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Pd-Catalyzed Regioselective Arylation on the C-5 Position of *N*-Aryl 1,2,3-Triazoles

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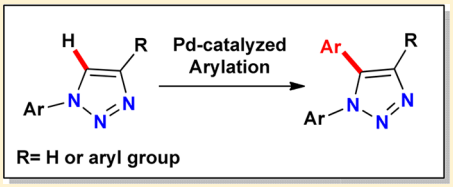
Supporting Information

ABSTRACT: We herein report a highly efficient method for the arylation at the C-5 position of *N*-aryl 1,2,3-triazoles via a direct palladium catalyzed arylation reaction. The optimal reaction conditions required a combination of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine as catalyst, and Cs_2CO_3 as the base under inert atmosphere. A variety of C-5 substituted *N*-aryl 1,2,3-triazoles were prepared using these conditions with yields in the 70−88% range. Regioselective C-5 arylations were also performed on 1,4-disubstituted 1,2,3-triazoles. The regioselectivity in triazole substitution at the C-5 position was confirmed by single crystal XRD. In addition, computational investigations of key steps of the catalytic cycle using the density functional theory have provided a rationalization to the selective C-5 arylation of *N*-aryl 1,2,3-triazoles.



INTRODUCTION

1,2,3-Triazoles and its derivative have a wide range of applications in biological science as HIV protease inhibitors, anticancer drugs (like 1,2,3-triazolo[4,5-*d*] pyrimidines), antituberculosis drugs, antifungal agents, and antibacterial drugs (like 5-(4-methyl-1,2,3-triazole)methyl oxazolidinones), as well as in material science as energetic materials, lubricants, dyes, and photostabilizers.[1,2] Unique properties of 1,2,3-triazole such as rigidity and stability of the triazole core in vivo, hydrogen bonding capability, and dipole moment are considered as decisive factors for their improved biological activity.[3] Owing to the importance of triazole compounds especially in biological sciences, various synthetic approaches for the construction of triazole have been developed in the recent years.[4] For instance, Hüisgen's 1,3-dipolar [3 + 2]-cycloaddition of azides and alkynes is one of the popular methods for the synthesis of the triazole core.[5] Generally, toward the synthesis of 1,2,3-triazoles, chemists have either used commercially available alkynes or prepared in situ alkynes by typical procedures.[6] However, these methods usually provide a mixture of regioisomeric products and require a strong electron withdrawing group on the alkyne moiety. Besides, these methods have limited scope for substitution at the post-triazole stage and also the choice of substituents depends on the feasibility of cycloaddition. Consequently, significant efforts have been undertaken toward regioselective synthesis of substituted 1,2,3-trizaoles. These methods include metalation of the triazole and subsequent addition of an electrophile,[7] cross-coupling of 5-halo-1,2,3-triazoles,[8] and reaction of azides with bromo-magnesium acetylides, followed by the addition of an electrophile (Chart 1).[9]

Despite these remarkable advances, generally applicable methods for the regioselective synthesis of substituted 1,2,3-triazoles are still desirable. Recently, Pd-catalyzed direct arylation and heteroarylation have emerged as a valuable alternative to the conventional methods used for the functionalization of heterocycle.[10] The direct Pd-catalyzed arylation reactions have also shown to be efficient in the functionalization of 1,2,4-triazole[11] as well as 1,4-disubstituted 1,2,3-triazole (Chart 2).[12] However, to the best of our knowledge, reports on the regioselective arylation of 1,2,3-triazoles are extremely scanty in the literature.

In this article, we describe a straightforward method for the synthesis of C-5 substituted *N*-aryl 1,2,3-triazole using a direct Pd-catalyzed arylation reaction. The reactions proceeded

Chart 1. Synthesis of C-5 Substituted 1,2,3-Triazole by Ruthenium Catalysis

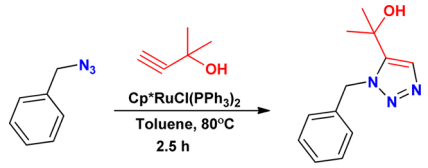
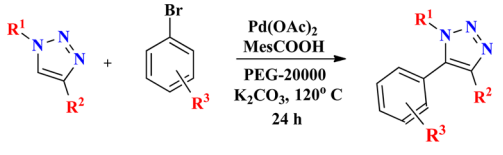


Chart 2. Synthesis of C-5 Substituted 1,2,3-Triazole by Pd Catalysis



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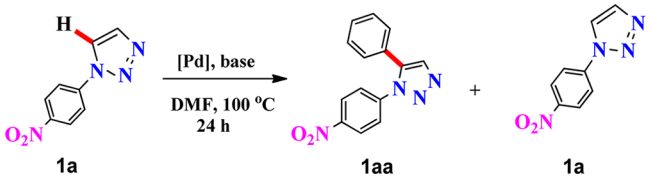
efficiently in the presence of catalytic amounts of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine to give desired products in good yields. In addition, through DFT calculations, we have provided a detailed explanation for the regioselective C-5 arylation of *N*-aryl 1,2,3-triazoles.

RESULTS AND DISCUSSION

Initial screening reactions were performed with a Pd catalyst under ligand free conditions (Table 1), but full consumption of

Table 1. Optimization of Reaction Conditions



[Pd] (mole %)	ligand	base (equiv)	yield (%) 1aa	1a
$Pd(OAc)_2$(10)		K_2CO_3	45	55
$Pd(OAc)_2$ (10)		Cs_2CO_3	45	55
$Pd(OAc)_2$ (10)	pavilic acid	Cs_2CO_3	35	
$Pd(OAc)_2$(10)	Ph_3P	Cs_2CO_3	50	50
$Pd(OAc)_2$ (5)	$(o\text{-tolyl})_3P$	Cs_2CO_3	65	35
$Pd(OAc)_2$ (10)	$(o\text{-tolyl})_3P$	K_2CO_3	70	
$Pd(OAc)_2$ (10)	**$(o\text{-tolyl})_3P$**	**Cs_2CO_3**	**72**	

starting material (**1a**) was not observed. Thereafter, combinations of Pd catalyst and pivalic acid medium were tried to maximize product yield. When the arylation reaction was performed with $Pd(OAc)_2$ (10 mol %) and phosphine ligand (PPh_3) (20 mol %), it gave enhanced yield (50%). By using the PPh_3 ligand, the starting material was not consumed totally, so that by replacing the PPh_3 ligand with slightly electron rich and steric ligand like tris(*o*-tolyl)phophine gave good yield of the product (72%). This method was found to be more efficient, and high reigoselectivity was obtained for C-5 arylation on *N*-aryl substituted 1,2,3-triazole. It was found that the C-5 arylation, on monosubstituted 1,2,3-triazole with aryl iodide in the presence of $Pd(OAc)_2$, tris(*o*-tolyl)phosphine, and Cs_2CO_3 under inert atmosphere, offered C-5 arylated triazoles in good yields. Changing the base to K_2CO_3 from Cs_2CO_3 did not show any effect on the rate of reaction and offered slightly lower yield. This reaction proceeded smoothly with electron deficient(4-nitrophenyl), electron rich (*m*-anisole), and bulky (1-naphthyl) aryl iodides presumably via the mechanism shown in Scheme 1.[13]

Thus, a variety of aryl-substituted 1,2,3-triazoles, containing electron withdrawing aryl groups and electron donating aryl groups on nitrogen, were shown to proceed to C-5 arylation successfully (Table 2). It indicates that a variety of functional groups such as methoxy, nitro, methyl, and trifluoromethyl tolerated these conditions.

By using the above conditions, highly reigoselective C-5 arylated triazoles were synthesized. *N*-Phenyl 1,2,3-triazole (**1b**) has two characteristic proton peaks at δ 7.86 and 8.01 ppm on the triazole ring. After arylation on **1b** with the Pd catalyst, arylated product **1(ba)** was obtained. We observed that in the ^1H NMR of **1(ba)**, the δ 8.01 ppm peak had disappeared on triazole ring. Similarly for 1,4-disubstituted 1,2,3-triazole (**1h**), which has only one characteristic peak on the triazole ring at δ 7.81 ppm, on arylation the triazole ring proton of (**1ha**) peak disappeared. It indicates that the arylation occurred at C-5 position. The C-5 center of *N*-aryl substituted 1,2,3-triazole has greater nucleophilic character compared to that of the C-4. The

Scheme 1. Proposed Catalytic Cycle for the Pd Catalyzed Arylation of *N*-Aryl 1,2,3-Triazole

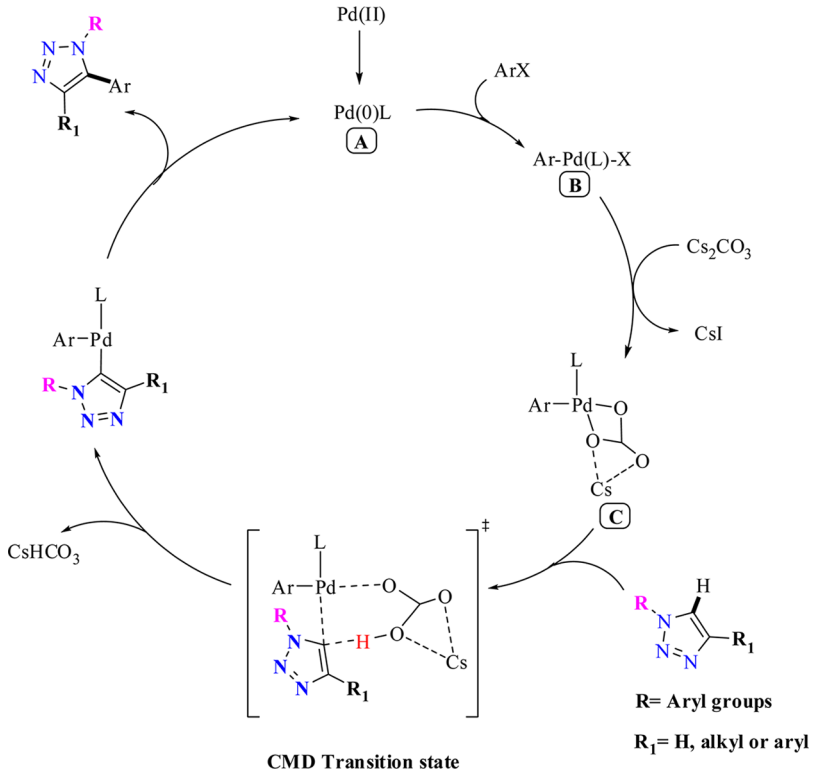


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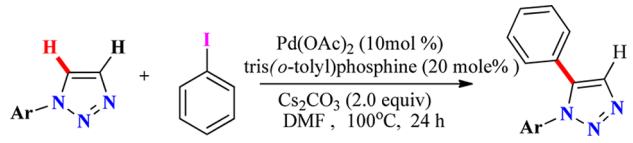
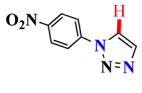
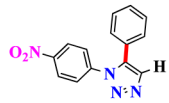
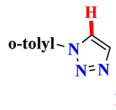
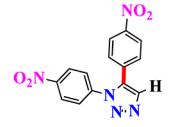
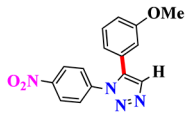
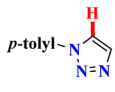
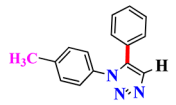
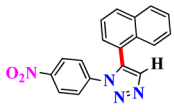
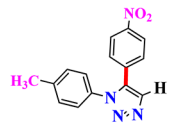
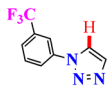
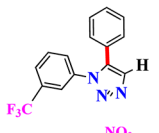
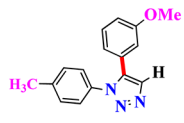
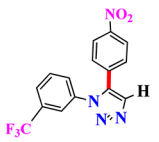
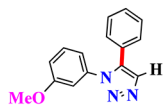
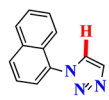
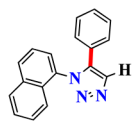
Table 2. C-5 Arylation of *N*-Aryl Substituted 1,2,3-Triazole



Triazole	Product		Yield (%)	Triazole	Product		Yield (%)
 1a		1aa	72	 1d		1da	75
		1ab	69	 1e		1ea	84
		1ac	72	 1c		1ca	82
		1ad	80			1cb	66
 1f		1fa	81			1cc	72
		1fb	71	 1g		1ga	83
 1b		1ba	76	 1i		1ia	72
		1bb	75				

electropositive nature of C-4 was observed clearly in ^{1}H NMR spectra; C-4 protons have more δ value compared to that of the C-5 proton, and it indicates the polarizable character of respective carbons. The ^{15}N NMR of **1jb** showed three nitrogen peaks in the spectrum at δ −130.85 (N_1), −31.88 (N_2), and −17.13 (N_3). It was observed that the intensity N_1 peak is low as compared to the other two nitrogen atoms because it was attached to the aromatic ring and tertiary nitrogen atom. This peak (N_1) was confirmed by the ^{15}N-HMBE NMR Spectrum.

Similarly, by using this same condition on 1,4-disubstituted 1,2,3-triazole, C-5 arylation was achieved in good yields (Table 3). It can be inferred that this reaction even works smoothly at highly hindered substitutions in the vicinity of C-5. It showed the C-5 center as being a more favorable site for arylation in comparison to C-4.

The proposed catalytic cycle for the Pd-catalyzed arylation of *N*-aryl 1,2,3-triazole is shown in Scheme 1.[13,14] In the first step, the phosphine ligand reduces the Pd(II) species to Pd (0) active species (**A**), and subsequently, the aryl palladium intermediate (**B**) is generated through oxidative addition of aryl iodide to Pd(0). The coordination of the base to intermediate (**B**) followed by C−H bond activation via the CMD pathway gives the tricoordinated Pd intermediate. Reductive C−C coupling in the final step affords the desired C-5 arylated triazole by releasing the Pd (0) species to complete the catalytic cycle.

The C-5 arylated triazole structure was confirmed by single crystal XRD (CCDC deposit number CCDC 1032133). In the crystal structure of the **1fa** shown in Figure 1, the two substituents are placed on vicinal atoms (N-1 and C-5) and away from each other in the same plane of the triazole ring. It indicates the new **C5−C6** bond has been formed between triazole carbon (C-5) and aryl iodide (C-6). The bond length of C−C bond is 1.47 Å, and the bond angles between C−C−C and C−C−N are 128.56° and 127.72°, respectively. The central triazole ring appears planar without much distortion because of the remote spatial orientation of the substituents.

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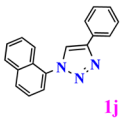
Table 3. Arylation on the C-5 Position of 1,4-Disubstituted 1,2,3-Triazole

Triazole	Product	Yield (%)
 1h	 1ha	86
	 1hb	81
 1j	 1ja	83
	 1jb	82

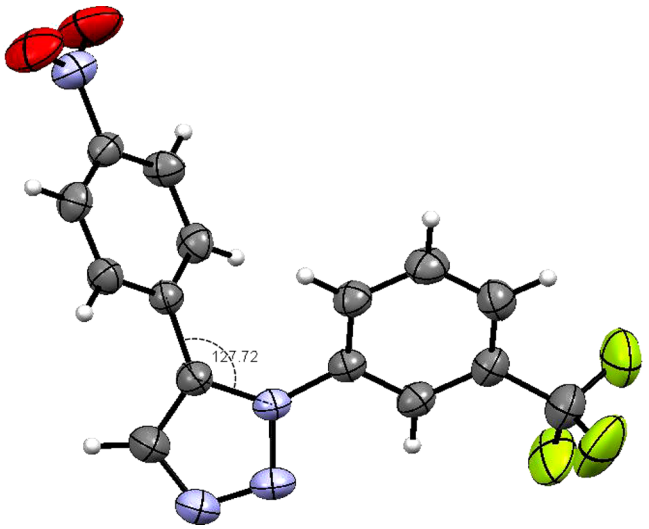


Figure 1. ORTEP single crystal XRD of **1fb**.

COMPUTATIONAL STUDIES

The Pd-catalyzed arylation reaction described in this work is highly regioselective and provides C-5 substituted 1,2,3 triazole as a major product. To gain better insights into the origin of the regioselectivity of the reaction, computational investigations on key steps of the catalytic cycle shown in Scheme 1 were carried out using the density functional theory (DFT) methods. To save computational time, we have considered trimethyl phosphine Pd(Pd-PMe_3) instead of tris(*o*-tolyl)phosphine Pd as a Pd(0) active species and triazole **1b** as a model substrate for our calculations. Experimentally, tris(*o*-tolyl)phosphine is used as a ligand. The bulkiness of tri(*o*-tolyl)phosphine may prevent double or more coordination to the palladium in the catalytic cycle. So we restricted our calculations to a monotrimethyl phosphine Pd(0) active species. All energies are calculated relative to the preceding intermediate as well as separated reactants. The calculated free energies and activation free energies of intermediates and transition states, respectively, obtained at the M06L levels are summarized in Scheme 2.

On the basis of the catalytic cycle shown in Scheme 1, Pd-catalyzed arylation involves four key steps namely, oxidative addition, ligand exchange, C−H bond activation, and reductive elimination. We began our computational investigation with oxidative addition of iodobenzene to monoligated trimethyl-phosphine Pd active species (**A**). Initial coordination of iodobenzene to **A** leads to an intermediate in which Pd coordinates to the C−I bond of iodobenzene. The initial coordination of iodobenzene to A is predicted to be exoergic by 12.3 kcal/mol. The intermediate undergoes oxidative addition via **TS(A → B)** to afford a three coordinated Pd species (**B**) with a marginal barrier of 0.3 kcal/mol. Prior to the deprotonation step, it is expected that the carbonate ion (CO_3^{2-}) coordinates to **B** by replacing the halide ion. The substitution of I^- by the carbonate ion in **B** provides tetra-coordinated Pd intermediate **C**, and the process of halide exchange by the carbonate ion in **B** is found to be exoergic by 8.8 kcal/mol. The next step involves an entry of substrate **1b** in the catalytic cycle. The coordination of **1b** to **C** leads to η^1−C−Pd coordinated complex **D**, which further enables the deprotonation of the C4/C5 proton of **1b** presumably assisted by C−H bond activation. The mechanism of Pd-catalyzed reactions involving C−H bond activation has been extensively investigated using computational methods, and four different routes have been proposed for C−H bond activation, which includes oxidative addition of the C-H bond, electrophilic aromatic substitution, concerted metalation−deprotonation (CMD), and the σ-bond metathesis pathway.[15] In most of the reactions, the CMD pathway represents the preferred pathway for the C−H bond activation and deprotonation step.[16] In the present reaction also, the CMD route for the deprotonation of C-4 or C-5 proton of **1b** seems to be the relevant pathway since it involves the coordination of the base (carbonate) to the Pd complex. Transition states (TSs) for the deprotonation of C-4 (**TS(D_{C4} → E)**) and C-5 proton (**TS(D_{C5} → F)**) of substrate **1b** corresponding to the CMD pathway were located at the M06L level and are shown in Figure 2. The computed activation barrier (30.2 kcal/mol) for the **TS(D_{C4} → E)** is found to be higher compared to the barrier (25.8 kcal/mol) for **TS(D_{C5} → F)**. Calculations clearly favor the deprotonation at the C-5 position of **1b**, which is in accordance with the experimental observations.

The optimized structures of transition states **TS(D_{C4} → E)** and **TS(D_{C5} → F)** are provide in Figure 2. It is noticed that the formation of the Pd···C(substrate) bond and the cleavage of the C···H bond occur in a fairly concerted manner as can be seen from the corresponding distances (2.35 and 1.38 Å in TS(D_{C4} → E); 2.29 and 1.30 Å in TS(D_{C5} → F)). These TSs are further confirmed by the intrinsic reaction coordinate (IRC) calculations. It has been shown that the interaction between the catalyst and substrate and distortion in structures of the catalyst and substrate at the CMD transition state can be crucial factors in controlling the selectivity of the reaction.[17] Hence, to identify the contribution of distortion and interaction energies of Pd-complexes **C** (catalyst) and **1b** (substrate), distortion/interaction analysis was performed on the **TS(D_{C4} → E)** and **TS(D_{C5} → F)**. In this approach, the interaction energies E_{int} between **C** and **1b** in the transition states and the distortion energies E_{dis} associated with **C** and **1b** in the transition states compared to their ground state geometries were evaluated. Results of distortion/interaction analysis are summarized in Figure 2. The E_{int} at the **TS(D_{C4} → E)** is found to be 14.2 kcal/mol higher than the E_{int} at the **TS(D_{C5} → F)**.

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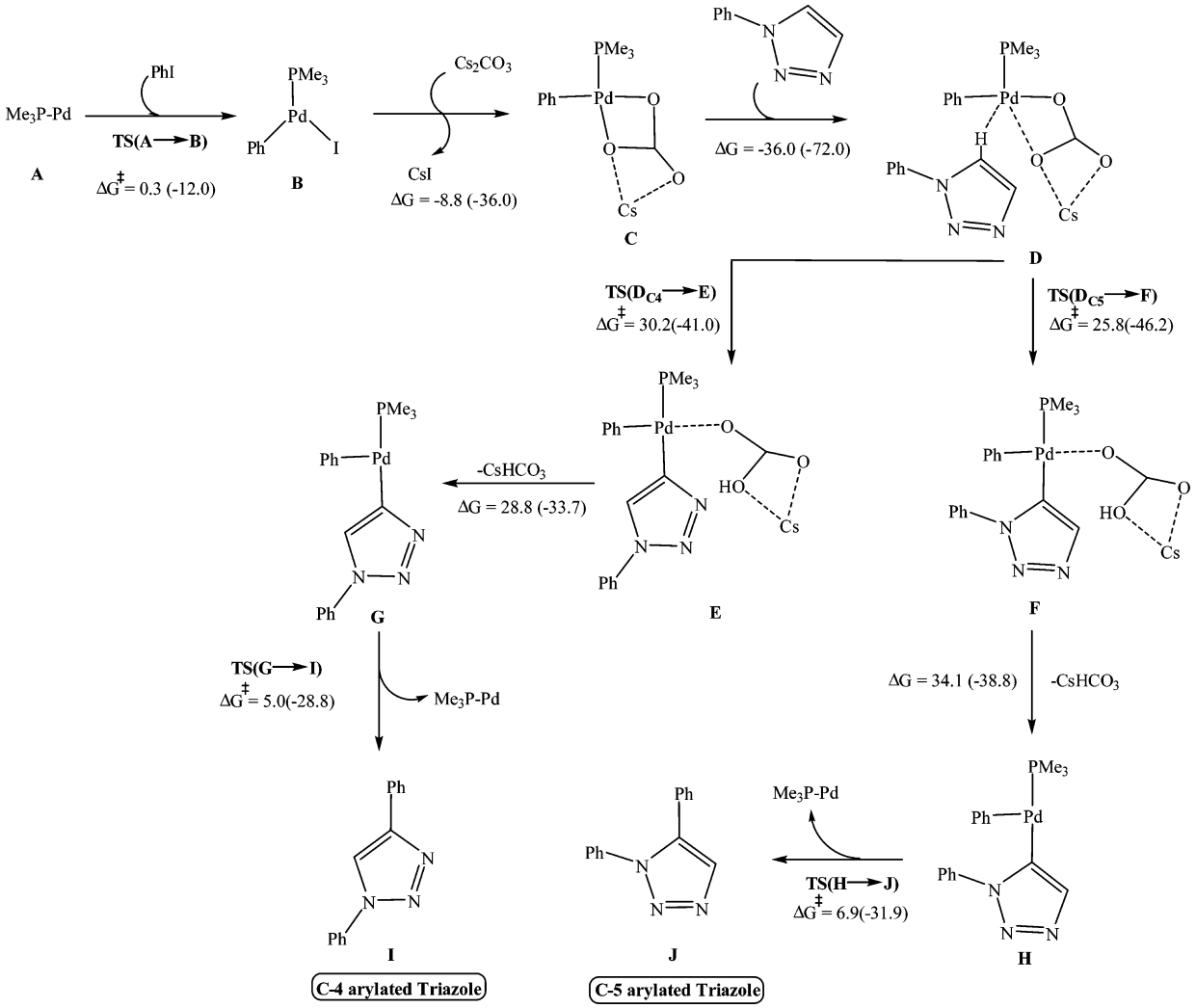
Scheme 2. Intermediates Involved in the Pd-Catalyzed Arylation of *N*-Aryl 1,2,3-Triazole[a]



[a]Free energies and activation free energies computed relative to preceding reacting complexes or intermediate are shown. Values in parentheses indicate free energies and activation free energies computed relative to the separated Pd active species **A**, **1b**, iodobenzene, and Cs_2CO_3.

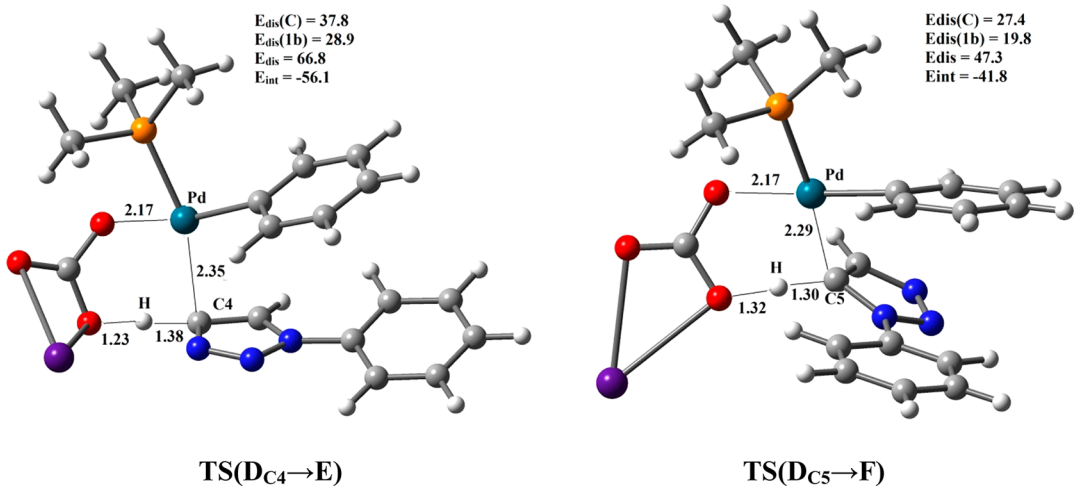


Figure 2. C−H activation transition states corresponding to the CMD pathway.

However, the stabilizing interactions are compensated by the high distortion energies of **C** and **1b** in the **TS(D$_{C4}$ → E)**. The total distortion energy (E_{dis}) associated with **TS(D$_{C4}$ → E)** is estimated to be 19.5 kcal/mol higher than the E_{dis} associated with **TS(D$_{C5}$ → F)**. Overall, deprotonation in the **TS(D$_{C5}$ → F)** is more favorable than the deprotonation in **TS(D$_{C4}$ → E)**

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mainly because of lower degrees of distortion in **C** and substrate **1b** at the **TS(D_{C5} → F)** as compared to their ground state geometries.

In the next step, the intermediates **E** and **F** release $CsHCO_3$ to form tricoordinated Pd complexes **G** and **H**, respectively. Finally, reductive C−C coupling occurs in **G** and **H** via three membered transition states (**TS(G → I)** and **TS(H → J)**) to release the C-4 and C-5 arylated triazole, respectively. The computed barriers for this step are less than 7 kcal/mol. After releasing the arylated product, the active catalytic species Pd(0)-PMe_3 is regenerated to complete the catalytic cycle.

CONCLUSIONS

We have demonstrated a straightforward method for the synthesis of C-5 substituted *N*-aryl 1,2,3-triazoles. By using a combination of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine as catalyst, arylation of *N*-aryl 1,2,3-triazole has been achieved regiospecifically at the C-5 position of triazoles. The scope of this method further extended for the arylation of 1,4-disubstituted 1,2,3-trizaole. The origin of C-5 selectivity of the reaction has been revealed by means of theoretical investigations of the catalytic cycle of the reaction, results of which are in agreement with experimental outcomes. The distortion/interaction analysis on the CMD transition states suggested that energetic cost associated with the distortion of substrate and Pd-catalyst at the transition state can be a crucial factor in the discrimination of two transition states which leads to the isomeric products.

EXPERIMENTAL SECTION

General Procedure. A solution of azide (1.00 equiv) and trimethysilyl (TMS)-acetylene (1.5 equiv) was taken in MeOH/H_2O (1:1 ratio 5 mL) in a 50 mL round-bottomed flask. $CuSO_4$ (0.1 equiv), sodium ascorbate (0.2 equiv), and K_2CO_3 (2.0 equiv) were added, and then the reaction mixture was closed tightly with a stopper and stirred rapidly for 24 h. Upon completion of the reaction, the reaction mixture was diluted with EtOAc, and the organic layer was separated. This was washed with water, brine, and dried over Na_2SO_4. The filtrate was concentrated under vacuum and afforded the crude product. The crude product was purified by column chromatography by using silica gel (100−200 mesh) with hexane/EtOAc as elutant. By using the above-mentioned procedure, the following triazole compounds from **1a** to **1j** were prepared.

1-(4-Nitrophenyl)-1H-1,2,3-triazole[23] ***(1a)***. Yield: 245 mg (70%). ^{1}H NMR (300 MHz): δ ppm 7.93 (s, 1 H) 8.02 (d, J = 9.06 Hz, 2 H) 8.14 (s, 1 H) 8.45 (t, J = 1.00 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 120.8, 121.8, 125.8, 135.5, 141.4. IR (Neat, cm^{-1}): 2918, 2850, 1596, 1515, 1335, 1234, 1027, 851.

1-Phenyl-1H-1,2,3-triazole[23] ***1(b)***. Yield: 390 mg (68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.45 ppm (s, 1 H). 7.51−7.56 (m, 2 H), 7.75 (dd, J = 1.1 Hz, 8.7, 2 H), 7.86 (d, J = 0.9 Hz, 1 H), 8.00 (d, J = 1.2 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 120.9, 121.9, 128.9, 129.9, 134.6, 137.2.

1-(p-Tolyl)-1H-1,2,3-triazole[24] ***(1c)***. Yield: 369 (62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.42 (s, 3 H) 7.32 (d, J = 8.41 Hz, 2 H) 7.59−7.64 (m, 2 H) 7.83 (d, J = 1.01 Hz, 1 H) 7.95 (d, J = 1.01 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 21.3, 120.8, 121.9, 130.44, 134.5, 134.9, 139.0. IR (Neat, cm^{-1}): 3129, 2991, 1737, 1518, 1319, 1113, 1039, 809.

4-(1H-1,2,3-Triazol-1-yl)pyridine ***(1e)***. Yield: 218 mg (71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.78−7.73 (m, 2 H), 7.91 (d, J = 1.3 Hz, 1 H), 8.12 (d, J = 1.3 Hz, 1 H), 8.83−8.78 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 114.0, 121.3, 135.3,143.2, 151.9.

1-(4-(Trifluoromethyl)phenyl)-1H-1,2,3-triazole[25] ***(1f)***. Yield: 220 mg (52%), ^{1}H NMR (500 MHz, $CDCl_3$); δ ppm 7.67−7.76 (m, 2 H) 7.90 (d, J = 0.92 Hz, 1 H) 7.97−8.01 (m, 1 H) 8.05 (d, J = 0.61 Hz, 1 H) 8.07 (d, J = 1.22 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 117.3, 117.8, 121.7, 123.7, 125.3−125.6, 130.6, 134.9, 137.4. IR (Neat, cm^{-1}): 3128, 2924, 2854, 1486, 1339, 1235, 1173, 1034, 895.

1-(3-Methoxyphenyl)-1H-1,2,3-triazole[25] ***(1g)***. Yield: 185 mg (63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.89 (s, 3 H), 6.98 (ddd, J = 0.8, 2.5, 8.4 Hz, 1 H), 7.29- 7.25 (m, 1 H), 7.36 (t, J = 2.3 Hz, 1 H), 7.45−7.39 (m, 1 H), 7.84 (d, J = 1.0 Hz, 1 H), 7.99 (d, J = 1.2 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 55.6, 106.5, 112.5, 114.6, 121.8, 130.5, 134.4, 138.1, 160.6. IR (Neat, cm^{-1}): 3126, 2924, 2852, 1607, 1455, 1164, 1124, 1097, 1031, 992,

4-Cyclopropyl-1-phenyl-1H-1,2,3-triazole ***1(h)***. Yield: 373 mg (65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.02−0.96 (m, 2 H), 1.10−1.04 (m, 2 H), 2.07 (m, 1 H), 7.81 (s, 1 H), 7.99−7.94 (m, 2 H), 8.44−8.39 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 6.7, 8.0, 113.39, 117.6, 120.1, 125.5, 126.4, 141.3, 147.0, 152.0. IR (Neat, cm^{-1}): 3097, 3003, 2923, 2852, 1595, 1512, 1408, 1223, 1110, 854. HRMS [M + H]$^+$: calculated for $C_{11}H_{11}N_4O_2$, 231.0882; found, 231.0899

1-(Naphthalen-1-yl)-1H-1,2,3-triazole[26] ***(1i)***. Yield: 569 mg (66%). ^{1}H NMR (500 MHz, $CDCl_3$); δ ppm 7.53−7.62 (m, 5 H) 7.94−7.99 (m, 3 H) 8.04 (brs. One H). ^{13}C NMR (126 MHz, CDCl3): δ ppm 122.3, 123.6, 125.01, 126.3, 127.11, 127.9, 128.3, 128.7, 130.4, 133.8, 134.1. IR (Neat, cm^{-1}): 3125, 2925, 2855, 1598, 1471, 1312, 1228, 1018, 772.

1-(Naphthalen-1-yl)-4-phenyl-1H-1,2,3-triazole[27] ***(1j)***. Yield: 801 mg (81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.38−7.44 (m, 1 H) 7.51 (t, J = 7.74 Hz, 2 H) 7.55−7.69 (m, 4 H) 7.73 (d, J = 7.74 Hz, 1 H) 7.96−8.03 (m, 3 H) 8.06 (d, J = 8.08 Hz, 1 H) 8.18 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 122.5, 123.7, 125.1, 125.9, 127.2, 128.0, 128.4, 128.5, 128.6, 129.1, 130.4, 130.6, 133.8, 134.3, 147.8. IR (Neat, cm^{-1}): 3134, 2944, 1600, 1426, 1378, 1074, 1025, 910.

General Procedure for the Synthesis of Compounds 1,4-Disubstituted of 1,2,3-Triazoles. To a dried 2-necked round-bottomed flask were added monosubstituted 1,2,3-triazole (1.0 equiv), aryl iodide (1.2 equiv), Cs_2CO_3 (2.0 equiv), and tris(*o*-tolyl)phosphine (20 mol %) and DMF (3.0 mL). Then the reaction mixture was degassed for 10 min at room temperature. After that, $Pd(AcO_2)_2$ (10 mol %) was added to the reaction mixture, and the closed reaction setup was placed under N_2 atmosphere. The reaction mixture (RM) was stirred at room temperature for 5 min and then heated slowly up to 100 °C for 20 h. The RM was periodically monitored by TLC. After completion of the reaction, the RM was diluted with EtOAc and washed with water (twice), the organic layer was separated, and again washed with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and afforded the crude product. The crude product was purified by column chromatography by using silica gel (100−200 mesh) with hexane/EtOAc as eluant. By using the above-mentioned procedure, the following triazole compounds from **1aa** to **1jb** were prepared.

1-(4-Nitrophenyl)-5-phenyl-1H-1,2,3-triazole[28] ***(1aa)***. Yield: 101 mg (72%). M. P., 157−160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.23−7.26 (m, 2 H) 7.39−7.49 (m, 3 H) 7.55−7.62 (m, 2 H) 7.89 (s, 1 H) 8.26−8.36 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 125.1, 125.5, 126.3, 128.9, 129.5, 130.2, 134.4, 138.2, 141.5, 147.7. IR (Neat, cm^{-1}): 3082, 2924, 2857, 1600, 1517, 1343, 1237, 1040, 983, 851. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 15.00 min (major).

1,5-Bis(4-nitrophenyl)-1H-1,2,3-triazoles[29] ***(1ab)***. Yield: 107 mg (69%). M.P.: 187−190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.45−7.48 (m, 2 H) 7.57−7.60 (m, 2 H) 8.01 (s, 1 H) 8.28−8.31 (m, 2 H) 8.35−8.38 (m, 2 H).^{13}C NMR (126 MHz, $CDCl_3$);δ ppm 124.7, 125.5, 125.7, 129.8, 132.5, 135.1, 148.1, 148.6. IR (Neat, cm^{-1}): 3108, 2922, 1342, 1108, 1038, 981, 849. [M + H]$^+$: calculated for $C_{14}H_9N_5O_4$, 312.0733; found, 312.0734. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 10.05 min (minor),11.5 min (major).

5-(3-Methoxyphenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole ***(1ac)***. Yield: 109 mg (72%). M.P.: 96−98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.78 (s, 3 H), 6.82−6.77 (m, 2 H), 7.01−6.97 (m, 1

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H), 7.33 (s, 1 H), 7.63−7.59 (m, 2 H), 7.89 (s, 1 H), 8.31 (d, J = 9.1 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 55.6, 114.8, 115.3, 117.5, 121.2, 125.0, 125.4, 130.6, 134.4, 138.1, 141.5, 147.7, 160.2. IR (Neat, cm^{-1}): 3012, 2924, 2853, 1590, 1342, 1227, 1111, 853. [M + H]$^+$: calculated for $C_{15}H_{12}N_4O_3$, 297.0988; found, 297.0985. Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 59.90; H, 4.1; N, 18.58.

5-(Naphthalen-1-yl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (**1ad**). Yield: 198 mg (80%). M.P.: 131−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.40 (dd, J = 7.0, 1.2 Hz, 1 H), 7.45−7.50 (m, 1 H), 7.50−7.53 (m, 2 H), 7.53−7.59 (m, 3 H), 7.96 (d, J = 8.2 Hz, 1 H), 8.01 (s, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 8.12−8.17 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 123.7 124.0, 124.3, 124.8, 125.3, 127.0, 127.7, 128.9, 129.0, 130.9, 131.4, 133.7, 136.1, 141.3, 147.2. IR (Neat, cm^{-1}): 3058, 2934, 2854, 1597, 1474, 1232, 1015, 962, 802. Anal. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71; O, 10.12. Found: C, 67.92; H, 3.83, N, 17.63.

1,5-Diphenyl-1H-1,2,3-triazole[30] (**1ba**) **154**. Yield: 111 mg (76%), M.P.: 109−112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm7.21−7.25 (m, 2 H) 7.33−7.36 (m, 1 H) 7.36−7.39 (m, 4 H) 7.43−7.46 (m, 3 H) 7.87 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 125.4, 126.9, 128.8, 129.1, 129.4, 129.6, 133.6, 136.8, 137.9. IR (Neat, cm^{-1}): 3061, 2923, 1596, 1493, 1452, 1233, 1128, 984, 835. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 12.86 min (major), 17.88 min (minor).

5-(4-Nitrophenyl)-1-phenyl-1H-1,23-triazole[31] (**1bb**). Yield: 135 mg (75%). M.P.: 139−141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.33−7.37 (m, 2 H) 7.40−7.43 (m, 2 H) 7.46−7.52 (m, 3 H) 7.99 (s, 1 H) 8.19−8.22 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 124.3, 125.5, 129.5, 129.9, 130.1, 133.2, 134.4, 135.8, 136.2, 148.1. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 7.13 min (major).

5-Phenyl-1-(p-tolyl)-1H-1,2,3-triazole (**1ca**). Yield 119 mg (82%). M.P.: 75−77 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.40 (s, 3 H) 7.22−7.25 (m, 6 H) 7.33−7.37 (m, 3 H) 7.85 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$); δ ppm 21.4, 125.2, 127.1, 128.8, 129.0, 129.3, 130.1, 133.5, 134.3, 137.8, 139.5. IR (Neat, cm^{-1}): 2922, 2857, 1452, 1276, 1232, 1044, 984, 823. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 11.27 min (major),14.71 min (minor).

5-(4-Nitrophenyl)-1-(p-tolyl)-1H-1,2,3-triazole (**1cb**). Yield: 117 mg (66%). M.P.: 71−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.40−2.47 (m, 3 H) 7.20−7.25 (m, 2 H) 7.26−7.30 (m, 2 H) 7.39−7.44 (m, 2 H) 7.98 (s, 1 H) 8.19- 8.23 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 21.4, 124.3, 125.3, 129.4, 130.5, 133.4, 133.7, 134.2, 135.8, 140.4, 148.1. IR (Neat, cm^{-1}): 3114, 2921, 1334, 1230, 1192, 1037, 986, 809. [M + H]$^+$: calculated for $C_{15}H_{12}N_4O_2$, 281.1039; found, 281.1033. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 11.16 min (major), 13.2 min (minor).

5-(3-Methoxyphenyl)-1-(p-tolyl)-1H-1,2,3-triazole (**1cc**). Yield: 123 mg (72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.40 (s, 3 H) 3.70 (s, 3 H) 6.75 (dd, J = 2.44, 1.53 Hz, 1 H) 6.79−6.82 (m, 1 H) 6.90 (ddd, J = 8.39, 2.59, 0.92 Hz, 1 H) 7.23−7.27 (m, 5 H) 7.85 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 21.4, 55.4, 114.3, 114.9, 120.8, 121.1, 125.2, 128.2, 130.1, 133.5, 134.4, 137.7, 139.6, 159.8. [M + H]$^+$: calculated for $C_{16}H_{15}N_3O$, 266.1293; found, 266.1301. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 5.00 min (major).

5-Phenyl-1-(o-tolyl)-1H-1,2,3-triazole[32] (**1da**). Yield: 109 mg (75%). M.P.: 71−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.96 (s, 3 H), 7.20−7.16 (m, 2 H), 7.34−7.27 (m, 6 H), 7.44−7.40 (m, 1 H), 7.95 (s, 1H). ^{13}CNMR (126 MHz, $CDCl_3$): δ ppm 17.7, 126.8, 127.2, 127.8, 129.0, 129.3, 130.0, 130.3, 131.5, 132.5, 135.4, 136.1, 138.8. IR (Neat, cm^{-1}): 3055, 2924, 2858, 1492, 1231, 1122, 984, 834. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 13.75 min (major), 19.65 min (minor).

4-(5-Phenyl-1H-1,2,3-triazole-1-yl)pyridine[33] (**1ea**). Yield: 121 mg (84%). M.P.: 199−201 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.31−7.26 (m, 2 H), 7.38−7.35 (m, 2 H), 7.51−7.43 (m, 3 H), 7.88 (s, 1 H), 8.76−8.68 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 118.3, 126.2, 128.8, 129.3, 129.9, 134.4, 137.8, 143.4, 151.3. IR (Neat, cm^{-1}): 2922, 2852, 1587, 1452, 1406, 1224, 1132, 1049. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 3.5 min (minor), 6.3 min (major).

5-Phenyl-1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (**1fa**). Yield: 109 mg (81%). M.P.: 110−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.20−7.25 (m, 2 H) 7.34−7.44 (m, 3 H) 7.49−7.58 (m, 2 H) 7.67−7.73 (m, 2 H) 7.85−7.89 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 122.05, 122.3, 125.8, 126.1, 126.4, 128.2, 128.8, 129.3, 129.8, 130.2, 132.1, 132.3, 133.9, 137.1, 138.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm −62.95. IR (Neat, cm^{-1}): 3068, 2924, 2855, 1601, 1520, 1462, 1262, 1170, 1063. [M + H]$^+$: calculated for $C_{15}H_{10}F_3N_3$, 290.0827; found, 231.0819. Anal. Calcd for $C_{15}H_{10}F_3N_3$: C, 62.28; H, 3.48; N, 14.53. Found: C, 62.00; H, 3.12; N, 14.17.

5-(4-Nitrophenyl)1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (**1fb**). Yield: 110 mg (71%). M.P.: 133−136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.41−7.46 (m, 2 H) 7.49 (d, J = 7.93 Hz, 1 H) 7.62 (t, J = 7.93 Hz, 1 H) 7.75 (s, 1 H) 7.77−7.81 (m, 1 H) 8.01 (s, 1 H) 8.24−8.29 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 122.4, 124.5, 126.7, 128.3, 129.6, 130.6, 134.7, 136.0, 136.6, 148.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm −62.95. IR (Neat, cm^{-1}): 3061, 2924, 2854, 1601, 1520, 1461, 1323, 1171, 1062, 999. [M + H]$^+$: calculated for $C_{15}H_9F_3N_4O_2$, 335.0756; found, 335.0744. Anal. Calcd for $C_{15}H_9F_3N_4O_2$: C, 53.90; H, 2.71; N, 16.76. Found: C, 54.20; H, 3.0; N, 16.94.

1-(3-Methoxyphenyl)-5-phenyl-1H-1,2,3-triazole (**1ga**). Yield: 108 mg (84%). M.P.: 85−88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm3.75 (s, 3 H) 6.88 (ddd, J = 0.9, 2.0, 7.9 Hz, 1 H), 6.99−6.93 (m, 2 H), 7.26−7.23 (m, 2 H), 7.29 (t, J = 8.1 Hz, 1 H), 7.38−7.32 (m, 3 H),7.85 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 55.7, 110.8, 115.6, 117.5, 127.0, 128.8, 129.0, 129.4, 130.2, 133.6, 137.7, 137.9, 160.3. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.49; H, 5.2; N, 16.9.

4-Cyclopropyl-1-(4-nitrophenyl)-5-diphenyl-1H-1,2,3-triazole (**1ha**). Yield: 150 mg (86%). M.P.: 127−130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.95−1.01 (m, 2 H) 1.11−1.17 (m, 2 H) 1.87 (tt, J = 8.41, 5.05 Hz, 1 H) 7.25−7.31 (m, 2 H) 7.43−7.48 (m, 3 H) 7.48−7.53 (m, 2 H) 8.20−8.28 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 6.3, 8.1, 124.9, 124.9, 127.1, 129.4, 129.7, 129.8, 134.1, 141.7, 147.3, 148.3. IR (Neat, cm^{-1}): 3087, 2956, 2853, 1597, 1500, 1277, 1058, 991, 854. [M + H]$^+$: calculated for $C_{17}H_{15}N_4O_2$, 307.1195; found, 307.1196. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 67.02; H, 5.1; N, 18.62.

4-Cyclopropyl-5-(3-methoxyphenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (**1hb**). Yield: 196 mg (89%). M.P.: 139−141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.29−8.24 (m, 2 H), 7.57−7.52 (m, 2 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.00 (dd, J = 0.9, 2.6, Hz, 1H), 6.87−6.81 (m, 2 H), 3.80 (s, 3 H), 1.94−1.87 (m, 1 H), 1.18−1.13 (m, 2 H), 1.03−0.97 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 6.2, 7.9, 55.4, 114.6, 115.6, 122.0, 124.7, 128.1, 130.4, 133.8, 137.5, 141.5, 147.1, 148.2, 160.0. IR (Neat, cm^{-1}): 2922, 2852, 1595, 1342, 1283, 1051, 907, 852. [M + H]$^+$: calculated for $C_{18}H_{17}N_4O_3$, 337.1300; found, 337.1271. Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66; O, 14.27. Found: C, 64.09; H, 4.7; N, 16.04.

1-(Naphthalen-1-yl)-5-phenyl-1H-1,2,3-triazole[34] (**1ia**). Yield: 132 mg (72%). M.P.: 120−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.11−7.15 (m, 2 H) 7.15−7.21 (m, 2 H) 7.21−7.26 (m, 1 H) 7.38 (d, J =8.54 Hz, 1 H) 7.41−7.57 (m, 4 H) 7.93−8.03 (m, 2 H) 8.04 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 122.7, 125.1, 125.6, 126.5, 127.2, 127.9, 128.0, 128.4, 128.9, 129.3, 129.9, 130.7, 132.6, 133.2, 134.3, 139.8. IR (Neat, cm^{-1}): 3058, 2934, 2854, 1597, 1474, 1232, 1015, 962, 802. HPLC (20% acetonitile in water, flow rate 0.5 mL/min) t_R = 11.58 min (minor), 14.77 min (major), 20.07 min (minor).

1-(Naphthalen-1-yl)-4,5-diphenyl-1H-1,2,3-triazole (**1ja**). Yield: 159 mg (83%). M.P.: 161−163 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.09−7.14 (m, 2 H) 7.14−7.20 (m, 2 H) 7.21−7.26 (m, 1 H) 7.32−7.40 (m, 5 H) 7.42−7.57 (m, 5 H) 7.68−7.72 (m, 2 H) 7.88−7.96 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 122.7, 124.9, 125.8, 127.1, 127.5, 127.9, 128.1, 128.3, 128.7, 128.9, 129.4, 129.7, 130.2, 130.6, 130.9, 132.9, 134.1, 136.1, 144.2. IR (Neat, cm^{-1}): 3058, 2924, 2854, 1600, 1445, 1162, 1021, 917, 801. [M + H]$^+$: calculated

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for $C_{24}H_{17}N_3$, 348.1501; found, 348.1497. Anal. Calcd for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.63; H, 4.94; N, 11.89.

*5-(3-Methoxyphenyl)-1-(naphthalene-1-yl)-4-phenyl-1H-1,2,3-triazole (**1jb**).* Yield: 171 mg (82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.44 (s, 3 H) 6.61 (dd, J = 2.44, 1.60 Hz, 1 H) 6.68−6.78 (m, 2 H) 7.07 (t, J = 7.91 Hz, 1 H) 7.29−7.41 (m, 4 H) 7.42−7.57 (m, 4 H) 7.69−7.76 (m, 2 H) 7.86−7.98 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 55.1, 114.8, 115.4, 122.3, 122.8, 124.9, 125.8, 127.1, 127.5, 127.9, 128.2, 128.3, 128.7, 130.0, 130.3, 130.6, 130.9, 132.9, 134.1, 135.9, 144.2, 159.6. IR (Neat, cm^{-1}): 3058, 2924, 2854, 1600, 1445, 1211, 1162, 1021, 917, 801. $[M + H]^+$: calculated for $C_{25}H_{19}N_3O$, 378.1601; found, 378.1595. Anal. Calcd for $C_{25}H_{19}N_3O$, C, 79.55; H, 5.07; N, 11.13. Found: C, 79.18; H, 5.06; N, 10.73.

Computational Methods. All calculations were performed with the Gaussian09 quantum chemical programs.[18] DFT was applied throughout using the M06L functional.[19] For geometry optimizations, the DFT calculations employed the 6-311G** basis set for C, H, N, O, and P[20] and the Lanl2dz effective core potential and the associated double-ζ basis set for Pd and Cs.[21] Geometry optimizations were carried out in the gas phase without any constraints. The optimized stationary points were characterized as local minima or transition structures by harmonic force constant analysis, and IRC calculations were performed to verify the transition state structures.[22]

■ ASSOCIATED CONTENT

Supporting Information

NMR (^{1}H, ^{13}C, ^{19}F, ^{15}N) spectra, HPLC graphs, single crystal XRD data, and computational studies data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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