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Pd(II) pincer type complex catalyzed tandem C-H and N-H activation of acetanilide in aqueous media: A concise access to functionalized carbazoles in a single step

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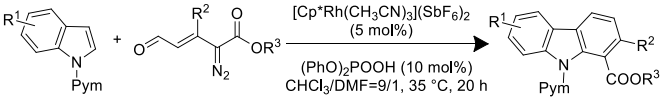
One-pot, tandem C–H and N–H activation of acetanilides with aryl boronic acids to realize functionalized carbazoles were conveniently performed under aerobic conditions using a novel *NNO* pincer type Pd(II)complex [Pd(L)Cl] (where L = nicotinic acid (phenyl-pyridin-2-yl-methylene)-hydrazide or furan-2-carboxylic acid (phenyl-pyridin-2-yl-methylene)-hydrazide) as a catalyst in neat water and very low (0.01 mol%) amount of catalyst. It is worth to note recyclability up to six consecutive runs and column chromatography free isolation of the titled heterocycles in an excellent yield.

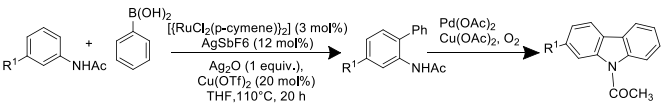
Introduction

Key to pharmaceutical compounds are carbazole cores (Fig. 1).[1] They lead to well-known antitumor, antibacterial, anti-tuberculosis, anti-inflammatory, psychotropic and anti-histaminic drugs.[2] Numerous synthetic methodologies were reported in literature for the construction of carbazole architectures.[3] However, those strategies involved multiple steps, such as the preparation of key starting materials followed by sequential reaction schemes and involved harsh reaction conditions to produce the target compounds.[3] Hence, a facile and sustainable synthetic approach towards the construction of carbazole moieties is desirable. Transition metal-catalyzed, chelation-assisted activation of C–H and N–H bonds has emerged as an effective synthetic method.[4] Specifically, utilizing one-pot C–C and C–N bond forming reactions were key to the synthesis of nitrogen-containing heterocycles.[5] In this context, various functional groups with coordination ability, such as acetamino (NH–COR)[6a] amides,[6b] imines,[6c] pyridines,[6d,e] pyridine-*N*-oxide,[6f] *o*-phenylcarbamates[6g] and

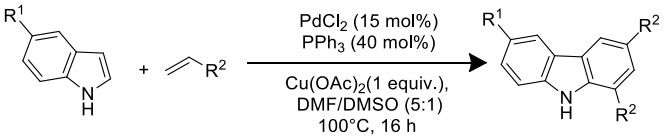
Huggen Wang's report[7a]



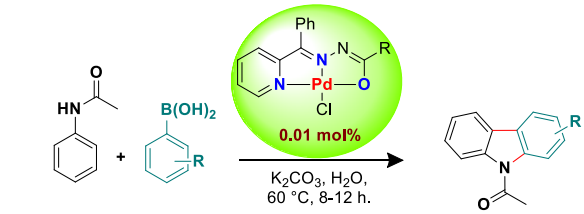
Jeganmohan's report[11]



Akhilesh K. Verma's report[7b]



This Work



- Water as a solvent
- One-pot operation
- Without oxidant
- Coloumn chromatography free methodology
- Scalability
- Reusability
- Wide scope of coupling partners
- Open flask condition

Scheme 1 Selected reports for the synthesis of carbazoles

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Electronic Supplementary Information (ESI) available: Copies of 1H and 13C NMR spectra, Single-crystal XRD data of the complexes, experimental procedures See DOI: 10.1039/x0xx00000x

methoxy benzamide[6h] were employed in the palladium-catalyzed C–C and C–N bond forming reactions. Among those, palladium catalyzed *ortho*-arylation of acetamino (NH–COR) coordinated aromatics with several electrophiles has been extensively studied (Scheme 1).[7] A wide range of arylating agents like aromatic boranes, stannenes and silanes were utilized in coupling reactions. Due to the inherent advantages of boronic acids such as low toxicity, stability to ambient conditions including humidity and the facile removal of boron-containing side products, aromatic boranes are widely chosen in such coupling reactions.[8] However, very few reports were published on employing organoboron reagents as the coupling partner in palladium catalyzed C–H and N–H activation reactions.[9]

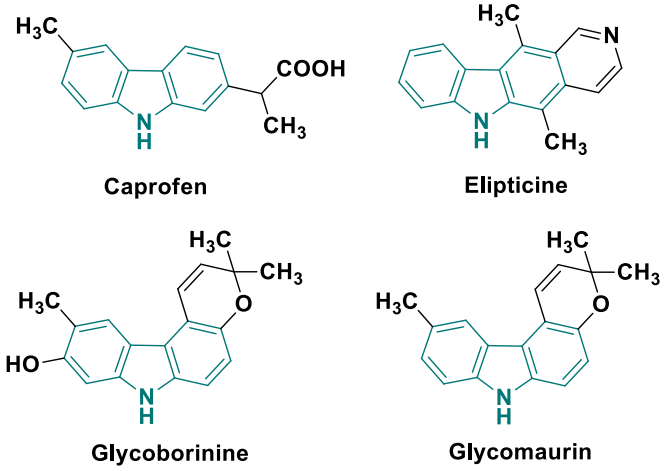


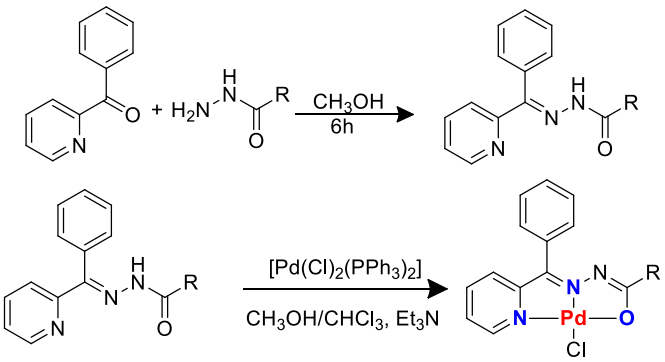
Fig. 1 Carbazole based drugs

In 2010, H. Lipshutz's group demonstrated *ortho*-arylation of aryl ureas with aryl boronic acids or aryl iodide catalyzed by cationic palladium complexes.[10a, b] However, their approach required 10 mol % of palladium complex as catalyst to obtain an *ortho*-arylated product *via* C–H activation. Later, Jeganmohan's group reported Ru(II) complex catalyzed *ortho*-arylation of acetanilide with aryl boronic acids to *ortho*-arylated acetanilides, which were subsequently converted into phenanthridine and carbazole derivatives by using Ph_3PO and Tf_2O or palladium or $Cu(OTf)_2$ catalysts and obtain 90% yield.[11a] Particularly, M.-J. Wu and co-workers[11b] reported one-pot synthesis of 9-(pyridin-2-yl)-9H-carbazoles through the simultaneous C–H activation and palladium(II)-catalyzed cross-coupling of N-phenylpyridin-2-amines with potassium aryltrifluoroborates in presence of silver acetate as an oxidant.

Based on state-of-the-art techniques, we are currently interested to develop new pincer type complexes as catalysts for activation of C–H and N–H bonds. Owing to high stability and reactivity, pincer complexes have been widely utilized as catalyst for a variety of organic reactions including C–H and N–H bond activation.[12] Previously, we examined pincer type palladium(II) complexes for C–C bond formation reactions.[13] In continuation of our ongoing research,[13] we wish to present herewith two new palladium(II) complexes incorporating *NNO* pincer type ligand for one-pot, single step synthesis of functionalized carbazoles *via* C–H and N–H activation of acetanilide with aryl boronic acids. We believe that the catalytic system presented below deserves merit as it doesn't require organic solvents, elevated temperatures, oxidant, additives and phase transfer reagents. To the best of our insight, this is the first report on the utility of pincer type palladium(II) complexes for the one-pot construction of *N*-acetylcarbazoles with low catalyst loading (0.01 mol%) under aerobic conditions in aqueous media.

Results and discussion

Treatment of Pd(II) precursor $[PdCl_2(PPh_3)_2]$ with pincer type ligands, namely, isonicotinic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (HL1) or furan-2-carboxylic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (HL2) yielded complexes of the type [Pd(L)Cl] as shown in scheme **2** (complex **1** and **2**).



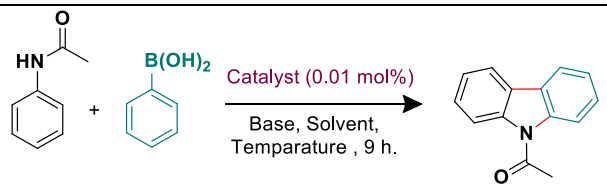
Where R = 3-pyridyl (complex **1**) or 2-furyl (complex **2**)

Scheme 2 Synthesis of *NNO* pincer type ligands and their Pd(II) complexes **1** and **2**.

Characterization of the newly synthesized complexes **1** and **2** were carried out by means of elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy (details are given in the Experimental section). In particular, the exact coordination mode of the pincer type ligand is fully supported by the single-crystal XRD data. Infra-red spectra of the ligands were recorded using KBr pellets. The free pincer type ligands (HL1 and HL2) showed the characteristic N–H and the C=O bands of the amide functionality at 3025, 3060 and 1641, 1680cm^{-1}, respectively. A sharp band was observed at 1571 and 1581 cm^{-1}, respectively due to the presence of C=N stretching of the free ligands.[14] The IR spectra of complexes **1** and **2** didn't display any bands assignable to the N–H or the C=O group of the amide functionality proving that the ligands (HL1 and HL2) underwent enolisation followed by deprotonation prior to coordination with the palladium(II) ion.[14] Furthermore, a new band due to the C=N–N=C group was observed at 1478 and 1474 cm^{-1}, respectively.[14] Thus, pincer type ligands HL1 and HL2 were coordinated to palladium(II) ion *via* the pyridyl nitrogen, azomethine nitrogen and the imidolate oxygen. ^{1}H and ^{13}C NMR spectral data of the complexes **1** and **2**, recorded in $CDCl_3$, are presented in the Experimental section. The ^{1}H NMR spectra of these complexes didn't show any N–H proton signals meaning oxygen is coordinated to the palladium ion in the imidolate form. Aromatic protons of the ligands present in complexes **1** and **2** showed resonances in the region of 7.00–7.81 ppm.[15] Downfield resonance in the ^{13}C NMR spectra of the complexes **1** and **2** at 161.6 and 165.6 ppm, respectively, owed their presence to coordinated carbon of imidolate functionality(N=C–O). Signals featuring in the region of 165.3–124.7 ppm were assigned to various aromatic carbons present in complexes **1**and **2**.[15]

The single-crystal XRD studies of the complexes **1** and **2** showed the pincer type ligands (HL1 and HL2) adopting to the palladium ion in an uni-negative tridentate manner constituting pyridyl nitrogen, azomethine nitrogen and the deprotonated imidol oxygen as donor atoms forming two different five membered chelate rings with the palladium ion while the fourth coordination site is occupied by a chloride ion. The Pd(II) center in complexes **1** and **2** adopted a distorted square-planar geometry. The bond lengths and bite angles are very similar to those observed for other palladium(II) complexes.[16] The perspective ORTEP view of complexes **1** and **2** are shown in Fig. 2 and 3. Details on the data collection, structure refinements, bond angles and bond distances are gathered in ESI (Table S1 &S2)

Table 1 Optimization of reaction conditions.[a]



Entry	Catalyst	Base	Solvent	Yield (%)*
1	Complex 1	No base	H_2O	10
2	Complex 1	KOH	H_2O	72
3	Complex 1	K_2CO_3	H_2O	89
4	Complex 1	NaOH	H_2O	76
5	Complex 1	Na_2CO_3	H_2O	70
6	Complex 1	CH_3COONa	H_2O	56
7	Complex 1	Et_3N	H_2O	51
8	Complex 1	Pyridine	H_2O	38
9	Complex 1	K_2CO_3	THF	72
10	Complex 1	K_2CO_3	H_2O	89
11	Complex 1	K_2CO_3	DMF	74
12	Complex 1	K_2CO_3	CH_3CN	63
13	Complex 1	K_2CO_3	DMSO	59
14	Complex 1	K_2CO_3	MeOH	72
15	Complex 1	K_2CO_3	EtOH	75
16	Complex 1	K_2CO_3	toluene	65
17	Complex 1	K_2CO_3	benzene	53
18	Complex 1	K_2CO_3	$CHCl_3$	61
19	Complex 1	K_2CO_3	DCM	53
20	**Complex 2**	**K_2CO_3**	**H_2O**	**93**

[a] = Reaction conditions: acetanilide (2 mmol), phenylboronic acid (2 mmol) K_2CO_3 (4, mmol), H_2O and catalyst (0.01 mol %) stirred at 60 °C for 8-10 h. * Isolated yield

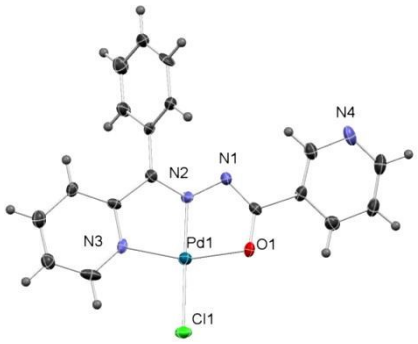


Fig. 2 ORTEP diagram of complex **1** with thermal ellipsoids at the 50 % probability level.

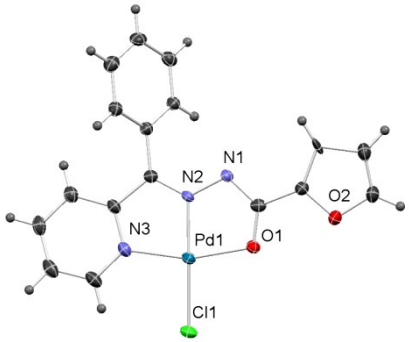


Fig. 3 ORTEP diagram of complex **2** with thermal ellipsoids at the 50 % probability level.

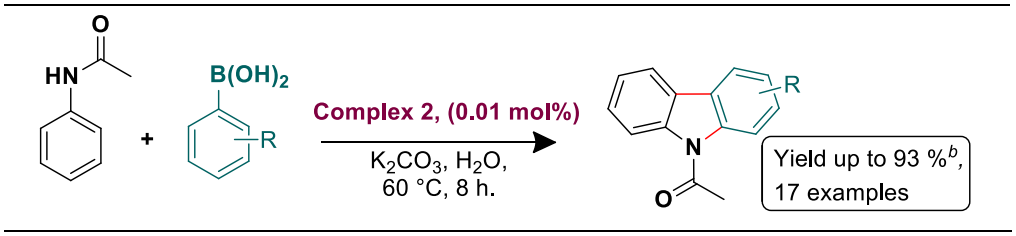
We directed our attention on the identification of suitable reaction conditions for efficient C–H and N–H activation of acetanilide with phenyl boronic acid. For this purpose, acetanilide (2 mmol) and phenylboronic acid (2 mmol) were used as model substrates in presence of complex **1** as catalyst (0.01 mol %). Reaction without any base realized only 10% of isolated yield. Yields of the functionalized carbazoles as product were optimized by screening with complexes **1** and **2** as catalysts and various bases and solvents. K_2CO_3 proved to be the most effective base (Table 1, entry 3). We focused next on finding an appropriate solvent, where upon H_2O emerged as the optimal choice out of THF, DMF, DMSO, CH_3CN, MeOH, EtOH, toluene, benzene, $CHCl_3$ and DCM (Table 1, entry 10). Complex **2** proved to be less effective than **1**. The enhanced catalytic activity of complex **2** is correlated to the presence of a furan moiety (Table 1, entry 23).[17] We also tested the above reaction at a range of temperatures starting from room temperature. Best yield of the heterocyclic product (93%) was achieved at 60 °C. The yield of the product decreased significantly for temperatures above 60 °C. Thus, the following conditions were utilized further on: acetanilide (2 mmol), aryl boronic acid (2 mmol) K_2CO_3 (4 mmol), H_2O and complex **2** as catalyst (0.01 mol %), 60 °C. The molecular identity of the isolated products was confirmed by ^1H, ^{13}C NMR and mass spectroscopy (see ESI) and compared with literature.[11]

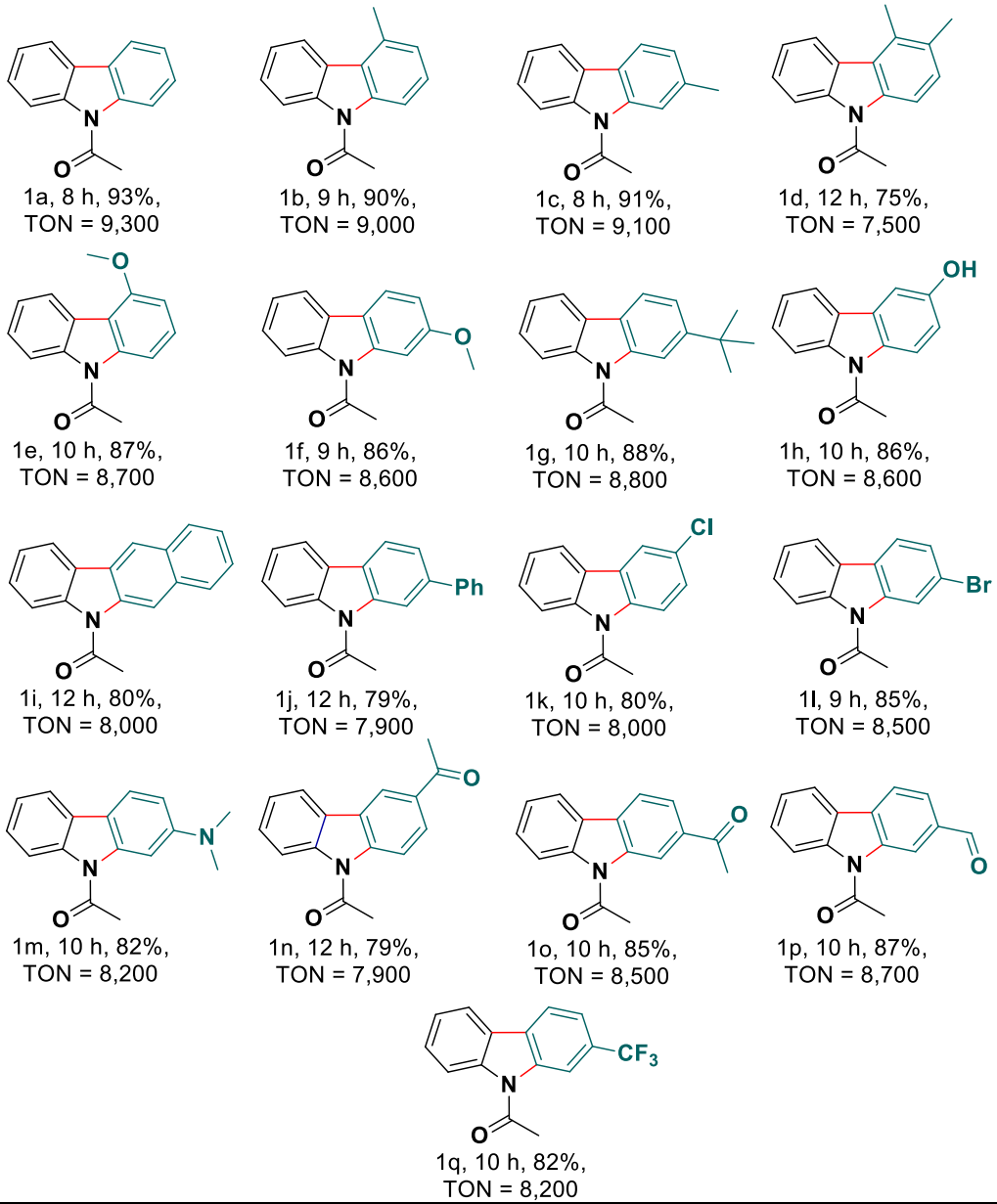
The substrate scope of various aryl boronic acids possessing both activating and deactivating groups was tested at above described optimized conditions. Excellent yields with high regioselectivity were observed for most of these substrates (Table 2 and 3). Aryl boronic acids featuring strongly activating groups such as $-OCH_3$, $-OH$ and $-N(CH_3)_2$ underwent the reaction smoothly to give significant yields (Table 2, entries 1e, 1f, 1h and 1m). Incorporation of sterically demanding 2, 3-dimethylphenylboronic acid and 4-*t*-butylphenylboronic acid did not affect the reaction notably and afforded the respective products in 75% and 88% yield (Table 2, entries 1d and 1g). On the other hand, substitution of weakly activating groups like $-CH_3$ at either *ortho* or *para* positions of boronic acid gave 90 and 91 % yield (Table 2, entries 1b and 1c). Both, naphthyl and biphenyl boronic acids converted into the desired products (Table 2, entries 1i and 1j).

It is gratifying to note that electron-deficient aryl boronic acids were well tolerated and weakly deactivating halogens such as −Cl and −Br provided good yields (80 & 85%) of the expected product (Table 1, entries 1k and 1l). The presence of halogens (chloro/bromo) in the targeted heterocyclic derivatives (Table 2, entries 1k and 1l) hints at further functionalization through cross coupling at respective positions. Moderately deactivating groups like formyl or acetyl occupying the *para* position of phenylboronic acids were well tolerated to afford 87% of the desired product (Table 1, entry 1p). In addition, boronic acid bearing a strongly deactivating $-CF_3$ group at the *para* position, gave 82% of the desired product and thus revealed that electronegativity of trifluromethyl as a substituent was insignificant (Table 1, entry 1q).

The same protocol used above was applied to *N*-naphthalen-2-yl-acetamide, which possesses a napthyl unit in place of a phenyl. Aryl boronic acids bearing electron- donating/withdrawing groups actively participated and afforded the expected products in good isolated yields (Table 3 entries 2a-2q). During the course of this catalytic reaction, we didn't observe any homo coupled products of aryl boronic acids.

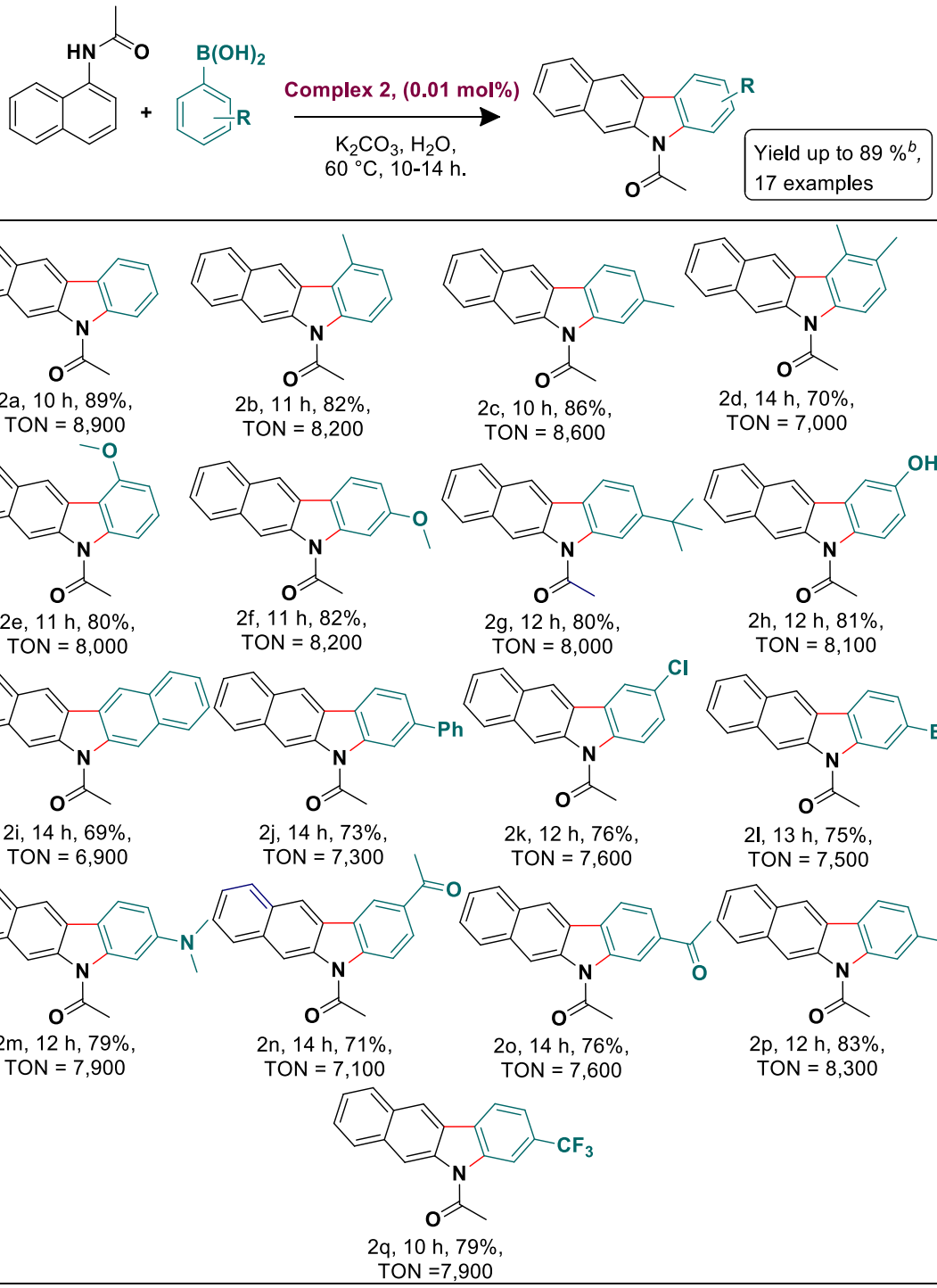
Table 2 Coupling of acetanilide and aryl boronic acids to functionalized carbazoles (1a–1q) *via* C-H and N-H activation under optimized reaction conditions.[a]





[a] = Reaction conditions: acetanilide (2 mmol), aryl boronic acid (2 mmol) K_2CO_3 (4, mmol), H_2O and catalyst (0.01 mol %) stirred at 60 °C for 8-12 h. TON = turnover number = ratio of moles of product formed to moles of catalyst used. [b]= Isolated yield.

Table 3 Coupling of *N*-naphthalen-2-yl-acetamide and aryl boronic acids to functionalized benzo[b]carbazoles (2a–2q) *via* C-H and N-H activation under optimized reaction conditions.[a]



[a] = Reaction conditions: *N*-naphthalen-2-yl-acetamide (2 mmol), aryl boronic acid (2 mmol) K_2CO_3 (4, mmol), H_2O and catalyst (0.01 mol %) stirred at 60 °C for 10-14 h. TON = turnover number = ratio of moles of product formed to moles of catalyst used. [b]= Isolated yield.

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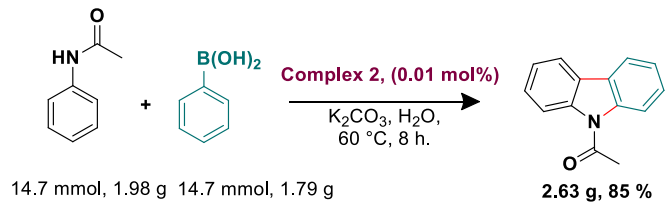
The gram scale synthesis was examined using 14.7 mmol of acetanilide with 14.7 mmole of phenylboronic acid as representative examples. The reaction readily occurred to afford the target product **1a** in 85% yield (Scheme 3).



Scheme 3 Gram scale synthesis of **1a**.

Recently, M.-J. Wu *et al*[11b] documented a Pd(II) catalyzed synthesis of N-pryidylcarbazoles *via* tandem C–H activataion of *N*-phenylpyridin-2-amines with potassium aryltrifluoroborates. However, their strategy suffered from the formation of a side product, use of an oxidant, higher temperature and longer duration (48 h). Hence, we are of the opinion that our present methodology is superior to that of them.

We tried above reaction with low catalyst loading, ranging from 0.01–0.0001 mol % under optimized conditions, but only low yields were obtained, as was reported earlier.[19] However, use of 0.0001 mol% catalyst resulted in high turnover numbers (Table 4).

Table 4 Catalyst loading test

Entry	Mol %	Isolated yield %	TON
1	0.01	93	9,300
2	0.001	85	85,000
3	0.0001	76	760,000

The lifetime of a catalytic system and its level of reusability are vital factors in homogeneous catalysis.[20] In this regard, we found that the present catalytic system remains active after recycling for up to 6 consecutive runs (see Fig. 4), with a gradual decrease of the activity after each cycle.[21] The stability of recovered catalyst was identified by melting point data, R_f value of TLC and ^1H NMR spectra. (Detailed procedure of recovery and reusability is given in the experimental section).

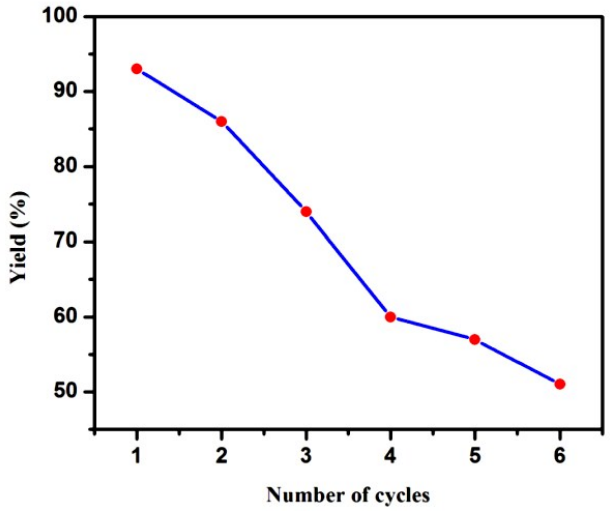
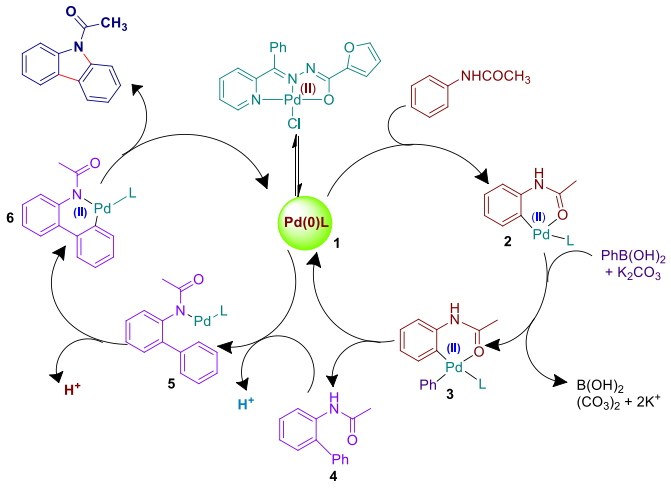


Fig. 4 Reusability of catalyst **2**

Based on the reported metal-catalyzed C–H and N–H bond activation reactions, we propose a plausible mechanism to understand the formation of carbazole derivatives in Scheme **4**.[6, 9, 10, 18] The first step involves the active species **1** to undergo an oxidative addition of acetanilide to form intermediate **2**, a six membered palladacycle. Transmetallation of phenylboronic acid into intermediate **2** in the presence of K_2CO_3 generates intermediate **3** which, on reductive elimination, yielded the *ortho*-arylated intermediate **4** with the regeneration of Pd(0) active species **1**. The catalytic cycle proceeds with subsequent deprotonation of the N-H group in **4** to form a palladium complex **5**. Through palladium as C-H activator, intermediate **5** undergoes a C-H activation at the appropriate carbon resulting in a six membered palladacycle, **6**. Reductive elimination of **6** lets access *N*-acetylcarbazole with regeneration of active Pd(0) species **1** for the next catalytic cycle.



Scheme 4 Proposed mechanism for the catalytic reaction of acetanilide with phenylboronic acid.

Conclusions

In summary, we presented the design and synthesis of a couple of new, water-soluble pincer type Pd(II) complexes [Pd(L)Cl]as catalysts for the C-H and N-H activation of acetanilide/*N*-naphthalen-2-yl-acetamide with diverse aryl boronic acids in aqueous medium to achieve *N*-acetyl carbazoles. The chosen catalytic reaction proceeded efficiently with low catalyst loading (0.01 mol %) under aerobic conditions, displaying a broad substrate scope and functional compatibility. The catalytic system can be effectively recycled up to six consecutive runs. We feel that the present palladium catalyzed methodology offers a simple and green route to synthesize a series of biologically important functionalized carbazoles in one-pot synthesis with excellent yields. The scientific merit of this interesting study is highlighted by the fact that this is a simple but valuable approach towards a series of highly functionalized carbazoles by excluding the need of product isolation using column chromatography.

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