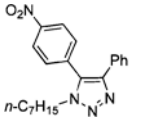
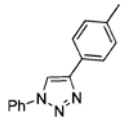
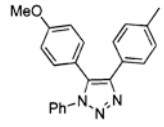
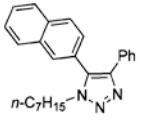
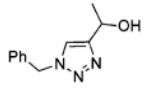
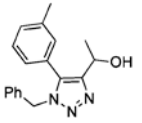
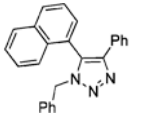
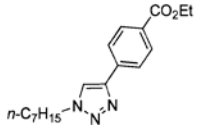
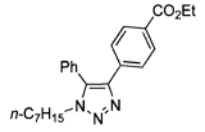


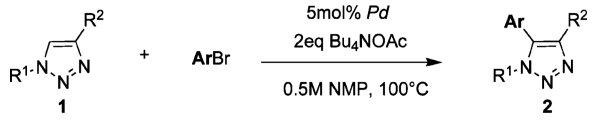
Scheme 3.
Proposed Mechanism for Arylation of 1,2,3-Triazoles

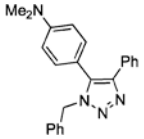
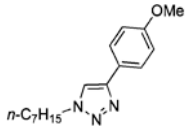
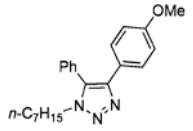
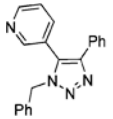
Table 1

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]



#	Triazole	Time, h	Product	Yield, %[a]	#	Triazole	Time, h	Product	Yield, %[a]
6	"	10	 **2f**	90 [c]	13	 **1h**	24	 **2m**	89 [b]
7	"	10	 **2g**	77 [d]					

[a] Isolated yield; 0.5 mmol scale.

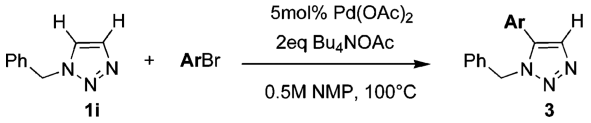
[b] $Pd(PPh_3)_2Cl_2$ was used as the catalyst.

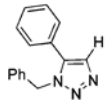
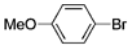
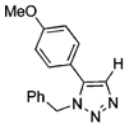
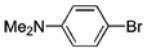
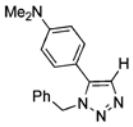
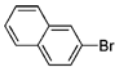
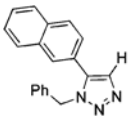
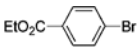
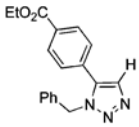
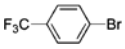
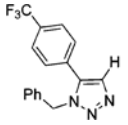
[c] $Pd(OAc)_2$ was used as the catalyst.

[d] $Pd_2(dba)_3{\cdot}CHCl_3$ was used as the catalyst.

Table 2

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



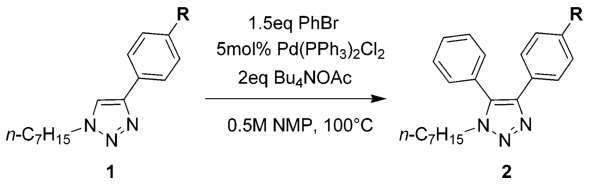
#	ArBr	Product		Yield, %[a]
1	Ph		**3a**	80[b]
2			**3b**	71 [b]
3			**3c**	83
4			**3d**	77[b]
5			**3e**	64
6			**3f**	67

[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.

Table 3

Kinetic Studies



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