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Design and applications of new phosphine-free tetradentate Pd-catalyst: Regioselective C-H activation on 1-substituted 1,2,3-triazoles and indoles(NH-free)

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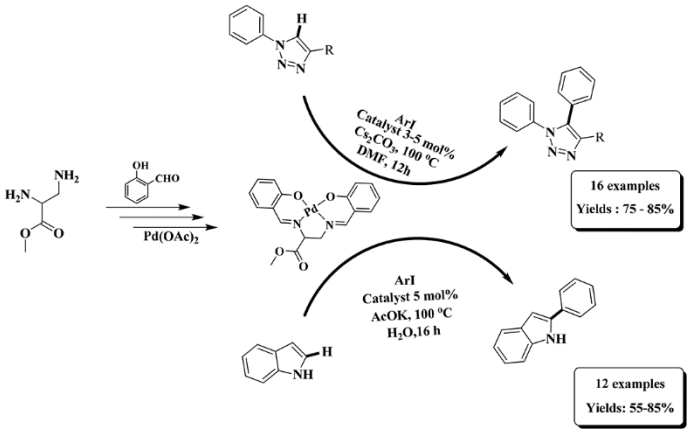
Supplementary data (general experimental details, characterization data) copies of the ^{1}H NMR and LC-MS of all synthesized compounds associated with this article can be found, in the online version

ABSTRACT

This article describes the synthesis of a new phosphine free tetradentate Pd catalyst by using DL-2,3-diaminopropionic acid. The complex was characterized by Mass, IR, and ^{1}HNMR. The catalyst is air stable at room temperature and non-hygroscopic. Application of this new catalyst to regioselective C-H activation on 1-substituted 1,2,3-triazole and indoles with aryl iodides to get corresponding C-5 and C-2 arylated products with satisfactory yields. All the products were characterized by spectroscopic studies.

GRAPHICAL ABSTRACT



KEYWORDS

Introduction

C-H activation of aromatic and hetero aromatics became area of interest as it has many advantages to achieve new C-C bonds without the requirement of halo groups or any other leaving groups. So far, many metals have been used for the C-H activation[1–6] like Ru, Pd, Ni, Cu & Fe and also developed several ligands (phosphine and non-phosphine) to enhance the reactivity as well as to increase the scope of the reactions. The wide range of significance of C-C bond construction in organic and material synthesis induced to work on highly active and stable Pd catalyst which is very versatile and effective. Since last few years several research groups have worked on the Pd with different ligands such as phosphines,[7] nitrogen and carbon containing ligands.[8] By adding these ligands, increasing the bulkiness and electron donating functional groups will help to proceed both oxidative and reductive elimination steps in catalytic cycle and achieve desire product formation.

Till date, a number of phosphine free ligands,[8,9] were invented to avoid phosphine ligands as they are very toxic, air sensitive and expensive. Common ligands used to complex with Pd are monodentate, bidentate, tri and tetradentate donors by using various substrates

having electron donating nature. The Palladium catalyst having multifunctional donor ligands may provide stability and active Pd species. From the literature, N4-tetradentate dicarboxyamidate/dipyridyl palladium (II) and Amido/Pyridyl Carboxylate Palladium (II) were used for heck reactions.[10] N -donor ligands shows significant catalytic activity with aryl halides and anionic amides (deprotonated amides) ligands strongly donate to metal center and stabilizing various oxidation states of metal center. This type of Pd complex impart thermodynamic stability to active metal species. Most of these complexes are applied for C-C bond formation and a very few reports are available on C-H activation. Therefore, these factors are motivated towards designing of a new phosphine free Pd catalyst and application in C-C bond formation by C-H activation.

1, 2, 3-triazole and indole based heterocycles are the corner stone of medicinal chemistry due to their important biological activities and their wide applications in the synthesis of pharmaceuticals, receptors, fluorinated hydrogels, antibiotics, antitubercular agents, ligands, surfactants, nucleosides, and their applications in radiochemistry.[11–15] So far, there are only a few references are available on Palladium catalyzed regioselective C-H activation on 1,2,3-triazoles and indoles by using phosphine ligands or additives.[16] Gevorgyan group has first developed a method for direct Pd-catalyzed arylation on 1,2,3-triazoles by using $Pd(PPh_3)_2Cl_2/Bu_4NOAc$ and later Oshima team has developed same transformation in microwave at 250 ^oC by using $Pd(OAc)_2/PCy_3$ catalytic system. Recently, Banerjee team reported same transformation by using $Pd(OAc)_2$ with the combination of $(o\text{-tolyl})_3P$ as ligand. Whereas C-H activation on indoles at C-2 position in presence of Pd catalyst and phosphine ligands also been reported. To avoid phosphine ligands and additives, we have designed and developed a new tetradentate phosphine free Pd catalyst and applied for the regioselective C-H

activation on 1,2,3-triazoles without using any other additives under relatively mild reaction conditions.

In this article, we describe the synthesis of Pd (II) complex of tetradentate imino/hydroxyl methyl carboxylate and found the catalytic activity for C-C bond formation on 1,2,3-triazoles and Indoles. Herein, imino nitrogen atoms acts as donor ligands and anionic oxygen atoms coordinate with Pd towards oxidative addition. As we have previous experience with Co-Salen complexes which are prepared by using this 2,3-diamino propionic acid for chiral cycloaddition reactions,[17] same here we used it for making Pd- salen complex to achieve regioselective C-H activation.

New Pd catalyst (5) was synthesized from DL-2,3-diaminopropionic acid monohydrochloride in 3 steps (Scheme 1). Esterification of compound 1 was performed with thionyl chloride in methanol at 80 °C for 16h to offered compound 2, which further treated with 2-hydroxy benzaldehyde, in dichloromethane for 16h to get di imine (compound 4). The purified compound 4 was reacted with $Pd(OAc)_2$in THF at rt to obtain Pd(0) complex (compound 5) as yellow solid after washings with diethyl ether. The obtained Pd complex is soluble in polar solvents such as acetonitrile, methanol, dimethylsulphoxide, dimethylformamide etc. and found to be non-hygroscopic and air stable at room temperature. It was characterized by IR, ^{1}H-NMR and Mass spectroscopy. ^{1}H NMR of compound-4 indicates two phenolic hydrogens appears at δ12.966ppm to δ12.985ppm and which were absent after formation of Pd complex (5). Also, imine attached protons were shifted to up filed to δ8.308ppm from δ8.658in ligand **4.** The elemental analysis of compound 5 is in good agreement with the molecular formula proposed and it appears that compound 4 coordinates to the Pd metal. It was confirmed by mass analysis

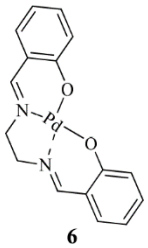
(M-1 = 428.9; exact mass of complex is 430.01). These results indicate that Pd was coordinated with two imine and hydroxyl functional groups to act as tetradentate ligand.

Result and discussion

Activity of Pd catalyst initially, we examined for C-C coupling between 1-substituted-1,2,3-triazoles[16,18] and aryl iodides through C-H activation. To achieve ideal reaction conditions screened different parameters such as temperature, solvent, bases and catalyst loading (**Table 1**). In case of DMSO, 1, 4-Dioxane, NMP, H_2O and toluene as solvents achieved minor amount of product (8-12%; entries 1-7) by LCMS. In case of bases, mostly focused on K_2CO_3 and Cs_2CO_3 because these are mild and water soluble. Organic bases (Et_3N; entry 9) did not initiate the reaction. Combination of DMF with Cs_2CO_3 works much better than the entry 8 (DMF/K_2CO_3). Finally, better yields were achieved by taking 3mol % of Pd catalyst in DMF by using Cs_2CO_3 as base (entry-12). Here (Tabel-1) arylation was observed exclusively at C-5 position of 1,2,3-triazole because of its electrophilic nature of C-5 carbon and it was supported by NOE analysis. Irradiation on H-4 at δ8.33ppm giving signal enhancement of H-13, 17 at δ7.56ppm . This spatial interaction indicating that 4 –nitro benzene group attacked on 5^{th} position. The arylation was occurs at C-5 position of triazole because of the energy of the transition state of C-5 is less than the C-4 transition state as reported in the literature.[16]

After establishing the optimal reaction conditions, the C-H activation of 1-subsituted-1,2,3-trizoles bearing electron donating, withdrawing and neutral functional groups with various aryl iodides to determine the generality of this catalytic method (**Table 2**). All the reactions with different aryl iodides and various 1-subsituted-1,2,3-trizoles proceeded to satisfactory yields indicating less effect of electronic properties of substituents presence on both the reactants. Also

tested 1,4-substituted-1,2,3-trizoles towards C-H activation and found same reactivity compared to 1-subsituted-1,2,3-trizoles (entries: 5a, 8a, 11a, 13a & 14a). And also we tried with aryl bromide (bromo benzene) and aryl triflate (phenyl triflate) in place of aryl iodides with same optimized conditions, we observed that traces of desired product (< 5%) and major unreacted starting material. Instead of 2,3-diamino propionic acid we replaced with simple 1,2-diaminoethane treated with compound 3 for the preparation of Pd catalyst 6 and found the same regioselectivity but less yields compared to the Catalyst **5 (entries 13 and 21).** So here we focused more on preparation of catalyst 5 because chelated or bulky groups plays an important role in reductive elimination steps in Pd catalytic cyclic.



6

Result and discussion: C-H activation on Indoles at C-2 arylation

The optimization for suitable reaction conditions was initiated with model reaction using Indole (0.5 mmol) and iodobenzene (1 mmol) using different additives in presence of Pd catalyst (5mol %). Reaction solvent plays very crucial role in selectivity as well as overall yield. So we started our investigation with solvent screening. The product formation was poor in aprotic solvents such as toluene (etntry-6, 21%), DMF (entry 5 & 8, traces), THF (entry-9, 10%) and DMSO (32 to 50%). In aprotic solvents, we have found good yield with AgOAc (66%) as additive compare to oxone (32%), H_2O_2 (traces) and KOAc (no reaction) in DMSO.

Whereas in polar protic solvent such as PEG we obtained same yield (~50%) as in DMSO and AgOAc as additive, which forced us to screen more oxidizing reagents in PEG. Under identical conditions other additives such as PIDA, $NaIO_4$, H_2O_2 and KOAc gave well to moderate yield (entry 11 to 17). However, we noticed that when we used KOAc in DMSO and PEG we didn't observed any conversion, whereas in the mixture of solvent PEG and H_2O, KOAc shows promising conversion, which lead us to conclusion that may be water is playing crucial role for co-ordination of tetradentate catalyst, which results in good yields. Obviously another aspect is eco-friendly and economical reaction condition. In a parallel study, when we reduced catalyst loading to 2.5%, the reaction was not completed even after 48h, it shows only 30-40% of conversion. We also spent our time to optimize equivalence of aryl iodide. After some attempts, it was found that by adjusting the substrate ratio (1:2), increasing the catalyst loading (5mol %), 100 °C and prolonging the reaction time (12h), the yield was drastically elevate to 76% (entry 20).

With optimized reaction condition in hand, the substrate scope of this C-2 arylation reaction was investigated. The indole derivatives bearing electron donating groups such as 5,6-dimetoxy (entry 8) or mild electron withdrawing groups such as chloro indole (entry 10 and 12) reacts very well with aryl iodides and provide the products in good yields. In the case of iodo aryl derivatives with both electron donating (4-methyl, 3-methyl, 3-Br, 4-Cl, 4-isopropyl; entries-1, 2,3,4,8,10,11and 12), neutral and electron withdrawing (4-CF_3, entry 5) as well as bulkier groups on the aromatic ring (naphthalene; entry 9) participated smoothly in this reaction with an average to good yield of **3**. Particularly, this reaction also works well with bromo substituted aryl iodide (entry 3) which can function as handle for further transformations.

Experimental

Methyl 2,3-diaminopropanoate dihydrochloride (2)

Thionyl chloride (42.8g, 360 mmol) was added drop wise to a stirred suspension of 2, 3-dimaino propionic acid (5g, 48.07 mmol) in MeOH (75mL) over a period of 5min . The reaction mixture was heated to 80 °C for 16h . After that the reaction mixture was cooled and the volatiles were removed under reduced pressure to obtained compound 2(6.5g, 98%) as an off white solid. Crude mass complies, Crude compound directly used for next step.

Methyl 2, 3-bis ((E)-2-hydroxybenzylideneamino)propanoate (4)

To a stirred suspension of Diamine hydrochloride salt **2** (1.3g, 3.7 mmol) in dichloromethane (10mL), were added triethyl amine (1.3mL, 9.3 mmol) and $MgSO_4$ (1.8g, 14.9 mmol). After stirring for 1.5hours at room temperature a solution of the aldehyde **3**(1.57g, 7.46 mmol) in dichloromethane (5mL) was added. The reaction mixture was stirred at rt for 16h . After completion of reaction by TLC, the reaction mixture was diluted with dichloromethane and water separated the layers, organic layer was separated, dried over Na_2SO_4 concentrated under reduce pressure. The obtained crude compound was purified by grace system using 10-20% ethyl acetate gave pure compound as pale yellow solid (1.5g, 68%). M.P: 110-114 °C; ^{1}H NMR (DMSO, 400MHz): δ (ppm) 12.98 (d, *J* = 7.3Hz, 2H), 8.59-8.67 (m, 2H), 7.47 (s, 1H), 7.41-7.48 (m, 1H), 7.30-7.39 (m, 2H), 6.84-6.94 (m, 4H), 4.64 (dd, *J* = 6.2, 4.8Hz, 1H), 4.03-4.18 (m, 3H), 3.73 (s, 3H). LCMS (ESI +): *m/z* calcd for $C_{18}H_{18}N_2O_4$ $[M + H]^+$ 326.13; found 327.0. FT-IR (KBr) υ: 3487, 3053, 2997, 2928, 2908, 2742, 2357, 1732, 1625, 1573, 1489, 1446, 1392, 1274, 1203, 1109, 1055, 979, 889, 823, 750cm $^{-1}$

Catalyst 5

Ligand **4** (391mg, 1.2 mmol) was added to a stirred orange coloured suspension of palladium acetate (224.49mg, 1 mmol) in tetrahydrofuran (20mL) in one portion. After the solution was stirred for 12h at room temperature, a pale yellow precipitate was obtained. The solvent was removed completely under reduced pressure, and the resulting solid was washed with excess diethyl ether to obtain pure 5in 74% yield. Pale yellow colour solid; M.P:286-291 °C; ^{1}H NMR (DMSO, 400MHz): δ (ppm) 8.29 (d, *J* = 15.9Hz, 2H), 7.45 (dd, *J* = 7.9, 1.8Hz, 1H), 7.28-7.41 (m, 3H), 6.86 (t, *J* = 9.4Hz, 2H), 6.55-6.63 (m, 2H), 4.84 (d, *J* = 6.1Hz, 1H), 4.15-4.24 (m, 1H), 4.08-4.15(m, 1H), 3.73 (s, 3H); ^{13}CNMR (DMSO-d6, 400MHz) δ169.08,165.44,164.71,163.59,160.87,135.22,135.19,134.75,135.73,134.73,120.99,120.71,120.69,120.37,114.66,114.50,70.52,61.96,53.25. LCMS (ESI +): *m/z* calcd for $C_{18}H_{16}N_2O_4Pd$ [M-H] $^{+}$ 428.90; found FT-IR (KBr) υ: 3016, 2954, 2360, 1735, 1618, 1525, 1444, 1396, 1305, 1222, 1141, 1080, 1014, 900, 852, 752cm $^{-1}$.

General procedure for the synthesis of compounds C-5 arylation of 1-aryl-1, 2, 3-triazoles

To a stirred solution of N- substituted 1, 2, 3-triazole (1.0 eq), aryl iodide (1.1 eq), Cs_2CO_3 (2.0 eq) in DMF (3.0mL) was added Palladium catalyst **5** (3-5mol %) and the reaction mixture was stirred at 110 °C for 16h . The progress of reaction was monitored by TLC and after completion of SM, the reaction mixture was cooled and diluted with EtOAc and water, separated layers, aqueous layer was extracted with EtOAc(2 x10mL) combined organic layers were washed with water(25mL) followed by brine. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The obtained crude compound was purified by flash-column chromatography was performed using silica gel (100-200 mesh) with 5-20% ethyl acetate in hexane gave pure compound.

5-(4-nitrophenyl)-1-phenyl-1H-1,2,3-triazole[19] (1a)

Pale yellow solid; Yield: 82%; M.P:140- 144 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm) 8.31-8.32 (m, 1H), 8.19-8.25 (m, 2H), 8.00 (s, 1H), 7.46-7.54 (m, 3H), 7.40-7.44 (m, 2H), 7.33-7.38 (m, 2H). LCMS (ESI +): *m/z* calcd for $C_{14}H_{10}N_4O_2$ [M + H] $^+$ 266.08; found 267.10. FT-IR (KBr) υ: 3439, 3427, 2924,2852,2362,1734,1595,1531,1454,1346,1111,1053,844,759,682.80,574cm $^{-1}$

1, 5-diphenyl-1H-1, 2, 3-triazole[20] (2a)

Off white solid; Yield: 84%; M.P: 107-111 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm) 7.87 (s, 1H), 7.42-7.46 (m, 3H), 7.33-7.39 (m, 5H), 7.20-7.24 (m, 2H). LCMS (ESI +): *m/z* calcd for $C_{14}H_{11}N_3$ [M + H] $^+$ 221; found 222.1. FT-IR (KBr) υ: 3442, 2922, 2856,2360,1716,1589,1541,1487,1375,1303,1220,1136,1058,987,912,856,765.74,686,561cm $^{-1}$

General procedure for synthesis C-2 substuited indoles

A mixture of indole (0.5 mmol), aryl halide (1 mmol), KOAc (1.5 mmol), catalyst **5** (5mol %) and water (10 vol.) were vigorously stirred at 100 °C for 16h . Progress of reaction was monitored by TLC which shows consumption of SM and formation of new spot. Reaction mixture was allowed to come at room temperature; the reaction mixture was diluted with ethyl acetate (5mL) and filtered. The liquid phase was washed with water and dried over dry sodium sulfate and evaporated under reduced pressure left behind crude mass. Obtained crude compound was purified by flash column chromatography on silica gel (mesh size) using 10% ethyl acetate in pet ether as eluent gave compound 2a as white solid.

2-p-tolyl-1H-indole[21] (3a)

Off white solid; Yield: 83%; M.P: 130-134 °C; ^{1}H NMR ($CDCl_3$, 500MHz): δ (ppm) 8.30 (br s, 1H), 7.60-7.64 (m, 1H), 7.54-7.58 (m, 2H), 7.39 (dd, *J* = 8.1, 0.8Hz, 1H), 7.23-7.29 (m, 5H), 7.18 (td, *J* = 7.6, 1.2Hz, 1H), 7.09-7.13 (m, 1H), 6.78 (dd, *J* = 2.1, 0.9Hz, 1H), 2.40 (s, 4H). LCMS (ESI +): *m/z* calcd for C15H13N [M + H] $^{+}$ 207.10; found 208.1; FT-IR (KBr) υ: 3438.26, 3231.87, 3200.04, 3110.35, 3047.66, 2915.53, 2856.70, 1581.70, 1495.86, 1346.37 1294.29, 1183.38, 1043.53, 926.84, 824.60, 789.88, 609.53, 508.26cm -1

2-m-tolyl-1H-indole[22] (3b)

White solid; Yield: 78%; M.P: 137-141 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm) 8.33 (br s, 1H), 7.63 (d, *J* = 7.8Hz, 1H), 7.43-7.51 (m, 3H), 7.40 (d, *J* = 7.8Hz, 1H), 7.34 (t, *J* = 7.6Hz, 1H), 7.09-7.22 (m, 4H), 6.82 (d, *J* = 2.2Hz, 1H), 2.43 (s, 4H). LCMS (ESI +): *m/z* calcd for C15H13N [M + H] $^{+}$ 207.10; found 208.10; FT-IR (KBr) υ: 3421.87, 1610.63, 1540.23, 1502.61, 1432.21, 1329.98, 1236.42, 1176.63, 1117.80, 1064.75,1003.99, 932.62, 843.89, 798.56, 748.41, 692.47, 645.22, 591.21, 509.23cm -1

Conclusion

In conclusion, we have designed and developed a new phosphine free tetradentate Pd (0) catalyst and its application for regioselective C-H activation of 1-substituted 1,2,3-traizole and 1,4-substituted 1,2,3-traizole at C-5 position and regioselective C-2 arylation of indole (-NH free) with various aryl iodides. The desired products were obtained in satisfactory isolated yields. Synthetic applications of this tetradentate catalyst are under investigation in our organization.

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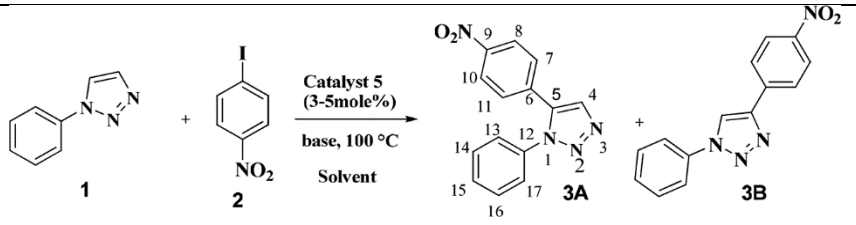
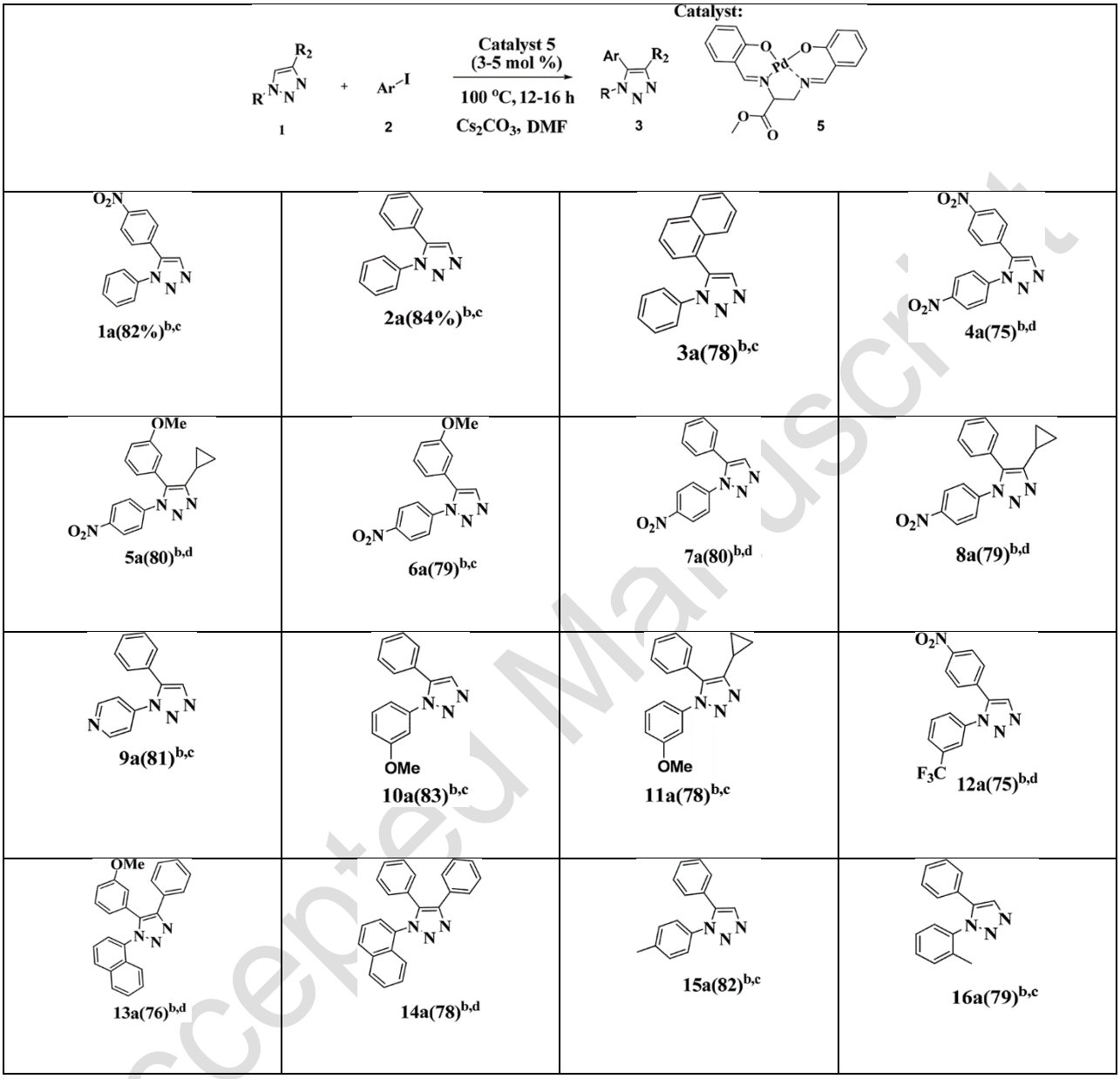
Table 1. Optimization conditions between 1-phenyl 1,2,3-triazole & 1-iodo-4-nitrobenzene.



Entry	Solvent	Base	Time (h)	Temp (°C)	Yield (%)[a,b]
1	DMSO	K_2CO_3	24	100	5
2	DMSO	Cs_2CO_3	24	100	10
3	1,4-dioxane	K_2CO_3	24	100	---
4	1,4-dioxane	Cs_2CO_3	24	100	Traces
5	NMP	Cs_2CO_3	16	150	8
6	H_2O	Cs_2CO_3	16	100	<12
7	Toluene	Cs_2CO_3	16	100	Traces
8	DMF	K_2CO_3	16	100	30
9	DMF	Et3N	16	100	---
10	DMF	$NaHCO_3$	16	100	trace
11	DMF	Na_2CO_3	16	100	<4
12	**DMF**	**Cs_2CO_3**	**12**	**100**	**82**
13	DMF	Cs_2CO_3	12	100	28 [c]

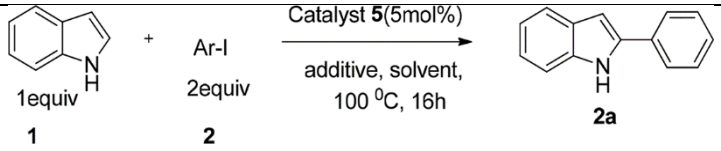
Reaction conditions: 1-phenyl 1,2,3-traizole(1 mmol), 1-iodo-4-nitro benzene(1mmol), catalyst 5(3-5mol %), base(2 eq) and solvent (2mL), [a]isolated yield, [b]exclusively 3A . [c] with Catalyst 6.

Table 2. Scope of substrates[a].



[a]Reaction conditions:1-phenyl 1,2,3-traizole(1 mmol), aryl halide (1mmol), catalyst 5 (3-5mol %), Cs_2CO_3(2 eq) and DMF (2mL), 100 °C, 12-16h, [b] Isolated yield after column chromatography, [c] Calayst used as 3mol %, 12h, [d] catalyst used as 5mol %, time 16h.

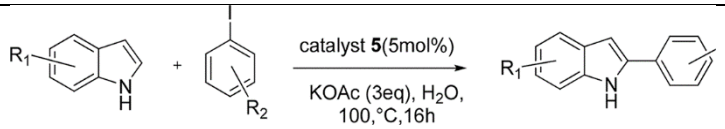
Table 3. Optimization of reaction conditions.

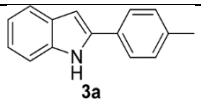
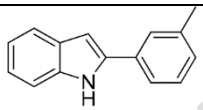
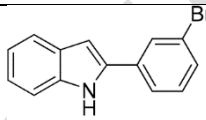
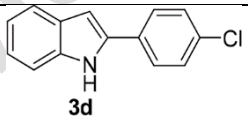
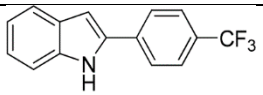
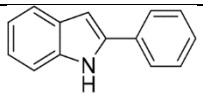
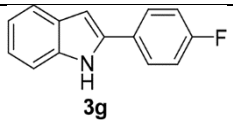
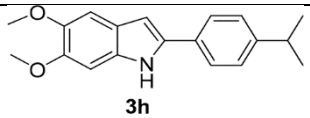


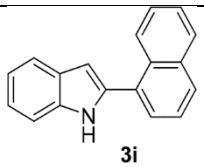
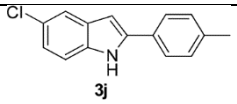
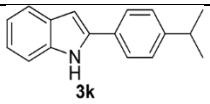
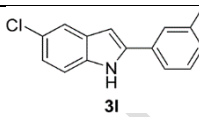
Entry	Catalyst (mol %)	Solvent	Additives	Yield (%)
1	$Pd(OAc)_2$(5)	DMSO	AgOAc	22
2	Catalyst-5 (10)	DMSO	AgOAc	66
3	Catalyst-5 (5)	DMSO	Oxone	32
4	Catalyst-5 (5)	DMSO	33% H_2O_2	--
6	Catalyst-5(5)	Toluene	AgOAc	21%
7	Catalyst-5 (5)	DMSO	KOAc	No reaction
8	Catalyst-5 (5)	DMF	AgOAc	Traces
9	Catalyst-5 (5)	THF	AgOAc	10
10	Catalyst-5 (5)	PEG	AgOAc	62
11	Catalyst-5 (5)	PEG	PIDA	42
12	Catalyst-5 (5)	PEG	$NaIO_4$	42
13	Catalyst-5 (5)	PEG	H_2O_2	21
14	Catalyst-5 (5)	PEG	MgO	42
16	Catalyst-5 (5)	PEG + H_2O	KOAc	56

17	Catalyst-5 (5)	PEG	CsOAc	52
18	Catalyst-5 (5)	H_2O	NMO	43
19	Catalyst-5 (5)	H_2O	AgOAc	68
20	**Catalyst-5 (5)**	**H_2O**	**KOAc**	**76**
21	Catalyst-6(5)	H_2O	KOAc	15

Table 4. Scope of direct C-2 Arylation of indoles with various aryl halides.



Entry	R1	R2	Product	Yield (%)[b]
1	H	4-Me	 **3a**	83
2	H	3-Me	 **3b**	78
3	H	3-Br	 **3c**	66
4	H	4-Cl	 **3d**	72
5	H	4-CF3	 **3e**	63
6	H	H	 **3f**	76
7	H	4-F	 **3g**	62
8	5,6-OMe	4-isopropyl	 **3h**	65

9	H	1-napthalene	 3i	56
10	5-Cl	4-Me	 3j	75
11	H	4-isopropyl	 3k	62
12	5-Cl	3-Me	 3l	68

[a]Reaction conditions: Indole (0.5mmol), aryl halide (1 mmol), KOAc (1.5 mmol), Catalyst (5mol %), H_2O (10 vol), 100°C,16h; [b] Isolated yield.

Scheme 1.