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Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo5026145 • Publication Date (Web): 24 Feb 2015

Just Accepted

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Pd-catalyzed Reigoselective Arylation on C-5 position of *N*-aryl 1,2,3-Triazoles

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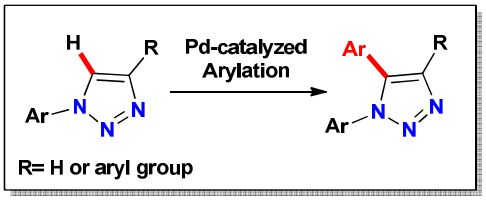
TOC graphics



Abstract:

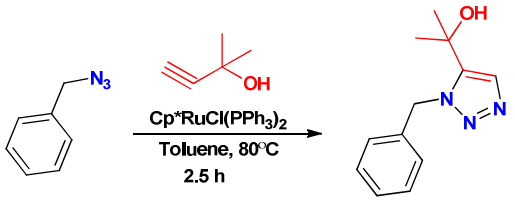
We herein report a highly efficient method for the arylation at C-5 position of *N*-aryl 1,2,3-Triazoles via a direct palladium catalyzed arylation reaction. The optimal reaction conditions required a combination of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine as catalyst, Cs_2CO_3 as the base under inert 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 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 (DFT) have provided the rationale for the selective C-5 arylation of N-aryl 1,2,3-Triazoles.

Key words: Triazoles, arylation, catalysis, DFT calculations, C-5 regioselectivity

Introduction

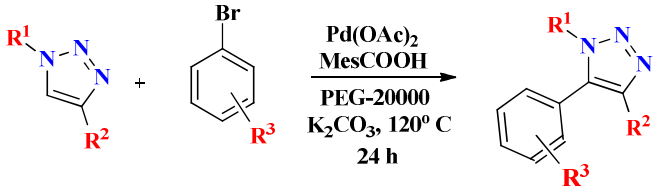
1,2,3-Triazoles and its derivative have a wide range of applications in biological science as HIV protease inhibitors, anti cancer drugs (like 1,2,3-triazolo[4,5-d] pyrimidines), antituberculosis drugs, antifungal agents, antibacterial drugs (like 5-(4-methyl-1,2,3-triazole)methyl oxazolidinones) as well as in material science as energetic materials, lubricants, dyes and photostabilisers.[1,2] Unique properties of 1,2,3-triazole such as rigidity and stability of triazole core in vivo, hydrogen bonding capability, 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 instances, Hüisgen's 1,3-dipolar [3+2]-cycloaddition of azides and alkynes is one of the popular methods for the synthesis of triazole core.[5] Generally towards 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 post-triazole stage and also the choice of substituents depends on the feasibility of cycloaddition. Consequently, significant efforts have been undertaken towards regioselective synthesis of substituted 1,2,3-trizaoles. These methods include metallation of the triazole and subsequent addition of electrophile,[7] cross-coupling of 5-halo-1,2,3-triazoles,[8] reaction of azides with bromo-magnesium acetylides followed by addition of electrophile.[9]

Reaction 1: Synthesis of C-5 substituted 1,2,3-triazole by ruthenium catalysis



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 functionilzation of heterocycle.[10] The direct Pd-catalyzed arylation reactions have also shown to be efficient in functionlization of 1,2,4-triazole[11] as well as 1,4-disubstituted 1,2,3-triazole.[12] However, to best of our knowledge, reports on the regioselective arylation of 1,2,3-triazoles are extremely scanty in the literature.

Reaction 2: Synthesis of C-5 substituted 1,2,3-triazole by Pd catalysis



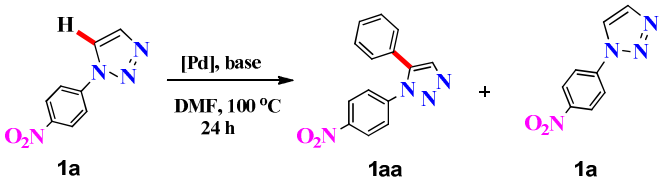
In this article, we describe a straightforward method for the synthesis of C-5 substituted *N*-aryl 1,2,3-triazole using a direct Pd-catalyzed arylation reaction. The reactions proceeded efficiently in the presence of catalytic amount of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine to give desired products 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 Pd catalyst under ligand free condition (table 1), but full consumption of starting material (**1a**) was not observed. Thereafter, combinations of Pd catalyst and pivalic acid medium were tried to maximise product yield. When 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 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 mono-substituted 1,2,3-triazole with aryl iodide in the presence of $Pd(OAc)_2$, tris(*o*-tolyl)phosphine and Cs_2CO_3 under inert atm, 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 mechanism shown in the scheme 1.[13]

Table 1: Optimization of reaction conditions



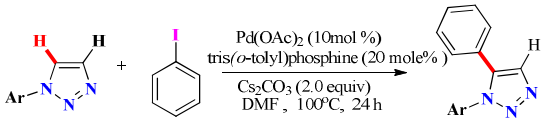
1a 1aa 1a

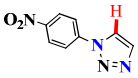
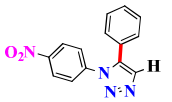
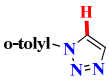
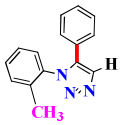
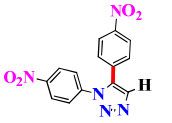
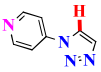
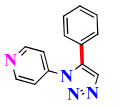
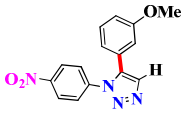
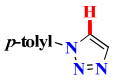
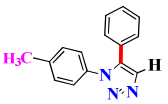
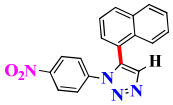
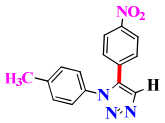
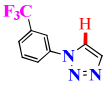
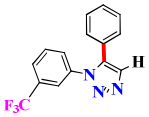
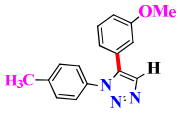
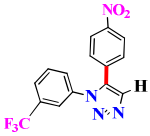
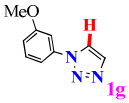
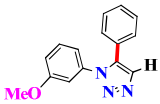
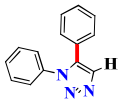
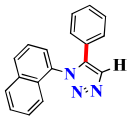
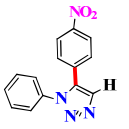
[Pd] (mole%)	Ligand	base (equiv)	yield (%) 1aa	1a
$Pd(OAc)_2$ (10)	—	K_2CO_3	45	55
$Pd(OAc)_2$ (10)	—	Cs_2CO_3	45	55
$Pd(OAc)_2$ (10)	Pavilic Acid	Cs_2CO_3	35	—
$Pd(OAc)_2$ (10)	Ph_3P	Cs_2CO_3	50	50
$Pd(OAc)_2$ (5)	$(o\text{-tolyl})_3P$	Cs_2CO_3	65	35
$Pd(OAc)_2$ (10)	$(o\text{-tolyl})_3P$	K_2CO_3	70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

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 1). It indicates, a variety of functional groups such as methoxy, nitro, methyl and trifluoromethyl tolerated these conditions.

By using above condition, highly reigoselective C-5 arylated triazoles were synthesized. *N*-phenyl 1,2,3-triazole **(1b)** having two characteristic proton peaks at δ 7.86 and 8.01 ppm on the triazole ring. After arylation on **1b** with Pd catalyst, arylated product 1**(ba)** was obtained. We observed that in ^{1}H-NMR of 1**(ba)**, δ 8.01 ppm peak has disappeared on triazole ring. Similarly for 1,4-disubstituted 1,2,3-triazole **(1h)** which have only one characteristic peak on triazole ring at δ 7.81ppm, on arylation the triazole ring proton of (**1ha)** peak disappeared. It indicates the arylation occurred at C-5 position. The C-5 centre of *N*-aryl substituted 1,2,3-triazole has greater nucleophilic character compared to the C-4. The electropositive nature of C-4 was observed clearly in ^{1}H-NMR spectra, C-4 proton have more δ value compared to C-5 proton, it indicates polarisable character of respective carbons. Whereas, ^{15}N-NMR of 1jb, it has showed three nitrogen peaks in the spectrum at δ -130.85 (N_1), -31.88 (N_2) and -17.13 (N_3) respectively. It was observed that the intensity N_1 peak is low as compare to other two nitrogen atoms, because it was attached to aromatic ring and tertiary nitrogen atom. This peak (N_1) was confirmed by ^{15}N-HMBE NMR spectra.

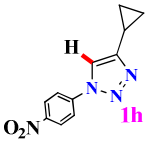
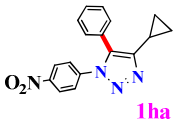
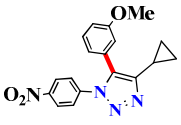
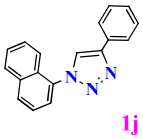
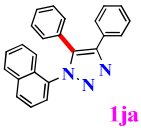
Table 2: C-5 arylation of *N*-aryl substituted 1,2,3-triazole



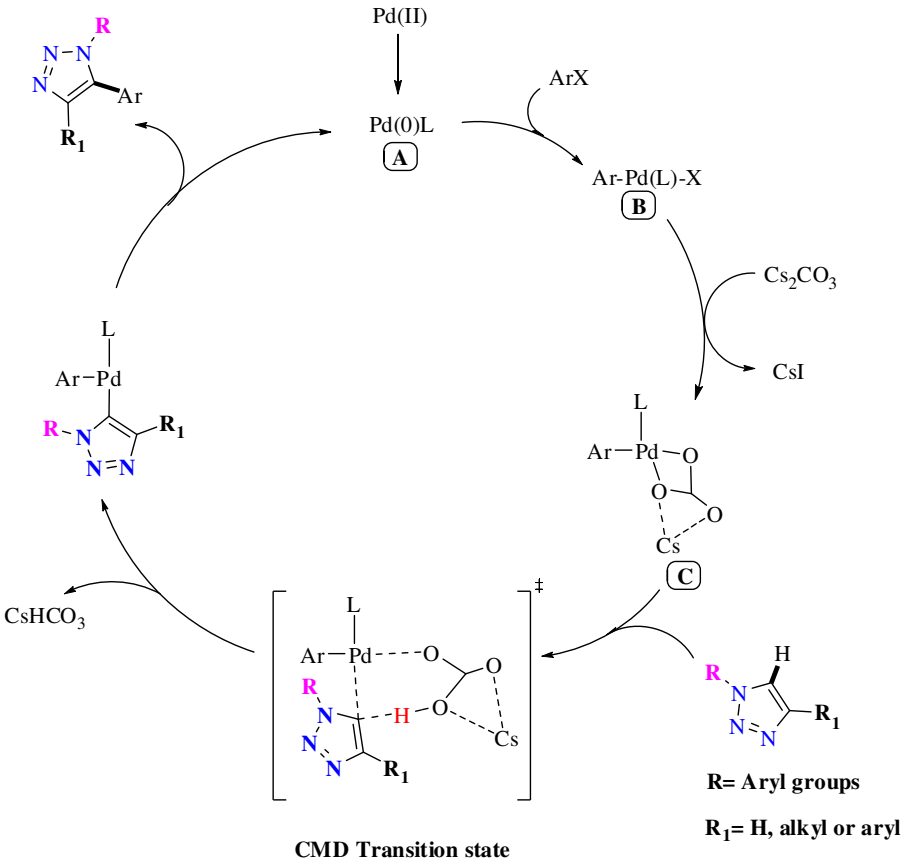
Triazole	Product	Yield (%)	Triazole	Product	Yield (%)
 1a	 1aa	72	 1d	 1da	75
	 1ab	69	 1e	 1ea	84
	 1ac	72	 1c	 1ca	82
	 1ad	80		 1cb	66
 1f	 1fa	81		 1cc	72
	 1fb	71	 1g	 1ga	83
 1b	 1ba	76	 1i	 1ia	72
	 1bb	75			

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 C5 centre more favourable site for arylation in comparison to C-4.

Table 3: Arylation on C-5 position of 1,4-disubstituted 1,2,3-triazole

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

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



Scheme 1: Proposed catalytic cycle for the Pd catalyzed arylation of *N*-aryl 1,2,3-triazole.

The C-5 arylated triazole structure was confirmed by single crystal XRD (ccdc deposited number **CCDC 1032133**). In the crystal structure of the **1fa** shown in the figure 1, the two substituents are placed on vicinal atoms (N-1 & C-5) and away from the 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 A° and bond angle between C-C-C and C-C-N are 128.56° & 127.72° respectively. The central triazole ring appears planar without much distortion because of remote spatial orientation of the substituents.

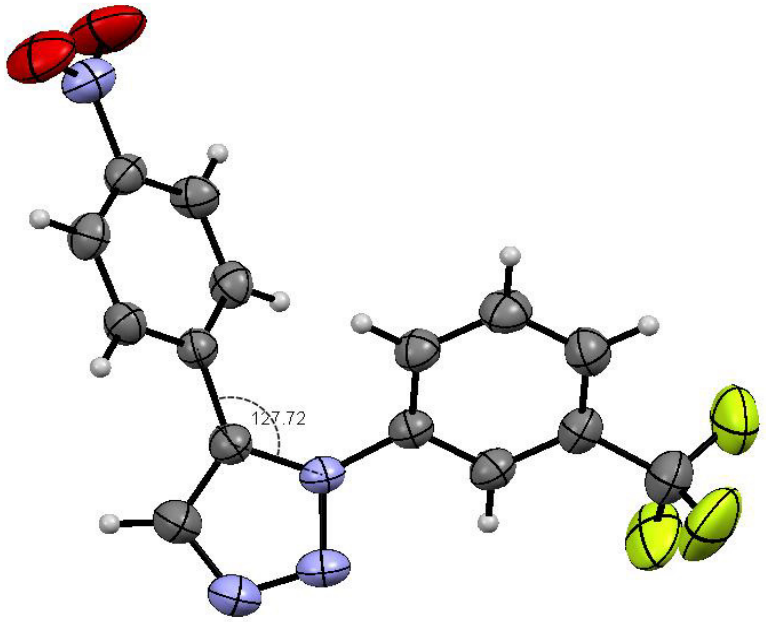
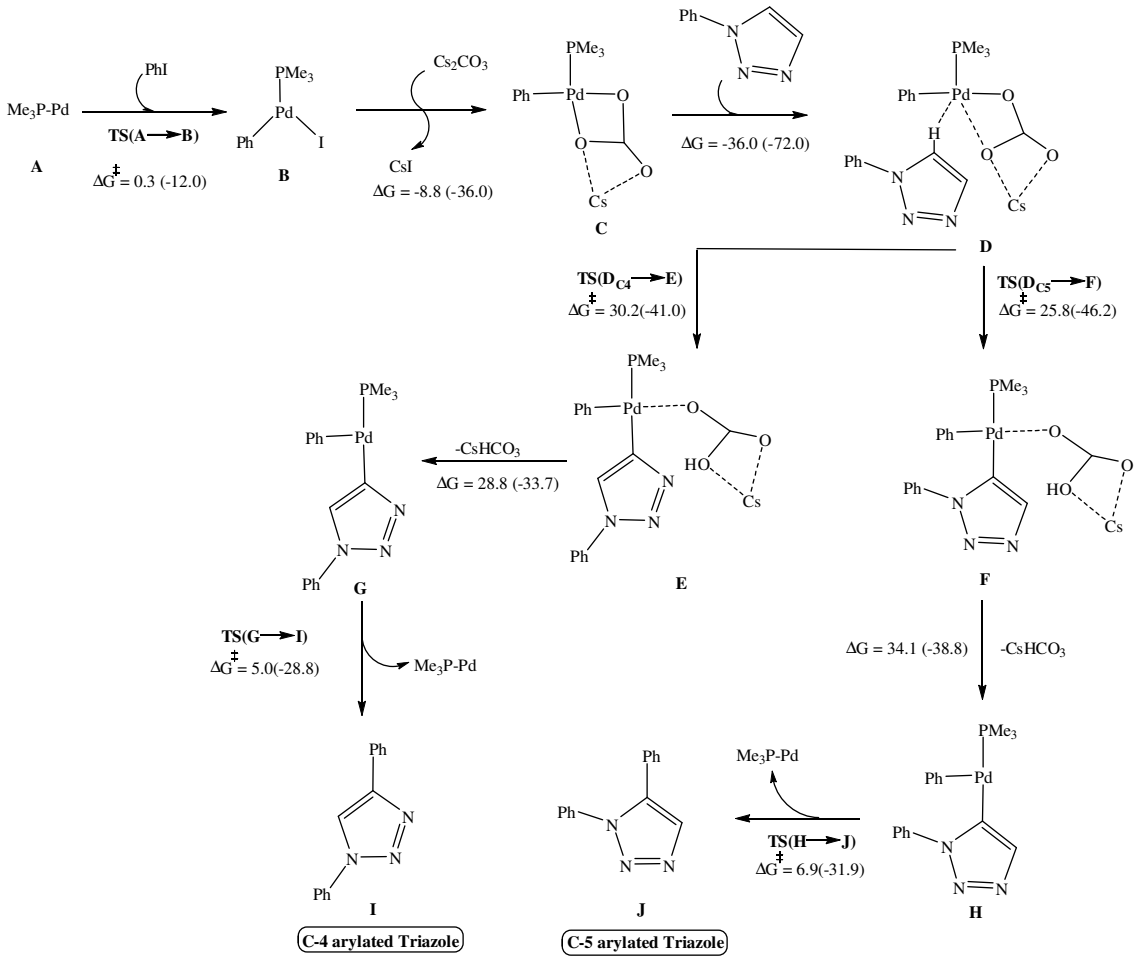


Figure 1. ORTEP single crystal XRD of **1fb**

Computational Studies

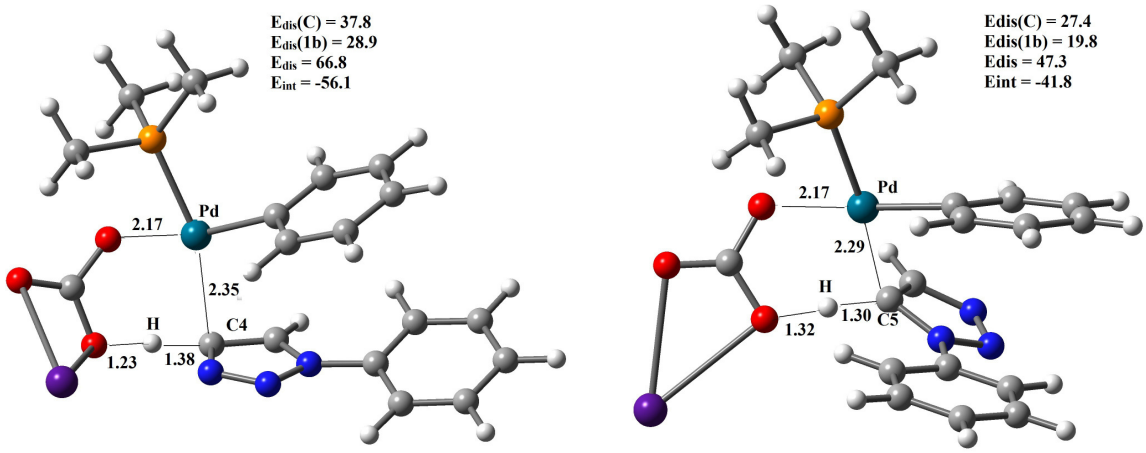
The Pd-catalyzed arylation reaction described in this work is highly regioselective and provides C-5 substituted 1,2,3 triazole as a major product. To gain better insights into the origin of the regioselectivity of the reaction, computational investigations on key steps of the catalytic cycle shown in the scheme 1 were carried out using the 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 mono-trimethyl phosphine Pd(0) active species. All energies are calculated relative to 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 the scheme 2.



Scheme 2. Intermediates involved in the Pd-catalyzed arylation of *N*-aryl 1,2,3 triazole. Free energies and activation free energies computed relative to preceding reacting complexes or intermediate are shown. Parenthesise values indicate free energies and activation free energies computed relative to separated Pd active species **A, 1b**, iodobenzene and Cs_2CO_3

On the basis of catalytic cycle shown in the 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 mono-ligated trimethylphosphine Pd active species (**A**). Initial coordination of iodobenzene to **A** leads to an intermediate in which, Pd coordinates to C–I bond of iodobenzene. The initial coordination of iodobenzene to A is predicted to be exoergic by 12.3

kcal/mol. 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 deprotonation step, it is expected that carbonate ion (CO_3^{2-}) coordinates to the **B** by replacing halide ion. The substitution of I^- by carbonate ion in **B** provides tetra-coordinated Pd intermediate **C**, and the process of halide exchange by carbonate ion in **B** is found to be exoergic by 8.8 kcal/mol. 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 deprotonation of 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 the C–H bond activation which includes oxidative addition of C- H bond, electrophilic aromatic substitution, concerted metallation-deprotonation (CMD) and σ-bond metathesis pathway.[15] In most of the reactions, CMD pathway represents the preferred pathway for the C–H bond activation and deprotonation step.[16] In present reaction also, the CMD route for the deprotonation of C-4 or C-5 proton of **1b** seems to be relevant pathway since it involves the coordination of 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 CMD pathway were located at the M06L level and shown in the 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 the **TS(D_{C5}→F)**. Calculations clearly favour the deprotonation at the C-5 position of **1b** which is in accordance with the experimental observations.



TS(D_{C4}→E) **TS(D_{C5}→F)**

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

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 Pd···C(substrate) bond and the cleavage of 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 catalyst and substrate and distortion in structures of catalyst and substrate at the CMD transition state can be crucial factors in controlling selectivity of reaction.[17] Hence, to identify the contribution of distortion and interaction energies of Pd-complex **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 energy E_{int} between **C** and **1b** in the transition state 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 interaction energy (E_{int}) at the **TS(D_{C4}→E)** is found to be 14.2 kcal/mol higher than the interaction energy (E_{int}) at the **TS(D_{C5}→F)**. However, the stabilizing interactions is 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 total distortion energy (E_{dis}) associated with **TS(D_{C5}→F)**. Overall, deprotonation in the **TS(D_{C5}→F)** is more favourable than the deprotonation in **TS(D_{C4}→E)** mainly because of lower degree of distortions 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 CsHCO3 to form tri-coordinated 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 arylated product, the active catalytic species Pd(0)L is regenerated to complete the catalytic cycle.

Conclusion

We have demonstrated a straightforward method for the synthesis of C-5 substituted *N*-aryl 1,2,3-triazoles. By using combination of $Pd(OAc)_2$ and tris(*o*-tolyl)phosphine as catalyst, arylation of *N*-aryl 1,2,3-triazole have 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 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 discrimination of two transition states which leads to the isomeric products.

Experimental section:

General procedure: A solution of azide (1.00 eq) and Trimethysilyl (TMS)-acetylene (1.5 eq) were taken in MeOH/H_2O (1:1 ratio 5 mL) in 50 mL round bottom flask. $CuSO_4$ (0.1 eq), Sodium Ascorbate (0.2 eq) and K_2CO_3 (2.0 eq) were added and then reaction mixture was closed tightly with stopper and stirred rapidly for 24 hr. Upon completion of 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, afforded crude product. The crude product was purified by column chromatography by using silica gel (100-200 mesh) with hexane: EtOAc as elutant.

By using above mentioned procedure the following triazoles compounds from 1a to 1j were prepared.

1-(4-nitrophenyl)-1*H*-1,2,3-triazole[23] **(1a):** Yield: 245 mg (70%), ^{1}H NMR (300MHz, 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 (126MHz, $CDCl_3$); 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-1*H*-1,2,3-triazole[23] **1(b):** Yield: 390 mg (68%), ^{1}H NMR (500MHz, $CDCl_3$), 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 (126MHz, $CDCl_3$); δ ppm 120.9, 121.9, 128.9, 129.9, 134.6, 137.2.

1-(*p*-tolyl)-1*H*-1, 2, 3-triazole[24] **(1c):** Yield: 369 (62%), ^{1}H NMR (500MHz, $CDCl_3$), 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* =1.01Hz, 1 H). ^{13}C NMR (126MHz, $CDCl_3$); 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-(1*H*-1, 2, 3-triazol-1-yl)pyridine (1e): Yield: 218 mg (71%), ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); δ ppm 114.0, 121.3, 135.3,143.2, 151.9.

1-(4-(trifluoromethyl)phenyl)-1*H*-1, 2, 3-triazole[25] **(1f):** Yield: 220 mg (52%), ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1, 2, 3-triazole[25] **(1g):** Yield: 185 mg (63%), ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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-1*H*-1,2,3-triazole 1(h): Yield: 373 mg (65%), ^{1}H NMR (500MHz, $CDCl_3$) : 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazole[26] **(1i):** Yield: 569 mg (66%), ^{1}H NMR (500MHz, $CDCl_3$); δ ppm 7.53 - 7.62 (m, 5 H) 7.94 - 7.99 (m, 3 H) 8.04 (brs. 1 H). ^{13}C NMR (126MHz, 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 (500MHz, $CDCl_3$); 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** (126MHz, $CDCl_3$); 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-dsubstituted of 1,2,3-triazoles: To a dried 2-neck round bottom flask, were added mono-substituted 1,2,3-triazole (1.0 eq), aryl iodide (1.2 eq), Cs_2CO_3 (2.0 eq) and tris(*o*-tolyl)phosphine (20 mol%) and DMF (3.0 mL). Then reaction mixture was degassed for 10 min at room temperature. After that $Pd(AcO_2)_2$ (10 mole%) was added to the reaction mixture and closed reaction setup was put under N_2 atmosphere. The reaction mixture (RM) was stirred at room temperature for 5 min, and then heated slowly upto 100°C for 20 hr. RM was periodically monitored by TLC. After completion of 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, afforded crude product. The crude product was purified by column chromatography by using silica gel (100-200 mesh) with hexane: EtOAc as eluant.

By using above mentioned procedure the following triazole compounds from **1aa to 1jb** were prepared.

1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole[28]**(1aa)**: Yield: 101 mg (72%) , M. P. ; 157 - 160 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazoles[29]**(1ab):** Yield: 107 mg (69%), M.P. : 187 -190 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazole (1ac): Yield: 109 mg (72%), M.P. : 96 -98 °C; ^{1}H NMR (500MHz, $CDCl_3$); δ ppm 3.78 (s, 3 H), 6.82 -6.77 (m, 2 H), 7.01 - 6.97 (m, 1 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 (126MHz, $CDCl_3$); 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 C15H12N4O3: 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 (500MHz, $CDCl_3$): 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 (126MHz, $CDCl_3$): 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 C18H12N4O2: 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-1*H*-1,2,3-triazole**[30] **(1ba) 154**: Yield: 111 mg (76%), M.P. : 109 – 112 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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-1*H*-1,23-triazole[31] **(1bb)**: Yield: 135 mg (75%); M.P.: 139 -141 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazole (1ca) : Yield 119 mg (82%); M.P.:75 -77 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazole (1cb): Yield: 117 mg (66%); M.P. : 71 -73 °C, ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazole (1cc): Yield: 123 mg (72%); ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, CDCl3); 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)-1*H*-1,2,3-triazole[32] **(1da)** : Yield: 109 mg (75%); M.P. : 71 -73 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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(126MHz, CDCl3); 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-1*H*-1,2,3-triazole-1-yl)pyridine[33] **(1ea)**: Yield: 121 mg (84%); M.P. : 199 -201 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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)-1*H*-1,2,3-triazole (1fa): Yield: 109 mg (81%); M.P. : 110 -113 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 (376MHz, $CDCl_3$): 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 C15H10F3N3: 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)-1*H*-1,2,3-triazole (1fb): Yield: 110 mg (71%); M.P. : 133 -136 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 (376MHz, $CDCl_3$): 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 C15H9F3N4O2: C, 53.90; H, 2.71; N, 16.76. Found: C, 54.20; H, 3.0; N, 16.94.

1-(3-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole (1ga): Yield: 108 mg (84%); M.P. : 85 - 88 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 C15H13N3O: 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-1*H*-1,2,3-triazole (1ha): Yield: 150 mg (86%); M.P. : 127 -130 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 C17H14N4O2 : 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)-1*H*-1,2,3-triazole (1hb): Yield: 196 mg (89%); M.P.: 139 -141 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 C18H16N4O3: 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-1*H*-1,2,3-triazole[34] **(1ia)**: **Yield:** 132 mg (72%); M.P. : 120 - 123 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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-1*H*-1,2,3-triazole (1ja): Yield: 159 mg (83%); M.P. : 161 -163 °C; ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 for $C_{24}H_{17}N_3$: 348.1501 found 348.1497. Anal. Calcd for C24H17N3: 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-1*H*-1,2,3-triazole (1jb): Yield: 171 mg (82%); ^{1}H NMR (500MHz, $CDCl_3$); 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 (126MHz, $CDCl_3$); 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 C25H19N3O: 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] Density functional theory 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, 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 intrinsic reaction coordinate (IRC) calculations were performed to verify the transition state structures. [22]

Acknowledgments

The authors would like to thank the Vice Chancellor, DIAT for providing the infrastructural facilities. Financial support from ER&IPR, DRDO towards **"DRDO-DIAT programme on Nano Materials"**, New Delhi is gratefully acknowledged.

Supporting Information

NMR (^{1}H, ^{13}C, ^{19}F, ^{15}N) spectra S3 – S22, HPLC graphs S23-S29, Single crystal XRD data S29-S32, Computational Studies data S33 – S38.

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