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Cu-Catalyzed arylation of amino group in the indazole ring: Regioselective synthesis of pyrazolo-carbazoles

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Cu (II)-Catalyzed cross-coupling of various aryl boronic acids with 5 and 6-amino indazoles has resulted the (arylamino)-indazoles. These resulted (arylamino)-indazoles have been utilized in synthesizing medicinally important pyrazole fused-carbazoles *via* Pd(II)-catalyzed cross-dehydrogenative coupling (CDC). This combined *N*-arylation/*C*-H arylation strategy has been successfully applied in regioselective synthesis of polyheterocycles 3,6-dihydropyrazolo[3,4-c]carbazoles and 1,6-dihydro pyrazolo[4,3-c]carbazoles. Quantum chemical analysis has been carried out to understand the regioselectivity and to trace the potential energy surface of the entire reaction on 5-*N*-aryl-indazole conversion to the corresponding carbazole.

Introduction

Transition–metal catalyzed *N*-arylations are important tools in organic synthesis.[1] Due to the wide application of nitrogen containing compounds in the synthesis of natural products, in biology and in material science; many synthetic methods have emerged over the years. Besides the Cu-catalyzed traditional Ullmann procedures,[2] the Pd-catalyzed *N*-arylation reaction championed by Buchwald and Hartwig has been a major breakthrough in this field.[3] Despite these significant improvements in this chemistry, limitation such as air and moisture sensitivity, functional-group tolerance and high cost of palladium still exists. In 1998 Chan[4] and Lam[5] independently reported a general applicable protocol for the *N*-arylation of amines in the presence of copper (II) acetate and boronic acids as coupling partner at room temperature. Collman made the procedure catalytic by using $[Cu(OH)TMEDA]_2Cl_2$ as Cu-source.[6] Due to the simplicity in reaction conditions and functional group tolerance this Cu-salt promoted Chan-Lam coupling[7] became a valuable tool particularly during structure activity relationship (SAR) study in medicinal chemistry.[8]

The indazole scaffold[9] has been classified as a privileged heterocyclic core and specially (arylamino)-indazoles are frequently described in different therapeutic areas (Fig. 1).[10] Despite their importance, methods for the arylation of the amino group in the indazole ring remain limited. The majority of the methods provide arylation at *N*-1 position,[11] with a few offering general protocols to *N*-arylation of *C*-amino group.[12] Thus a general method for the arylation of the amino group in the indazole ring would offer a valuable synthetic tool for the synthesis of these important molecules.

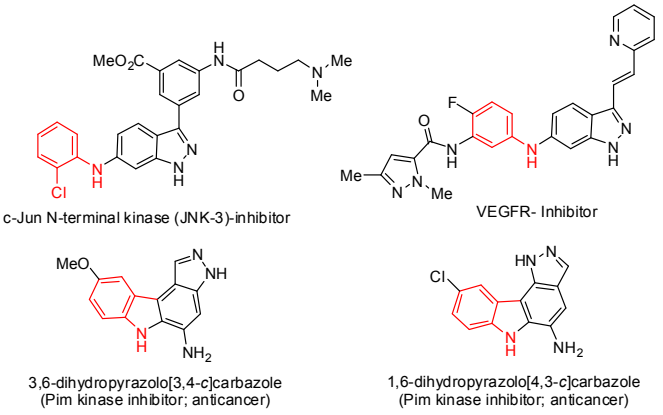
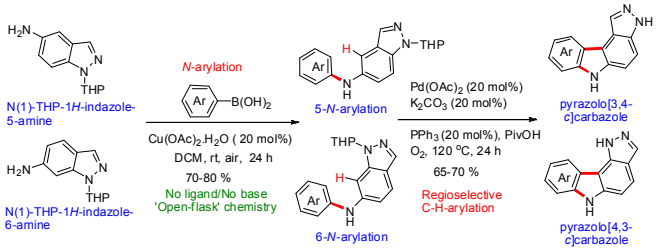


Fig.1 Biologically important (arylamino)-indazole and pyrazolo-carbazoles

Results and discussion

We have recently reported an efficient protocol for the Cu-catalyzed *N*-arylation of 2-amino-*N*-heterocycles with boronic acids under base and ligand free conditions.[13] This type of cross-coupling protocol would be of even greater appeal if it were to be applicable to a wider range of heterocyclic amines, allowing the synthesis of a variety of poly-heterocycles compounds.[14] Towards this endeavor herein, we wish to report the Cu-catalyzed arylation of the amino group in the indazole

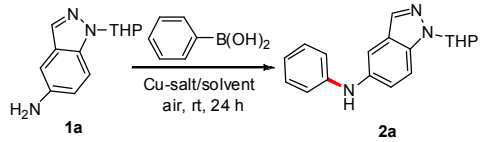
ring in air under base and ligand free conditions. We further report a new set of Pd-catalyzed optimized conditions for cross-dehydrogenative coupling (CDC) in regioselective synthesis of medicinally important heterocycles 3,6-dihydropyrazolo[3,4-c]carbazole[15] and 1,6-dihydropyrazolo [4,3-c]carbazoles[15] (Scheme 1).



Scheme 1. Formation of pyrazolo-carbazole *via* Cu-catalyzed *N*-arylation and Pd-catalyzed C-H arylation

In an effort to find an optimized catalytic system for the arylation of amino group in the indazole ring, a model reaction by using phenyl boronic acid and 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (**1a**) (synthesized by protection of nitro indazoles by using 3,4-dihydro pyran[16] followed by reduction of nitro with Pd/C in methanol) was investigated in detail (Table 1) by varying different Cu-source and solvents at room temperature for 24 h. Initially, we have carried out the cross-coupling reaction by using stoichiometric amount of $Cu(OAc)_2$ (1.0 equiv) in DCM to our delight the *N*-arylated product was isolated in 65% yield (entry1, Table1).

Table 1 Optimization of the reaction conditions [a]



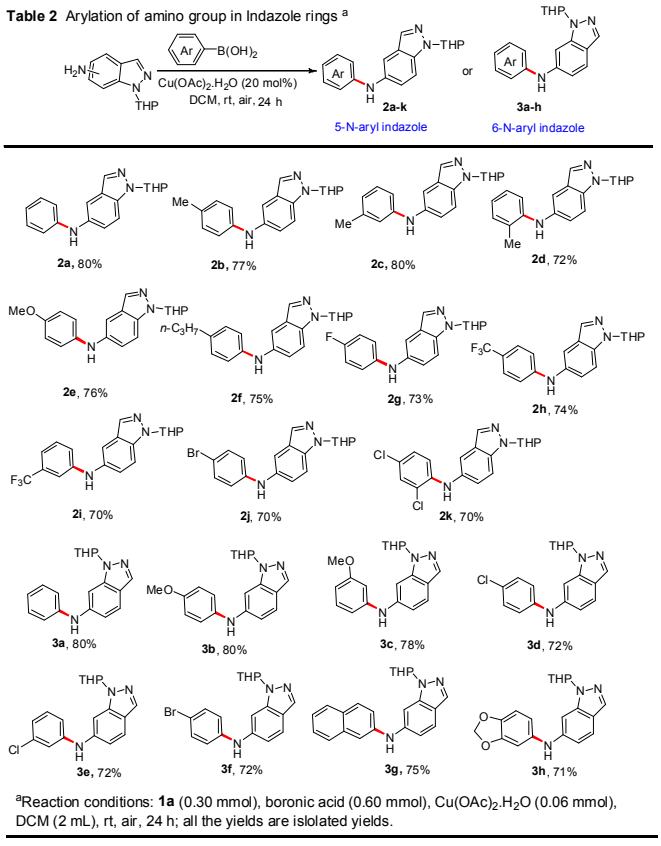
entry	Cu-salt	mol (%)	solvent	yield(%)[b]
1	$Cu(OAc)_2$	100	DCM	65
2[c]	$Cu(OAc)_2$	100	DCM	63
3[d]	$Cu(OAc)_2$	100	DCM	55
4	CuCl	100	DCM	20
5	$CuCl_2.2H_2O$	100	DCM	20
6	$Cu(NO_3)_2.3H_2O$	20	DCM	40
7	$Cu(OAc)_2.H_2O$	100	DCM	70
8	**$Cu(OAc)_2.H_2O$**	**20**	**DCM**	**80**
9	$Cu(OAc)_2.H_2O$	10	DCM	60
10	$Cu(OAc)_2.H_2O$	20	MeOH	30
11	$Cu(OAc)_2.H_2O$	20	MeCN	20
12	$Cu(OAc)_2.H_2O$	20	DCE	60
13	$Cu(OAc)_2.H_2O$	20	Toluene	40
14[e]	$Cu(OAc)_2.H_2O$	20	DCM	80
15[f]	$Cu(OAc)_2.H_2O$	20	DCM	20

[a]Reaction conditions: **1a** (1.0 equiv), phenyl boronic acid (2 equiv), $Cu(OAc)_2.H_2O$ (20 mol%), DCM (2 mL), rt ; [b]isolated yields; [c] Et_3N used as base; [d] pyridine used as base; [e] reaction under O_2 atmosphere; [f]reaction under N_2 atmosphere.

When we used different bases (entries 2-3, Table 1) with $Cu(OAc)_2$, in DCM no remarkable change was observed in the product yield (63-55%). We further screened other copper sources such as CuCl (entry 4, Table 1), $CuCl_2.2H_2O$ (entry 5, Table 1), $Cu(NO_3)_2.3H_2O$ (entry 6, Table 1) and it was observed that $Cu(OAc)_2.H_2O$ resulted in best yield 70% (entry 7, Table 1). Encouraged by this finding we performed the reaction catalytically and found 20 mol% $Cu(OAc)_2.H_2O$ was sufficient enough for smooth cross-coupling and the isolated yield was 80% (entry 8, Table 1). An attempt to further reduce the amount of $Cu(OAc)_2.H_2O$ (10 mol%) remained unsuccessful (entry 9, Table 1). Solvent (DCM) played an important role in this reaction as other solvents like MeOH, MeCN, DCE and toluene (entries 10-13, Table 1) were less effective. Reaction under 1atm O_2 did not show any further improvement in the yield of the reaction (entry 14, Table 1) while incomplete conversion and poor yields (20%) were observed under N_2 atmosphere (entry 15, Table 1) suggesting that O_2 (air) plays a vital role in the catalytic cycle.

With these results in hand the generality of this Cu-catalyzed reaction was examined with different 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-amines (Table 2). First the scope of this reaction was examined by using 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine with electronically diverse boronic acids (Table 2). Interestingly, all examined boronic acids underwent clean conversion to give desired *N*-aryl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (70-80%).

Table 2 Arylation of amino group in Indazole rings [a]



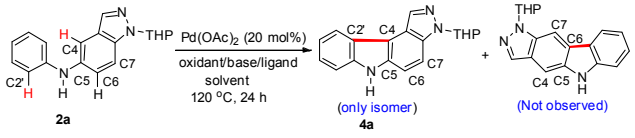
[a]Reaction conditions: **1a** (0.30 mmol), boronic acid (0.60 mmol), $Cu(OAc)_2.H_2O$ (0.06 mmol), DCM (2 mL), rt, air, 24 h; all the yields are islolated yields.

Substitution at the *p*- and *m*-position both electron donating (example **2b-2f**) and electron withdrawing group (example **2g, 2h,**

2i) gave very satisfactory yield (70-80%). We were pleased to find substitution at *o*-position not having much influence on the yield as 2-methylphenylboronic acid gave 72% (**2d**) yield. The *N*-arylation chemistry was also explored with bromo and chloro substituted boronic acids (**2j-k**, 70%). The amination in presence of chloro and bromo functionality provided useful handle for further cross-coupling reaction. To enhance the generality of the reaction conditions we choose 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine as our next substrate. To our delight the optimized conditions worked well in case of 6-amino indazoles (Table 2, **3a-h**). Reactivity studies with different boronic acids have been carried out as electronic nature of the boronic acids did not have any significant influence (**3a-f**, isolated yield 72-80 %) on the coupling reaction. Two bicyclic boronic acids were also investigated, in case of 2-napthylboronic acid the yield is 75% (**3g**) whereas benzo[*d*][1,3]dioxol-5-ylboronic acid resulted in 71% (**3h**) yield (Table 2).

Next we focused our attention to synthesize the pyrazole fused carbazoles[17,18] and we envisaged the *N*-arylated indazoles can act as good precursors and the important poly-heterocyclic compounds can be synthesized *via* Pd-catalyzed cross-dehydrogenative coupling (CDC).[19] Our investigations commenced with the optimization of conditions for the intramolecular C-H arylation of *N*-phenyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (**2a**) (Table 3). We began the studies with the use of some reaction parameters (e. g. pivalate salts, carbonate base) known to be essential for Pd-catalyzed intramolecular cross-dehydrogenative-coupling.[20] The initial choice of $Cu(OAc)_2$ as oxidant (entry1, Table 3) was not successful as the desired product was isolated in low yields (30%) (entry 1, Table 3).

Table 3 Optimization study of intramolecular C-H arylation[a]



2a **4a**

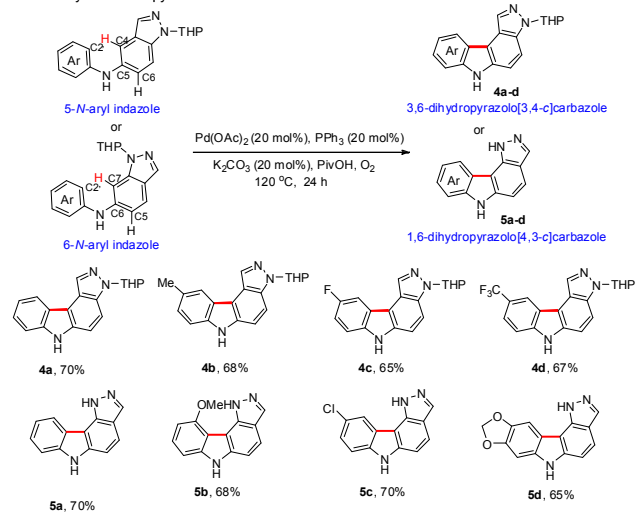
entry	oxidant	base	ligand	solvent	yield(%)[b]
1	$Cu(OAc)_2$	K_2CO_3	--	PivOH	30
2	O_2	K_2CO_3	--	PivOH	60
3	$K_2S_2O_8$	K_2CO_3	--	PivOH	20
4	Ag_2CO_3	K_2CO_3	--	PivOH	20
5	BQ	K_2CO_3	--	PivOH	45
6	$PhI(OAc)_2$	K_2CO_3	--	PivOH	n.r.
7	O_2	Cs_2CO_3	--	PivOH	40
8	O_2	K_2CO_3	--	AcOH	40
9	O_2	K_2CO_3	--	TFA	n.r.
10	**O_2**	**K_2CO_3**	**PPh_3**	**PivOH**	**70**
11	O_2	K_2CO_3	PCy_3	PivOH	45
12	O_2	K_2CO_3	$PCy_3.HBF_4$	PivOH	45
13	O_2	K_2CO_3	X-phos	PivOH	45
14[c]	O_2	K_2CO_3	PPh_3	PivOH	57

[a]Reaction conditions: **2a** (1.0 equiv), $Pd(OAc)_2$ (20 mol%.), K_2CO_3 (20 mol%), ligand (20 mol%), O_2; PivOH (1.5 mL), 120 °C, [b]isolated yields; [c]10 mol% Pd-catalyst was used; n. r. = no reaction.

Further oxidant screening (entries 2-6, Table 3) revealed that molecular oxygen (O_2) lead to single isomer (**4a**) in good yield 60% (entry 2, Table 3). Use of other commonly used carbonate base Cs_2CO_3, (entry 7, Table 3) proved inferior to K_2CO_3. Other solvents like AcOH given low yield 40% (entry 8, Table 3) and TFA (entry 9, Table 3) failed to promote the cyclization. Further, in the screening of ligands, the initial choice included those that have been used in the context of intramolecular C-H arylation (*e.g.* PPh_3, PCy_3, $PCy_3.HBF_4$, X-phos; entries 10-13, Table 3).[19] The desired product **4a** was obtained in good yield in case of PPh_3 (70%, entry10, Table 3).

Having the optimal conditions in hand for the intramolecular C-H arylation of **2a** (5-*N*-aryl indazole), we next examined the generality of those coupling reactions with respect to varied substitution patterns on the tethered aryl ring (Table 4). As shown in the Table 4, the method is compatible with electron-donating (**4b**) and electron-withdrawing (**4c**, **4d**) substituents. Notable, the reaction is regioselective and only the 3,6-dihydropyrazolo[3,4-c]carbazoles formed. We have further demonstrated the generality of this C-H arylation with 6-*N*-aryl indazoles. We were pleased to see that the reaction conditions proved general, delivering a variety of pyrazole annulated carbazoles *i.e.* 1,6-dihydropyrazolo[4,3-c]carbazoles (**5a-d**) in good yields as a single isomer from C7 site rather than C5. Electronic nature of the aryl ring did not have much influence on the cyclization yield. Phenyl ring bearing *m*-OMe group or *p*-Cl group gave the pyrazole annulated carbazoles **5b** (68%) and **5c** (70%) respectively. Novel pentacyclic 1,6-dihydro-[1,3]dioxolo[4,5-*b*]Pyrazolo [3,4-*g*]carbazole (**5d**, 65%) also was synthesized under this optimized conditions. Here we would like to report one interesting observation during this cyclization reaction 6-*N*-aryl-THP-protected indazoles gave the *in situ* THP deprotected compounds, whereas no deprotection happened during the cyclization of 5-*N*-aryl-indazoles.

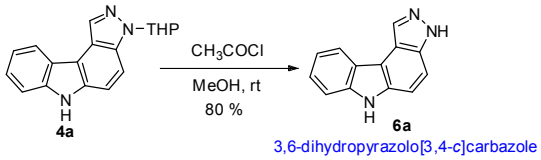
Table 4 Synthesis of pyrazolo-carbazoles[a]



[a]Reaction conditions: *N*-aryl-indazoles (0.20 mmol), $Pd(OAc)_2$, (0.04 mmol), PPh_3 (0.04 mmol), K_2CO_3 (0.04 mmol), PivOH (1.5 mL), O_2, 120 °C, 24 h.

Finally, 3,6-dihydropyrazolo[3,4-c]carbazole (**6a**) obtained upon THP-deprotection of 3-(tetrahydro-2*H*-pyran-2-yl)-3,6-dihydro

pyrazolo[3,4-c]carbazole (**4a**) by using acetyl chloride (Scheme 2).[21]



Scheme 2 THP-deprotection

In order to evaluate energetic factors associated with the regioselectivity for C4 position over C6 in 5-*N*-aryl-indazole, C−H activation energy barriers (ΔE_a) (concerted metalation-deprotonation step (CMD) for different sites (C4, C6 and C2′) were computed using density functional theory (B3LYP) and the details of energy barriers are given in Table 5 and the structures of the transition states (TS) are presented in Fig. 2. 5-*N*-aryl-indazole, in the presence of Pd catalyst is expected to give two products from C4 and C6 cyclization, however experimentally only C4 cyclized product 3,6-dihydropyrazolo[3,4-c]carbazole is observed. The estimated energy barrier (20.27 kcal/mol) for the C-H activation at C4 site was found to be lower compared to the barrier (23.10 kcal/mol) for the C-H activation at C6 site. The difference in the energy barriers between competitive sites is 2.83 kcal/mol, which is of sufficient magnitude to produce site selectivity in a variety of arenes.[22] The corresponding free energy barrier estimations also are smaller for C4-H activation in comparison to the C6-H activation (Table 5).

Table 5 Energy barriers, distortion and interaction energies (kcal/mol) associated with CMD transition states in 5-*N*-aryl-indazole and 6-*N*-aryl-indazole

Site	ΔE_a	ΔG_a	$E_{dist(ArH)}$	$E_{dist(L)}$	$E_{dist(Ar)}$	E_{int}	B_{Pd-C}
				5-*N*-aryl-indazoe			
C4	20.27	32.86	42.42	19.56	61.98	41.71	0.4681
C6	23.10	34.51	39.55	17.89	57.44	34.34	0.4278
C2′	22.23	34.27	42.51	19.05	61.55	39.32	0.4641
				6-*N*-aryl-indazole			
C5	22.07	34.56	41.70	18.54	60.24	38.17	0.455
C7	17.80	30.00	44.58	20.12	64.70	46.91	0.496
C2′	22.55	34.79	41.61	18.73	60.34	37.79	0.452

ΔE_a activation barrier. ΔG_a free energy of activation. $E_{dist(ArH/PdL)}$ distortion energy associated with the distortion of the Pd catalyst and the arene from their ground state structures to their structure in the TS. E_{int} interaction energy associated with electronic interaction of catalyst and arene in TS. B_{Pd-C} Wiberg bond index.

In palladium-acetate catalyzed reactions, the regioselectivity of C−H bond functionalization is controlled either by distortion energies (E_{dist}) of arenes or interaction energies (E_{int}) of catalyst with arene or by both factors.[22] In order to better understand the CMD rate determining step, the distortion−interaction analysis was performed for these sites. The total distortion energy associated with C4 site is 4.54 kcal/mol higher than C6 site (61.98 kcal/mol for C4 vs. 57.44 kcal/mol for C6) (Table 5). This is compensated by the higher interaction energy at the C4 site over C6 centre by 7.37 kcal/mol (more negative interaction energy indicate favorable interaction). Thus, in 5-*N*-aryl-indazole, interaction energy is the dominating factor in deciding the C4 site selectivity and its lower barrier. In addition, higher Wiberg bond index (B_{Pd-C}) indicates the high bond order, which was also found to be favorable in TS of C4 site over C6 site, which indicates that the site C4 showed strong Pd−C bonding interactions in the TS. In the case of 6-*N*-aryl-indazole the estimated barrier for the C-H activation at C7 site (17.80 kcal/mol) was found to be lower over the C-H activation barrier at C5 site (22.07 kcal/mol) (Table 5). In this case also, the regioselectivity is controlled by the interaction energy observed at the C7 centre. The estimated barriers in 5-*N*-aryl-indazole and 6-*N*-aryl-indazole respectively for C2′-H activation are 22.23 and 22.55 kcal/mol. These are clearly less favorable than the alternative paths, and hence need not to be considered further.

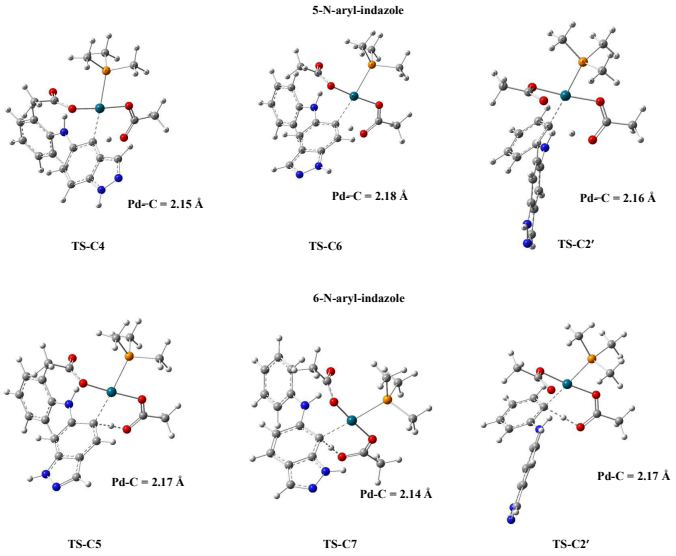


Fig. 2 3D Structures of the transition states of different competitive C-H activation sites in 5-*N*-aryl-indazole and 6-*N*-aryl-indazole.

Quantum chemical analysis was also employed to evaluate the energy requirements of the C-C bond formation reaction. The calculated potential energy surface for coupling of C4 and C2′ sites of 5-*N*-aryl-indazole, is shown in Fig. 3 and the 3D structures of the important transition states and intermediates on the potential energy surface are given in Fig. 4. This reaction starts with coordination of four-coordinated Pd at C4 site of 5-*N*-aryl-indazole. DFT calculation suggested that in the first step of the reaction, metallation (Pd) and deprotonation take place simultaneously in **TS-1**. This transition state is stabilized by the presence of hydrogen bond between the amino group (NH) of 5-*N*-aryl-indazole and acetate (O) of catalyst. The second bound acetate group of catalyst involves in the deprotonation of arene (C4-H). The estimated free energy barrier for first C-H activation is found to be 32.86 kcal/mol. The generated intermediate **IN-1** from **TS-1** is highly endothermic

by 29.81 kcal/mol. The intermediate **IN-1** gets converted to another intermediate **IN-2** after releasing acetic acid, this conversion is exothermic by 8.83 kcal/mol. The subsequent C-H activation step proceeds through **TS-2**. The free energy required for the second C-H activation step at C2′ (**IN2→TS2**) is about 19.28 kcal/mol, much less than the first C-H activation step at C4 centre (32.86 kcal/mol), this can be due to the proximity of the reaction centre in **IN-2**.

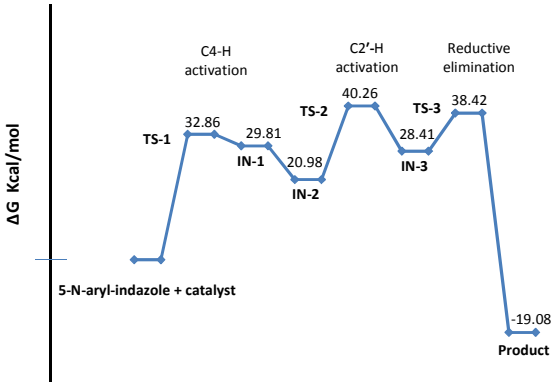


Fig. 3 Free energy profile of intramolecular cross coupling reaction of 5-*N*-aryl-indazole with Pd $(OAc)_2$ catalyst. (**TS-1** in this description of overall reaction is same as **TS-C4** given in Fig. 2)

Final step of the reaction is reductive elimination, in which carbon-carbon bond (cross coupling) is formed along with breaking of carbon-Pd bond. The transition state **TS-3** associated with this step is located about 10 kcal/mol above the **IN-3** and leads to the formation of highly exothermic product 3,6-dihydropyrazolo[3,4-c]carbazole. The overall barrier for the reaction is 40.26 kcal/mol and the overall free energy of the product formation is -19.08 kcal/mol.

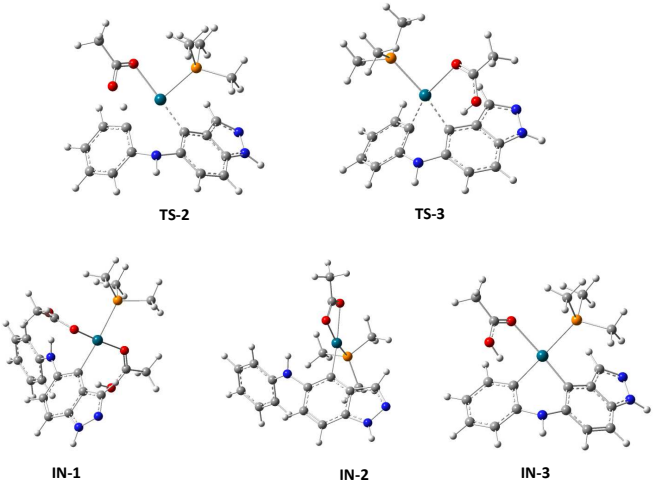
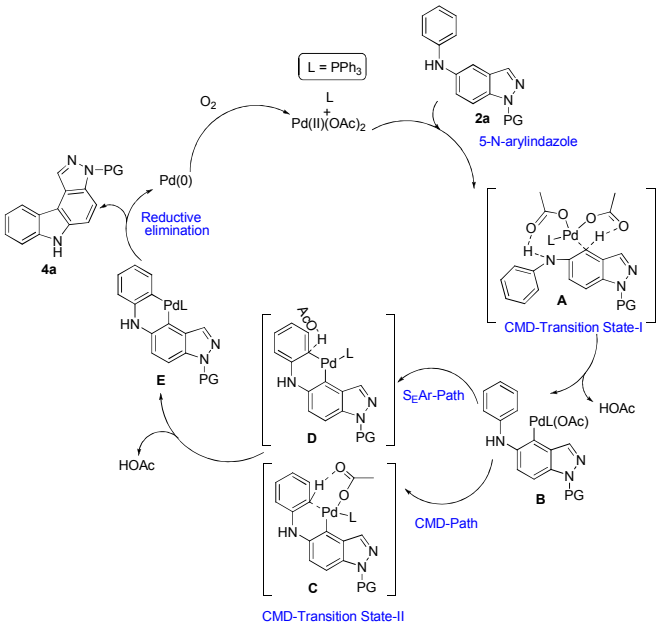


Fig. 4 The optimized geometries of the selected intermediates and transition states of the $Pd(OAc)_2$-catalyzed cross coupling reaction of 5-*N*-aryl-indazole. (For **TS-1,** see **TS-C4** in Fig. 2)

The above computational analysis led the authors to propose a plausible mechanism where the regioselective C-H bond activation of the hetero arene (**2a)** happened *via* a CMD mechanism (Scheme 3).[22] In this proposed mechanism, catalyst $Pd(OAc)_2$ induces C4-H activation of 5-*N*-aryl-indazole to give transition-state-complex **A**, finally leading to the intermediate **B**. The next step involves the conversion of **B** to **E** (an Ar-Pd-HetAr complex), which may go through either (i) a second CMD process[23] involving transition state **C** or (ii) through an electrophilic palladation *via* an S_EAr (electrophilic aromatic substitution) process involving transition state **D**. Quantum chemical calculations could identify only the transition state **C** for the CMD process but not the transition state **D** for the S_EAr process. Hence, it can be concluded that the second stage of the reactions (*i.e.* **B** to **E**) also goes through CMD mechanism. The palladacycle **E** undergoes reductive elimination to produce carbazole **4a** and palladium(0). To the best of our knowledge this reaction is rare example of in which two consecutive CMD mechanistic steps are involved in the final product generation.



Scheme 3 Proposed reaction mechanism (CMD Pathway)

Conclusion

In conclusion, we have developed an efficient Cu-catalyzed protocol for *N*-arylation of 5/6 amino indazoles. This open-flask chemistry can be carried out without the need of a ligand for Cu-catalyst or base to activate the amine. This chemistry is general and the reaction conditions is mild compared to Pd-catalyzed Buchwald-Hartwig cross-coupling make it a very attractive tool in the fast growing *N*-arylation chemistry. We further utilized these *N*-arylated indazoles as precursors for the synthesis of pyrazolo fused carbazoles *via* Pd-catalyzed intramolecular C-H arylation. This optimized cross-dehydrogenative coupling (CDC) is regioselective and diversely decorated pyrazole fused carbazole formed in high yields. In this cross-dehydrogenative-coupling (CDC) reaction the experimental and computational data support the involvement of a concerted metalation-deprotonation pathway (CMD) that able to predict the regioselectivity. Finally, the combined *N*-arylation/*C*-H

arylation strategy and the mechanistic understanding of regioselectivity, gave scope in establishing further improved reaction conditions and a greater acceptance of this approach in the preparation of heterocycle annulated biaryl compounds.

Experimental

General Information

All purchased chemicals were used without further purification. Thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F254 MERCK. TLC plates were visualized by exposing UV light or by iodine vapors. Organic solutions wereconcentrated by rotary evaporation on BUCHI-Switzerland; R-120 rotary evaporator and vacuum pump V-710. Flash column chromatography was performed on Merck flash silica gel 230-400 mesh size. Melting points of solid compounds were determined on BUCHI-B-545-Switzerland melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded with BUCKER 500 and 400 MHz NMR instruments. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). All the NMR spectra were processed in MestReNova. Mass spectra were recorded with VARIAN GC-MS-MS instrument. HRMS spectra were recorded with LCMS-QTOF Module No. G654A (UHD).

General procedure for the synthesis of copper-catalyzed *N*-arylation of 5, 6-amino-indazoles with boronic acids: (Procedure A)

A round bottom flask equipped with a magnetic stirrer bar was charged with phenyl boronic acid (73.2 mg, 0.60 mmol), Cu (OAc)$_2$·H_2O (11.98 mg, 0.06 mmol) in dichloro methane (2 mL), was added into the flask stirred for 5 minutes at room temperature. To this stirring suspension was added 5-amino indazole (65 mg, 0.30 mmol).The flask was kept open and the reaction mixture was stirred for 24 h in air at room temperature. The progress of the reaction was monitored by TLC and after completion of the reaction the solvent was removed with aid of a rotatory evaporator. The crude reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (3x15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (hexane/EtOAc; 8:2) to provide the desired product **2a**. By following the above general procedure A, 5-N-arylated indazoles (**2b-k**) and 6-*N*-arylated indazoles (**3a-h**) were synthesized.

***N*-Phenyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (2a):** Brown liquid (80% yield, 70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.37 (s, 1H), 7.24 – 7.14 (m, 3H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 5.66 (dd, *J* = 9.5, 2.3 Hz, 1H), 4.02 (d, *J* = 10.1 Hz, 1H), 3.71 (td, *J* = 11.0, 2.5 Hz, 1H), 2.53 (m, 1H), 2.15 – 2.01 (m, 2H), 1.76 – 1.57 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 136.7, 136.4, 133.3, 129.4, 125.4, 122.7, 119.9, 116.0, 110.9, 110.3, 85.5, 67.6, 29.4, 25.1, 22.7; MS (ESI): m/z = 294[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{20}N_3O$ [M+H]$^+$: 294.1601, found: 294.1596.

1-(Tetrahydro-2*H*-pyran-2-yl)-*N*-(p-tolyl)-1*H*-indazol-5-amine (2b): Brown liquid (77% yield, 70.91 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.33 (s, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.67 (dd, *J* = 9.4, 2.6 Hz, 1H), 4.06 – 4.00 (m, 1H), 3.73 (td, *J* = 11.2, 2.8 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.28 (s, 3H), 2.11 (m, 2H), 1.80 – 1.60 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 137.7, 136.1, 133.2, 129.9, 129.7, 125.4, 122.0, 117.1, 110.8, 108.8, 85.4, 67.5, 29.4, 25.1, 22.7, 20.6; MS (ESI): m/z = 308[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{22}N_3O$ [M+H]$^+$: 308.1758, found: 308.1752.

1-(Tetrahydro-2*H*-pyran-2-yl)-*N*-(m-tolyl)-1*H*-indazol-5-amine (2c): Brown liquid (80% yield, 73.68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.38 (s, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.76 (s, 2H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.67 (dd, *J* = 9.4, 2.1 Hz, 1H), 4.03 (d, *J* = 10.3 Hz, 1H), 3.73 (td, *J* = 10.8, 2.5 Hz, 1H), 2.56 (m, 1H), 2.27 (s, 3H), 2.18 – 2.01 (m, 2H), 1.80 – 1.58 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 139.2, 136.7, 136.3, 133.3, 129.2, 125.4, 122.8, 120.9, 116.8, 113.3, 110.8, 110.5, 85.5, 67.5, 29.4, 25.1, 22.6, 21.5; MS (ESI): m/z = 308[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{22}N_3O$ [M+H]$^+$: 308.1758, found: 308.1751.

1-(Tetrahydro-2*H*-pyran-2-yl)-*N*-(o-tolyl)-1*H*-indazol-5-amine (2d): Brown liquid (72% Yield, 66.31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.27 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.11 – 7.02 (m, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.68 (dd, *J* = 9.4, 2.5 Hz, 1H), 5.37 (br s, 1H), 4.04 (d, *J* = 11.9 Hz, 1H), 3.74 (td, *J* = 12.4 Hz, 1H), 2.56 (m, 1H), 2.27 (s, 3H), 2.19 – 2.04 (m, 2H), 1.73 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 137.2, 136.3, 133.3, 130.8, 126.8, 126.2, 125.4, 122.6, 120.7, 116.2, 110.9, 110.2, 85.4, 67.5, 29.4, 25.1, 22.7, 17.9; MS (ESI): m/z = 308[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{22}N_3O$ [M+H]$^+$: 308.1758, found: 308.1731.

***N*-(4-Methoxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (2e):** Brown liquid (76% yield, 73.64 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.15 (d, *J* = 1.2 Hz, 1H), 7.02 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 5.59 (dd, *J* = 9.4, 2.6 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.71 (s, 3H), 3.70 – 3.62 (m, 1H), 2.53 – 2.42 (m, 1H), 2.09 – 1.96 (m, 2H), 1.71 – 1.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 138.4, 137.1, 136.0, 133.1, 125.4, 121.0, 120.5, 114.8, 111.0, 107.6, 85.4, 67.4, 55.6, 29.4, 25.1, 22.6; MS (ESI): m/z = 324[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{22}N_3O_2$ [M+H]$^+$: 324.1707, found: 324.1700.

***N*-(4-Propylphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (2f):** Brown liquid (75% yield, 75.42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.23 (d, *J* = 1.6 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.56 (dd, *J* = 9.4, 2.5 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.62 (td, *J* = 11.0, 2.7 Hz, 1H), 2.51 – 2.38 (m, 3H), 2.06 – 1.93 (m, 2H), 1.63 (m, 2H), 1.52 (m, 3H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 137.5, 136.2, 134.8, 133.2, 129.3, 125.4, 122.1, 116.9, 110.9, 109.1, 85.5, 67.5, 37.3, 29.4,

25.1, 24.8, 22.7, 13.9; MS (ESI): m/z = 336[M+H]$^+$; HRMS (ESI): Calcd for $C_{21}H_{26}N_3O$ [M+H]$^+$: 336.2071, found: 336.2075.

***N*-(4-Fluorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (2g):** Brown liquid (73% yield, 68.17 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.32 (s, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 4H), 5.68 (dd, *J* = 9.4, 2.4 Hz, 1H), 5.58 (br s, 1H), 4.04 (d, *J* = 10.1 Hz, 1H), 3.78 – 3.70 (m, 1H), 2.56 (td, *J* = 13.3, 4.0 Hz, 1H), 2.19 – 2.04 (m, 2H), 1.80 – 1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.2, 140.9, 137.6, 136.2, 133.2, 125.4, 121.9, 118.4 (d, *J* = 7.6 Hz), 115.8 (d, *J* = 22.5 Hz), 111.0, 109.1, 85.5, 67.4, 29.4, 25.1, 22.6; MS (ESI): m/z = 312[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{19}FN_3O$ [M+H]$^+$: 312.1507, found: 312.1509.

1-(Tetrahydro-2*H*-pyran-2-yl)-*N*-(4-(trifluoromethyl)phenyl)-1*H*-indazol-5-amine(2h): Brown semi solid (74% yield, 80.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.46 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 10.8 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.98 (br s, 1H), 5.71 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.04 (d, *J* = 11.9 Hz, 1H), 3.75 (td, *J* = 11.3, 2.8 Hz, 1H), 2.57 (dt, *J* = 9.3, 6.5 Hz, 1H), 2.19 – 2.03 (m, 2H), 1.81 – 1.64 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 137.0, 134.6, 133.5, 126.6 (q, *J* = 3.7 Hz), 125.3, 123.7, 120.6 (q, *J* = 65.3, 32.6 Hz), 114.0, 113.4, 111.1, 85.5, 67.6, 29.4, 25.1, 22.6; MS (ESI): m/z = 362[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{19}F_3N_3O$ [M+H]$^+$: 362.1475, found: 362.1475.

1-(Tetrahydro-2*H*-pyran-2-yl)-*N*-(3-(trifluoromethyl)phenyl)-1*H*-indazol-5-amine (2i): Brown liquid (70% yield, 75.87 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.44 (s, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.11 (s, 1H), 7.06 (dd, *J* = 7.2, 4.1 Hz, 2H), 5.86 (br s, 1H), 5.71 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.11 – 4.00 (m, 1H), 3.76 (td, *J* = 11.2, 2.8 Hz, 1H), 2.65 – 2.50 (m, 1H), 2.20 – 2.04 (m, 2H), 1.82 – 1.63 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 136.9, 135.2, 133.4, 129.7, 125.4, 123.3, 118.1, 115.91 (q, *J* = 7.7, 3.8 Hz), 112.5, 111.62 (q, *J* = 3.8 Hz), 111.2, 85.6, 67.5, 29.4, 25.1, 22.6; MS (ESI): m/z = 362[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{19}F_3N_3O$ [M+H]$^+$: 362.1475, found: 362.1469.

***N*-(4-Bromophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (2j):** Brown solid (70% yield, 78.16 mg), mp. 139-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.38 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.69 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.11 – 4.00 (m, 1H), 3.74 (td, *J* = 11.1, 2.7 Hz, 1H), 2.58 (m, 1H), 2.20 – 2.03 (m, 2H), 1.80 – 1.62 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 136.5, 135.9, 133.3, 132.1, 125.3, 122.8, 117.3, 111.4, 111.2, 111.0, 85.5, 67.5, 29.4, 25.1, 22.6; MS (ESI): m/z = 372[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{19}BrN_3O$ [M+H]$^+$: 372.0706, found: 372.0706.

***N*-(2,4-Dichlorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-amine (2k):** Purification: Brown liquid (70% yield, 75.81 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.42 (s, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 7.16 (dd, *J* = 8.8, 1.7 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.00 (br s,1H), 5.64 (dd, *J* = 9.4, 2.3 Hz, 1H), 3.98 (d, *J* = 10.2 Hz, 1H), 3.73 – 3.61 (m, 1H), 2.54 – 2.43 (m, 1H), 2.27 – 2.20 (m, 2H), 2.03 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 137.2, 134.5, 133.4, 129.1, 127.5, 125.4, 124.2, 123.2, 120.4, 114.6, 114.2, 111.3, 85.6, 67.5, 29.6, 25.1, 22.5; MS (ESI): m/z = 362[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{18}Cl_2N_3O$ [M+H]$^+$: 362.0822, found: 362.0816.

***N*-Phenyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3a):** Brown liquid (80% yield, 70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.20 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.93 (br s, 1H), 5.58 (dd, *J* = 9.5, 2.6 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.70 (td, *J* = 11.2, 2.7 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.18 – 2.01 (m, 2H), 1.70 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 142.6, 140.9, 134.1, 129.4, 121.8, 121.4, 119.8, 118.4, 115.0, 95.8, 85.0, 67.5, 29.4, 25.1, 22.7; MS (ESI): m/z = 294[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{20}N_3O$ [M+H]$^+$: 294.1601, found: 294.1579.

***N*-(4-Methoxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3b):** Brown liquid (80% yield, 77.52 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 1H), 5.77 (br s, 1H), 5.52 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.81 (s, 3H), 3.67 (td, *J* = 11.0, 2.5 Hz, 1H), 2.59 – 2.46 (m, 1H), 2.17 – 1.97 (m, 2H), 1.68 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 144.8, 141.1, 135.3, 134.1, 122.7, 121.8, 118.9, 114.7, 113.7, 93.0, 84.7, 67.4, 55.6, 29.3, 25.1, 22.7; MS (ESI): m/z = 324[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{22}N_3O_2$ [M+H]$^+$: 324.1707, found: 324.1709.

***N*-(3-Methoxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3c):** Brown liquid (78% yield, 75.58 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.28 – 7.11 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.71 (s, 2H), 6.52 (d, *J* = 8.1 Hz, 1H), 5.97 (br s, 1H), 5.58 (d, *J* = 9.3 Hz, 1H), 4.00 (d, *J* = 10.9 Hz, 1H), 3.77 (s, 3H), 3.69 (m, 1H), 2.63 – 2.48 (m, 1H), 2.18 – 2.00 (m, 2H), 1.69 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 144.3, 142.2, 140.8, 134.0, 130.1, 121.8, 119.9, 115.3, 110.7, 106.8, 103.6, 96.5, 85.0, 67.4, 55.1, 29.3, 25.1, 22.6; MS (ESI): m/z = 324[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{22}N_3O_2$ [M+H]$^+$: 324.1707, found: 324.1707

***N*-(4-Chlorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine(3d):** Brown liquid (72% yield, 70.65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.15 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 5.96 (br s, 1H), 5.57 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.70 (td, *J* = 11.1, 2.7 Hz, 1H), 2.54 (m, 1H), 2.18 – 2.00 (m, 2H), 1.76 – 1.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.6, 140.8, 134.0, 129.3, 125.9, 121.9, 120.1, 119.4, 115.0, 96.4, 85.1, 67.4, 29.3, 25.1, 22.6; MS (ESI): m/z = 328[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{19}ClN_3O$ [M+H]$^+$: 328.1211, found: 328.1211.

***N*-(3-Chlorophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3e):** Brown liquid (72% yield, 70.65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 0.7 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 2.0 Hz, 1H), 6.97 – 6.93 (m, 1H), 6.92 – 6.88 (m, 2H), 5.97 (br s, 1H), 5.61 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.72 (m, 1H), 2.59 – 2.49 (m,

1H), 2.16 – 2.04 (m, 2H), 1.71 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 141.3, 140.6, 135.0, 134.0, 130.4, 122.0, 120.9, 120.4, 117.2, 115.6, 115.5, 97.7, 85.3, 67.5, 29.3, 25.1, 22.6; MS (ESI): m/z = 328[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{19}ClN_3O$ [M+H]$^+$: 328.1211, found: 328.1209.

***N*-(4-Bromophenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3f):** Brown liquid (72% yield, 80.39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.14 (s, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.81 (dd, *J* = 8.6, 1.5 Hz, 1H), 6.20 (br s, 1H), 5.55 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.98 (d, *J* = 10.7 Hz, 1H), 3.67 (m, 1H), 2.61 – 2.44 (m, 1H), 2.14 – 1.92 (m, 2H), 1.64 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 142.0, 140.8, 134.1, 132.2, 121.9, 120.0, 119.5, 115.2, 112.9, 96.4, 85.1, 67.5, 29.4, 25.1, 22.7; MS (ESI): m/z = 372[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{19}BrN_3O$ [M+H]$^+$: 372.0706, found: 372.0723.

***N*-(Naphthalen-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3g):** Brown liquid (75% yield, 77.20 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.49 (s, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.35 – 7.23 (m, 3H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.12 (br s, 1H), 5.58 (d, *J* = 7.9 Hz, 1H), 4.01 (d, *J* = 10.5 Hz, 1H), 3.68 (m, 1H), 2.60 – 2.49 (m, 1H), 2.13 – 2.01 (m, 2H), 1.68 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 140.9, 140.6, 134.6, 134.1, 129.4, 129.2, 127.7, 126.5, 123.7, 121.9, 120.4, 120.0, 115.3, 112.5, 96.5, 85.1, 67.5, 29.4, 25.1, 22.7; MS (ESI): m/z = 344[M+H]$^+$; HRMS (ESI): Calcd for $C_{22}H_{22}N_3O$ [M+H]$^+$: 344.1758, found: 344.1757.

***N*-(Benzo[*d*] [1, 3] dioxol-5-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-amine (3h):** Brown liquid (71% yield, 71.80 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 6.99 (s, 1H), 6.78 (s, 1H), 6.78 – 6.74 (m, 2H), 6.62 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.96 (s, 2H), 5.56 (dd, *J* = 9.4, 2.7 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.74 – 3.63 (m, 1H), 2.58 – 2.49 (m, 1H), 2.15 – 2.01 (m, 2H), 1.69 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 144.2, 143.2, 141.0, 136.9, 134.1, 121.8, 119.2, 113.9, 113.6, 108.6, 103.0, 101.1, 93.8, 84.8, 67.4, 29.3, 25.1, 22.6; MS (ESI): m/z = 338[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{20}N_3O_3$ [M+H]$^+$: 338.1499, found: 338.1501.

General Procedure for the synthesis of Pyrazolo-carbazoles through Pd-catalyzed dehydrogenative coupling: (procedure B)

5-*N*-Aryl indazole 2a (60 mg, 0.20 mmol), $Pd(OAc)_2$ (8.98 mg, 0.04 mmol), K_2CO_3 (5.52 mg, 0.04 mmol), PPh_3 (10.5 mg, 0.04 mmol) and pivalic acid (1.5 mL) are weighed to air and transferred into a R.B Flask. The flask was placed in an oil bath and the mixture was stirred under 1 atm O_2 at 120 ^{0}C for 24 h. The solution was then cooled to rt, the crude reaction mixture was diluted with 20 mL of saturated aqueous solution of Na_2CO_3 and extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/EtOAc) to afford the corresponding coupling product. By following the procedure B compounds (**4a-d**; **5a-d**) were synthesized.

3-(Tetrahydro-2*H*-pyran-2-yl)-3, 6-dihydropyrazolo [3, 4-c] carbazole: (4a). Purification: Hexane/EtOAc (7: 3). Brown liquid (70% yield, 40.74 mg); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.68 (s, 1H), 8.59 (s, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 5.94 (d, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 11.6 Hz, 1H), 3.86 – 3.79 (m, 1H), 2.64 (dd, *J* = 23.6, 11.6 Hz, 1H), 2.21 – 2.11 (m, 2H), 1.89 – 1.69 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 140.2, 136.6, 135.8, 131.5, 125.4, 123.4, 122, 119.8, 118.9, 113.3, 112.9, 112.1, 109.7, 86.1, 67.5, 30.0, 26.0, 23.3; IR (NaCl) ν (cm^{-1}) 3408, 2923, 2852, 1612, 1453, 1325, 1242, 1167, 1080, 1041, 1018; MS (ESI): m/z = 292[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{18}N_3O$ [M+H]$^+$: 292.1445, found: 292.1437.

9-Methyl-3-(tetrahydro-2*H*-pyran-2-yl)-3, 6-dihydropyrazolo [3, 4-c] carbazole: (4b). Purification: Hexane/EtOAc (7: 3), brown liquid (68% yield, 41.48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.20 (br s, 1H), 7.95 (s, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 4.8 Hz, 1H), 5.76 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.72 (m, 1H), 2.70 – 2.56 (m, 1H), 2.52 (s, 3H), 2.16 – 1.90 (m, 2H), 1.68 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 134.4, 133.3, 130.2, 127.7, 125.2, 121.6, 119.8, 116.9, 111.7, 110.8, 109.3, 107.0, 84.3, 66.2, 30.6, 23.8, 21.4, 20.2; IR (NaCl) ν (cm^{-1}) 3431, 2923, 2853, 1618, 1463, 1377, 1301, 1243, 1152, 1080, 1041, 1018; MS (ESI): m/z = 306[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{20}N_3O$ [M+H]$^+$: 306.1601, found: 306.1598.

9-Fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3, 6-dihydropyrazolo [3, 4-c] carbazole (4c): Purification: Hexane/EtOAc (7: 3), brown solid (65% yield, 40.18 mg), mp. 170-172 ^{0}C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.55 (br s, 1H), 8.49 (s, 1H), 7.93 (dd, *J* = 9.3, 2.1 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.46 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.06 (m, *J* = 9.2, 2.3 Hz, 1H), 5.79 (dd, *J* = 9.2, 2.3 Hz, 1H), 3.81 (d, *J* = 11.2 Hz, 1H), 3.73 – 3.60 (m, 1H), 2.54 – 2.41 (m, 1H), 1.99 (m, 2H), 1.66 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.0, 157.2, 137.2, 136.7, 136.5, 131.5, 118.8, 113.4, 113.1 (d, *J* = 9.6 Hz), 113.0 (d, *J* = 9.5 Hz), 110.6, 107.0, 106.8, 86.1, 67.6, 30.1, 26.0, 23.3; IR (NaCl) ν (cm^{-1}) 3415, 3344, 2925, 2853, 1721, 1576, 1490, 1461, 1426, 1376, 1328, 1297, 1280, 1261, 1241, 1206, 1151, 1080, 1062, 1041, 1019; MS (ESI): m/z = 310[M+H]$^+$; HRMS (ESI): Calcd for $C_{18}H_{17}FN_3O$ [M+H]$^+$: 310.1350, found: 310.1358.

3-(Tetrahydro-2*H*-pyran-2-yl)-9-(trifluoromethyl)-3,6-dihydro pyrazolo [3, 4-c] carbazole: (4d) Purification: Hexane/EtOAc (7: 3), brown semi solid (67% yield, 48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 8.49 (s, 1H), 8.46 (s, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.52 (m, 2H), 5.85 (dd, *J* = 9.3, 2.1 Hz, 1H), 4.08 (d, *J* = 11.7 Hz, 1H), 3.91 – 3.69 (m, 1H), 2.77 – 2.55 (m, 1H), 2.23 – 2.05 (m, 2H), 1.77 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 135.9, 135.1, 131.3, 122.2, 122.1, 122.1, 122.0, 121.8, 121.7, 121.7, 118.8, 118.8, 117.9, 113.1, 112.0, 111.1, 109.8, 85.8, 67.6, 29.7, 25.1, 22.6; IR (NaCl) ν (cm^{-1}) 3435, 2923, 2852, 1721, 1653, 1616, 1463, 1378, 1325, 1159, 1116, 1018; MS (ESI): m/z = 360[M+H]$^+$; HRMS (ESI): Calcd for $C_{19}H_{17}F_3N_3O$ [M+H]$^+$: 360.1318, found: 360.1317.

1, 6-Dihydropyrazolo [4, 3-c] carbazole (5a): Purification: Hexane/EtOAc (3:2), brown solid (70% yield, 28.98 mg), mp. 244-246 ^{o}C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.87 (s, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.34 – 7.24 (m, 1H).; ^{13}C NMR

(100 MHz, acetone-d_6) δ 139.9, 139.5, 136.2, 135.5, 125.0, 122.5, 121.7, 120.3, 119.3, 118.6, 111.9, 108.0, 105.7.; IR (NaCl) ν (cm^{-1}) 3400, 2922, 2851, 1639, 1614, 1493, 1460, 1418, 1390, 1350, 1337, 1281, 1244, 1191, 1152, 1118, 1075, 1040, 1020; MS (ESI): m/z = 208$[M+H]^+$; HRMS (ESI): Calcd for $C_{13}H_{10}N_3$ $[M+H]^+$: 208.0869, found: 208.0866.

10-Methoxy-1, 6-dihydropyrazolo [4, 3-c] carbazole: (5b)

Purification: Hexane/EtOAc (3: 2), brown solid (68% yield, 32.23 mg), mp. 206-208 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.70 (br s, 1H), 8.40 (d, J = 8.6 Hz, 1H), 8.13 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 8.6, 2.3 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 159.1, 140.8, 139.7, 135.8, 135.3, 122.4, 118.7, 117.8, 116.5, 109.7, 108.0, 105.8, 95.5, 55.7; IR (NaCl) ν (cm^{-1}) 3397, 2921, 2851, 1619, 1593, 1455, 1414, 1297, 1247, 1197, 1158, 1120, 1018; MS (ESI): m/z = 238$[M+H]^+$; HRMS (ESI): Calcd for $C_{14}H_{12}N_3O$ $[M+H]^+$: 238.0975, found: 238.0973.

9-Chloro-1, 6-dihydropyrazolo [4, 3-c] carbazole (5c):

Purification: Hexane/EtOAc (3: 2), brown semi solid (70% yield, 33.74 mg); ^{1}H NMR (400 MHz, acetone-d_6) δ 11.01 (br s, 1H), 8.59 (s, 1H), 8.17 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.46 – 7.34 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 140.6, 137.7, 135.8, 135.4, 125.4, 124.9, 123.5, 121.2, 120.3, 118.7, 113.2, 108.0, 105.0; IR (NaCl) ν (cm^{-1}) 3345, 2923, 2852, 1709, 1637, 1618, 1463, 1378, 1289, 1156, 1018; MS (ESI): m/z = 242$[M+H]^+$; HRMS (ESI): Calcd for $C_{13}H_9ClN_3$ $[M+H]^+$: 242.0480, found: 242.0482.

1,6-Dihydro-[1,3]dioxolo[4,5-b]pyrazolo[3,4-c]carbazole (5d):

Purification: Hexane/EtOAc (3: 2), brown semi solid (65% yield, 32.63 mg); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.57 (br s, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.98 (s, 1H), 5.91 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 147.2, 143.7, 139.5, 135.3, 134.9, 117.4, 115.7, 114.6, 114.3, 108.1, 106.2, 101.8, 100.6, 93.1; IR (NaCl) ν (cm^{-1}) 3344, 2923, 2853, 1710, 1622, 1469, 1417, 1325, 1304, 1209, 1161, 1115, 1080, 1040; MS (ESI): m/z = 252$[M+H]^+$; HRMS (ESI): Calcd for $C_{14}H_{10}N_3O_2$ $[M+H]^+$: 252.0768, found: 252.0771.

3,6-dihydropyrazolo [3, 4-c] carbazole (6a):

A round bottom flask equipped with a magnetic stirrer bar was charged with 3-(tetrahydro-2*H*-pyran-2-yl)-3, 6-dihydro Pyrazolo [3, 4-c] carbazole (**4a**) (40 mg, 1 eq), acetyl chloride (0.3 mL, 10 mol%) and methanol was added into the flask. The flask was kept open and the reaction mixture was stirred for 8 h in air at room temperature. The progress of the reaction was monitored by TLC and after completion of the reaction the solvent was removed with aid of a rotatory evaporator. The crude reaction mixture was diluted with ethyl acetate, washed with a saturated aqueous solution of $NaHCO_3$. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 3: 2) to provide the desired product **6a**. Brown solid; (80% yield, 18.16 mg), mp. 280-282 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.47 (br s, 1H), 8.46 (s, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 2.0 Hz, 2H), 7.46 (d, J = 8.2 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.13 (dd, J = 11.0, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 140.0, 137.7, 135.5, 131.9, 125.2, 123.5, 121.9, 119.7, 117.5, 113.3, 113.0, 112.1, 109.6; IR (NaCl) ν (cm^{-1}) 3399, 2922, 2851, 1724, 1614, 1463, 1377, 1322, 1251, 1158, 1117, 1019; HRMS (ESI): Calcd for $C_{13}H_{10}N_3$ $[M+H]^+$: 208.0869, found: 208.0864.

Computational details

Density Functional Theory (DFT)[24] calculations were carried out using GAUSSIAN09 software package.[25] The geometries of reactants, intermediates, products and transition states (TS) were optimized using B3LYP method[26] and the 6-31+G(d,p) basis set was used for all atoms except for modeling palladium atom for which LanL2DZ was used. The model system used as a catalyst in this theoretical study consists of a trimethylphosphine (PMe_3) ligand (in order to reduce computational time) and two acetate moieties attached to palladium. Use of this model system is justified because (i) the cross coupling reaction happens at a sight far from PR_3 (ii) several studies already reported using such a simplified model system.[27] For all the optimized structures, frequencies were computed analytically to characterize stationary points as minima or transition states. Each transition state was characterized by first-order saddle point with only one imaginary vibrational mode. The zero-point energy values and the free energy factors estimated during the second derivative analysis were scaled by a factor of 0.9806.[28] Wiberg bond index[29] was calculated to determine the bond orders of importation bonds in the transition states.

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Notes and references

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