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Pd-PEPPSI-IPent^{Cl}: a new highly efficient ligand-free and recyclable catalyst system for the synthesis of 2-substituted indoles *via* domino copper-free Sonogashira coupling/cyclization[†]

Murali Krishna Kolli,^{‡,ab} Nagul Meera Shaik,^{‡,bc} Govindasamy Chandrasekar,^{ID *a} Sridhar Chidara^{bc} and Ragu Babu Korupolu^b

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A pyridine-containing decidedly resourceful Pd-N-heterocyclic carbene complex, Pd-PEPPSI-IPent^{Cl} (PEPPSI = pyridine enhanced precatalyst preparation, stabilization, and initiation), is used as a first class recyclable catalytic system for the synthesis of 2-substituted indoles *via* domino copper-free Sonogashira coupling/cyclization. The catalyst showed a greater performance in the cascade reaction of various 2-bromo anilines with different terminal acetylenes under mild (60 °C) and green conditions (ethanol:water) even in the absence of a copper catalyst and an inert atmosphere. The catalyst is used for the first time in these reactions. The findings suggest that 0.1 mol% of the catalyst is sufficient, and that the catalyst is recyclable and can be reused for up to six cycles.

Introduction

Indole derivatives are recognized as important synthetic intermediates commonly found in pharmaceutically active agents and natural products.^{1a-e} Numerous methods have been developed thus far for the synthesis of indole derivatives by using non-metal mediated approaches including Fischer, Madelung, Reissert, Leimgruber-Batcho, and Gassman indole syntheses.^{2a-d} Other side applications include the use of metal/metal complex catalysts such as Au, Cu, Pd, Rh, Sb, Ru, Pt, Fe, and Nb.^{2e-m} N-Heterocyclic carbene (NHC) complexes play a vital role in catalysis and synthetic organic chemistry. More particularly Pd-N-heterocyclic carbene (Pd-NHC) complexes are playing a very important role in cross coupling reactions for C–C, C–O and C–N bond formations.³

Capretta *et al.*⁴ first reported a cross coupling reaction catalysed by Pd-N-heterocyclic carbene (Pd-NHC) in 2004. Several N-heterocyclic carbenes^{5a-f} (NHC) with nitrogen atoms substituted

with bulkier aromatic rings such as mesityl,^{6a-e} 2,6-diisopropylphenyl,^{7a-j} 2,6-diisopentylphenyl,⁸ 2,6-diisopropyl-4-tritylphenyl,⁹ calixarenyl,¹⁰ resorcinarenyl^{11a,b} and 2,6-di(diphenylmethyl)-4-methoxyphenyl^{12a,b} showed greater catalytic activities^{12c-f} in cross coupling reactions compared to the analogs bearing smaller substituents due to the steric effect. Glorius *et al.*^{13a,b} have explored the beneficial role of bulky *N*-substituents that display structural flexibility, thereby enabling the steric requirements of each individual step of the catalytic cycle in these reactions.¹⁴

The Sonogashira reaction has attained a greater degree of importance in synthetic organic chemistry for synthesizing industrially important compounds of heterocycles, arylated compounds, natural products, polymers and organic nanostructured materials. The Sonogashira reaction offers a simple and straightforward coupling of aryl halides with terminal acetylenes using a palladium catalyst and copper cocatalyst in a basic medium. The utility of the reaction required an inert atmosphere and moisture free conditions, since trace amounts of oxygen could lead to homo-coupled products by Glaser coupling¹⁵ as the copper-acetylide intermediate is extremely sensitive to aerobic conditions.^{16a-g} Therefore, achieving copper-free conditions that would provide tolerance under aerobic conditions would be a greater challenge in the Sonogashira coupling reactions. While the copper free conditions would ensure the coupling being tolerant to aerobic conditions, the amine-free conditions would circumvent the toxicity issues associated with the use of some of the amines.¹⁷

Bolm and co-workers explained the significance of copper catalysed Sonogashira reactions in the presence of chelating

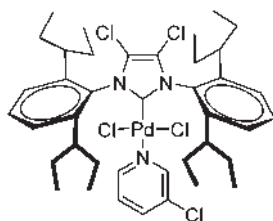
^a Department of Chemistry, SAS Division, VIT University, Chennai-600127, Tamilnadu, India. E-mail: gc_sekar78@yahoo.co.in, chandrasekar.g@vit.ac.in; Fax: +91 44 3993 2555; Tel: +91 44 39931237

^b Department of Medicinal Chemistry, GVK Biosciences Pvt. Ltd, IDA Nacharam, Hyderabad, Telangana, 500076, India

^c Department of Engineering Chemistry, Andhra University, Visakhapatnam, A.P., 530003, India

[†] Electronic supplementary information (ESI) available: General experimental section, characteristic data and copies of ¹H, D₂O exchange & ¹³C NMR, LCMS, IR and HRMS spectra. See DOI: 10.1039/c7nj01544e

[‡] Equal contribution.

Fig. 1 Pd-PEPPSI-IPent^{Cl}.

diamines.¹⁸ Surprisingly in 2014, Lu *et al.*,¹⁹ synthesized a new Pd-NHC(*n*) catalyst for a Sonogashira coupling reaction under aerobic and copper-free conditions. Organ *et al.*^{20a-c} developed a versatile Pd-NHC complexes using the PEPPSI (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) method with Pd(*n*) species bearing an NHC ligand, two halides and 3-chloro pyridyl group.^{20d} The striking catalyst Pd-PEPPSI-IPent^{Cl} (Fig. 1) is one such Pd-NHC based complex, which is air and moisture stable even for longer times.

Here our interest is to develop a new and highly efficient ligand-free and recyclable Pd-PEPPSI-IPent^{Cl} catalytic (synthesized and used) system for the one pot synthesis of 2-substituted indoles *via* Sonogashira coupling (without copper catalyst) followed by cyclization using a green approach. Sonogashira coupling under copper/amine free conditions was first reported by Ghosh *et al.*,²¹ and it was observed that PEPPSI type precatalysts with a more electron-rich metal centre show better activity.²² N-Heterocyclic carbenes for the highly desirable copper-free and amine-free Sonogashira coupling in air and a mixed-aqueous medium have been reported.¹⁴ In particular, the PEPPSI themed (NHC)PdCl₂(pyridine)-type precatalysts efficiently carried out the highly convenient copper-free and amine free Sonogashira coupling of aryl bromides with terminal acetylenes in air and a mixed aqueous medium.

Hence a remarkable challenge that is faced in the Sonogashira coupling reaction was overcome and it has been carried out under copper-free, amine-free and air atmosphere conditions. The synthesis of 2-substituted indoles starting from 2-bromoaniline is generally carried out in two steps by using various palladium catalysts^{23a,b} under inert conditions. In contrast to the stepwise synthesis, one pot transformations save time and resources, as they require only a single isolation and purification step. Furthermore, one pot synthetic methodologies are attractive since they produce highly functionalized products in one single synthetic procedure, often circumventing unwanted wastes. Initially, we have examined the preparation of Pd-PEPPSI-IPent^{Cl} by following the reported literature²⁴ with some modifications in order to improve the yields. So far solvents such as acetone, toluene, tetrahydrofuran, acetonitrile, 1,4-dioxane and dimethylformamide²⁵ are most frequently used for Sonogashira coupling reactions. But these are expensive, toxic, and difficult to recycle. Development of an inexpensive and environmentally acceptable method for the synthesis of 2-substituted indoles is therefore highly desirable.

As part of our interest taking into consideration the immense biological importance, synthesis, separation and

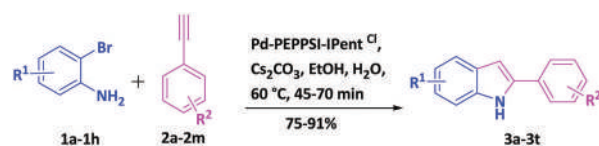
purification of compounds, and the expensiveness and recyclability of the catalyst and also looking into environmentally friendly reaction conditions, we now report a ligand-free one pot synthesis of 2-substituted indoles *via* Sonogashira coupling (copper/amine free) followed by cyclization using a Pd-PEPPSI-IPent^{Cl} catalyst in ethanol:water as a green reaction medium under mild reaction conditions.

Results and discussion

One pot synthesis of various 2-substituted indoles

The 2-substituted indoles synthesized from various 2-bromoanilines (**1a–1h**) and terminal acetylenes (**2a–2m**) are shown in Table 3 as outlined in Scheme 1. There are 20 compounds (**3a–3t**) which were prepared *via* various successive substitutions with aryl/heteroaryl moieties through Sonogashira coupling followed by cyclization using a common Pd-PEPPSI-IPent^{Cl} catalyst system. To accomplish the desired results, we optimized the reaction conditions by changing the reaction parameters such as catalyst, ligand, solvent and temperature.

In order to establish the optimal conditions for the Sonogashira coupling reaction, we selected the model reaction between 2-bromoaniline and phenyl acetylene in the presence of various palladium based catalysts, the ligand, and Cs₂CO₃ in an EtOH:H₂O (1:1) medium at 60 °C and the product yields are depicted in Table 1. It is very clear from the experimental results that the reaction did not proceed with PdCl₂ and Pd(OAc)₂ even in the presence and absence of the ligand (Table 1, entries 1–6). When the reaction was carried out with Pd(PPh₃)₄ in the absence of the ligand, the product obtained was less than 5% in yield (Table 1, entry 7). A much lower product yield was observed in the reactions catalyzed by using various palladium catalysts (Table 1, entries 8–12). However, interestingly a competitive product yield of 62% was observed using Pd-PEPPSI-*i*Pr (Table 1, entry 13) and this triggered us to screen various Pd-PEPPSI catalysts to enhance the product yield for convenient catalytic use. Catalysts such as Pd-PEPPSI-*i*Pent, SIPr, SONO-SP², and IPent^{Cl} were used for this reaction and increasing product yields were observed accordingly (Table 1, entries 14–17). On the other hand, an increase in temperature from 60 to 100 °C did not contribute to any increase in yield (Table 1, entry 18). Therefore, 60 °C was selected as the optimal temperature for further experiments. Moderate yields were observed when the reaction was carried out under microwave irradiation and in a sealed tube (Table 1, entries 19–20). It is noteworthy that Pd-PEPPSI-IPent^{Cl} was found to give superior results among other catalysts studied at this temperature even



Scheme 1 Synthesis of 2-substituted indoles using a Pd-PEPPSI-IPent^{Cl} catalyst. R¹ and R²: various aryl/hetero aryl groups and electron-donating/withdrawing groups.

1 **Table 1** Screening of the effect of various palladium catalysts for the
5 synthesis of 2-phenyl indole



Entry	Catalyst	Ligand	Time	Yield ^a (%)
1	PdCl ₂	None	12 h	0
2	PdCl ₂	TPP	12 h	0
3	PdCl ₂	Dppf	12 h	0
4	Pd(OAc) ₂	TPP	12 h	0
5	Pd(OAc) ₂	Xphos	12 h	0
6	Pd(OAc) ₂	Dppf	12 h	0
7	Pd(Ph ₃ P) ₄	None	12 h	<5
8	PdCl ₂ (dppf) ₂	None	12 h	5
9	PdCl ₂ (TPP) ₂	None	12 h	11
10	PdCl ₂ (CH ₃ CN) ₂	None	12 h	14
11	Pd ₂ (dba) ₃	Binap	12 h	18
12	Pd(H ₂ NCH ₂ CH ₂ NH ₂)Cl ₂	None	12 h	19
13	PEPPSI-iPr	None	3 h	62
14	PEPPSI-iPent	None	3 h	61
15	PEPPSI-SiPr	None	3 h	65
16	PEPPSI-SONO-SP ²	None	1.5 h	72
17	PEPPSI-IPent^{Cl}	None	50 min	91
18	PEPPSI-IPent ^{Cl}	None	50 min	81 ^b
19	PEPPSI-IPent ^{Cl}	None	50 min	85 ^c
20	PEPPSI-IPent ^{Cl}	None	50 min	71 ^d

25 Reaction conditions: 2-bromo aniline (3 mmol), Phenyl acetylene
(3 mmol), Cs₂CO₃ (6 mmol), PEPPSI-IPent^{Cl} (0.5 mol%) in EtOH:H₂O
(1:1, 10 mL) medium at 60 °C for 50 min.^a Isolated yield after column
purification. ^b Reaction temperature at 100 °C. ^c Reaction carried out in
a microwave apparatus (Anton paar, monowave). ^d Reaction carried out
in a sealed tube.

30 in the absence of the ligand and without a copper catalyst
(Table 1, entry 17).

We required a low loading catalyst ratio to carry out the
reaction in economical large scale synthesis. Hence we studied
the effectiveness of our catalyst with different mole percentages
of the Pd-PEPPSI-IPent^{Cl} catalyst in the above model reaction.
Fig. 2 represents the product yield of 3j with different reaction
times and different mole percentages of Pd-PEPPSI-IPent^{Cl}. An
increase in product yield with respect to the reaction time was
observed with different mole percentages of Pd-PEPPSI-IPent^{Cl}
catalysts used from 0.05 and 0.5. The reaction is completed
after 70 min with the product yield of 65% and 75% using 0.05
mol% and 0.08 mol% of the Pd-PEPPSI-IPent^{Cl} catalyst, respec-
tively. When the catalyst amount is increased to 0.1, 0.3 and 0.5
mol%, the reaction completes in a shorter reaction time of 50
min with 91% product yield. There is no increase in the product
yield when the catalyst amount was increased from 0.1 to 0.5
mol%. From the above results, it is clear that 0.1 mol% of the
catalyst is adequate to complete the reaction within 50 min.

The scope and the limitations of this reaction methodology
were studied using various electron-donating and electron-
withdrawing substituted 2-bromoanilines and aryl/heterocyclic
acetylenes and it was found that all compounds were success-
fully isolated in high yields (Table 3). Table 3 clearly shows that
the reaction time for the synthesis of compounds from 3a to 3t
varies from 45 to 70 min. The electron-donating groups present

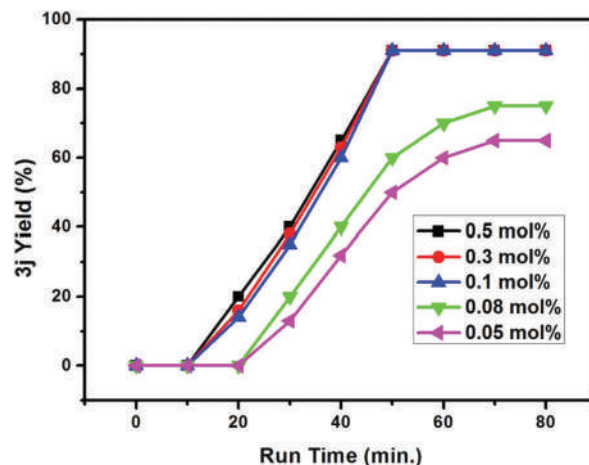


Fig. 2 Time course for the formation of compound 3j^p at variable con-
centrations of Pd-PEPPSI-IPent^{Cl}. Reaction conditions: 2-bromo aniline
(3 mmol), phenyl acetylene (3 mmol), Cs₂CO₃ (6 mmol), Pd-PEPPSI-IPent^{Cl}
in an EtOH:H₂O (1:1, 10 mL) medium at 60 °C for 50 min.^a Isolated yield
after column purification.

Table 2 Screening of the effect of various solvents

Entry	Solvent	Time (h)	Yield ^a (%)
1	Tetrahydrofuran	8	55
2	<i>N,N</i> -Dimethylformamide	6	73
3	1,4-Dioxane	6	71
4	1,4-Dioxane:water	6	77
5	Ethanol:water	0.5	91

Reaction conditions: 2-bromo aniline (3 mmol), phenyl acetylene
(3 mmol), Cs₂CO₃ (6 mmol), PEPPSI-IPent^{Cl} (0.5 mol%) in an EtOH:
H₂O (1:1, 10 mL) medium at 60 °C for 50 min. ^a Isolated yield after
column purification.

on amine/acetylene facilitate the reaction to complete in a
shorter reaction time compared to the electron-withdrawing
groups present on amine/acetylene compounds. The rate deter-
mining step of cyclization (Fig. 5) is based on the nucleophilic-
ity of the amine derivative (Sonogashira coupled product).
Hence when the electron-donating group is present on the
amine, it increases the nucleophilicity, which further enhances
the cyclization thereby resulting in a shorter reaction time. But
on the other hand when an electron-withdrawing group is
present on amine, it decreases the nucleophilicity of the amine,
thereby decreasing the rate of cyclization, which results in a
longer reaction time.

We studied the possibility of this method for a convenient
scale-up process for the preparation of 2-substituted indoles
(Table 2, entry 10) on 5 g and 10 g scales and the results showed
90% and 91% of product yield, respectively. This study clearly
indicates that the methodology is convenient for a scale-up
process and there is no remarkable product yield difference
between the R&D scale and a scaled up process.

With the optimized conditions in hand, we endeavoured to
catalyze the Sonogashira coupling reactions followed by cycli-
zation for compounds 1a–1h with terminal acetylenes 2a–2m.
All the reactions were carried out under a non-inert atmosphere

1 Table 3 Synthesis of various 2-substituted indoles using the Pd-PEPPSI-IPent^{Cl} catalyst

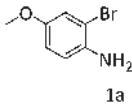
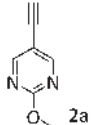
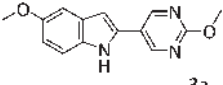
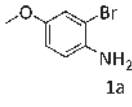
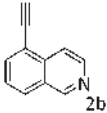
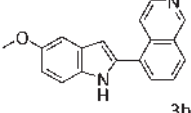
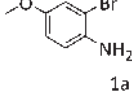
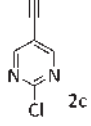
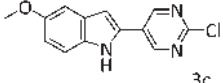
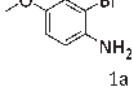
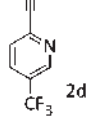
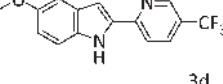
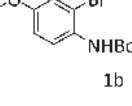
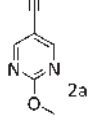
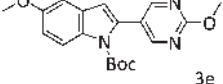
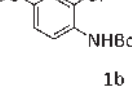
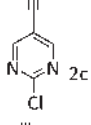
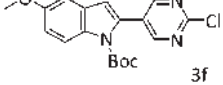
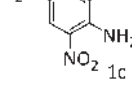
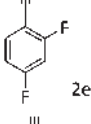
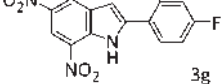
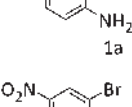
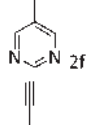
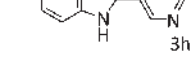
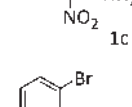
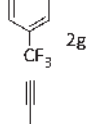
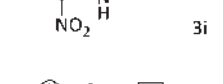
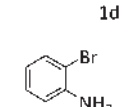
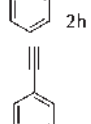
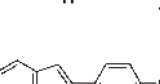
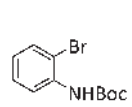
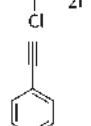
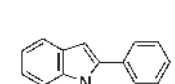
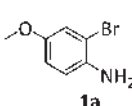
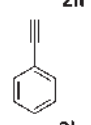
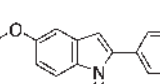

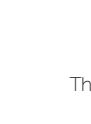

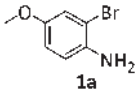
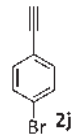
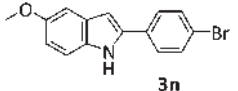
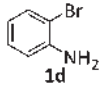
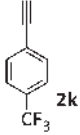
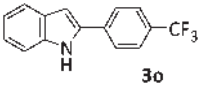
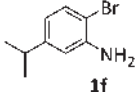
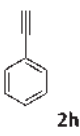
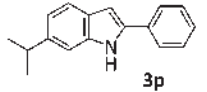
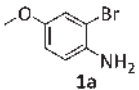
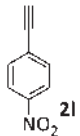
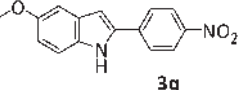
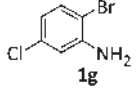
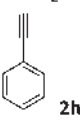
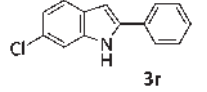
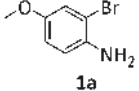
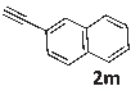
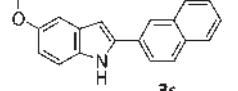
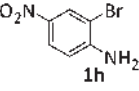
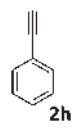
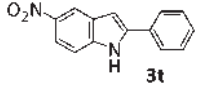
Entry	Bromo aniline	Acetylene	Product	Time (min)	Yield ^a (%)	M.p. (°C)
5 1	 1a	 2a	 3a	45	90	215–217
10 2	 1a	 2b	 3b	45	85	176–180
15 3	 1a	 2c	 3c	50	86	234–238
20 4	 1a	 2d	 3d	50	90	168–238
25 5	 1b	 2a	 3e	45	85	130–133
25 6	 1b	 2c	 3f	70	80	162–164
30 7	 1c	 2e	 3g	70	90	202–206
35 8	 1a	 2f	 3h	50	88	134–138
40 9	 1c	 2g	 3i	70	86	202–206
45 10	 1d	 2h	 3j	50	91	186–187 ^{b 26}
45 11	 1d	 2i	 3k	50	83	195–196 ^{b 27}
50 12	 1e	 2h	 3l	70	80	76–78 ^{b 28}
55 13	 1a	 2h	 3m	45	83	160–162 ^{b 29}

Table 3 (continued)

Entry	Bromo aniline	Acetylene	Product	Time (min)	Yield ^a (%)	M.p. (°C)
5 14				45	84	201–202 ^{b,30}
10 15				50	82	240–241 ^{b,31}
15 16				50	82	100–101 ^{b,32}
20 17				50	75	200–201 ^{b,33}
18				50	83	180–181 ^{b,34}
25 19				50	79	213–214 ^{b,35}
30 20				70	86	234–235 ^{b,36}

^a Isolated yield. ^b Spectral data (¹H, ¹³C NMR) of known compounds (3j–3t) were found to be identical with those reported in the literature.

and without the use of copper/amine to obtain various 2-substituted indoles (3a–3t) at different rates and variable yields. The synthesized compounds were characterized by IR, (¹H, ¹H-D₂O Ex. & ¹³C) NMR, LCMS, HRMS and IR spectra.

In the next study, we examined the recovery of the catalyst for the Sonogashira coupling reaction followed by cyclization of compound 3j with phenyl acetylene over six consecutive reaction cycles. After completion of the reaction (monitored through TLC), the catalyst was recovered from the reaction mixture by simple filtration, followed by hexane washings and then dried under vacuum at RT for 1 h. The recovered catalyst maintained a high catalytic activity with the product yield of 91% for three runs without any loss in its performance. After three cycles the catalyst was recovered from the reaction medium and it is washed with hexane, dried and then analysed using a ¹H NMR spectroscopic method. The ¹H NMR analysis showed that the recovered catalyst is very much stable even after three cycles. This is of much significance for the exploitation of the catalyst for different coupling reactions. The catalytic activity is decreased in the fourth, fifth and sixth run cycles to the product yield of 84%, 75% and 65%, respectively (Fig. 3).

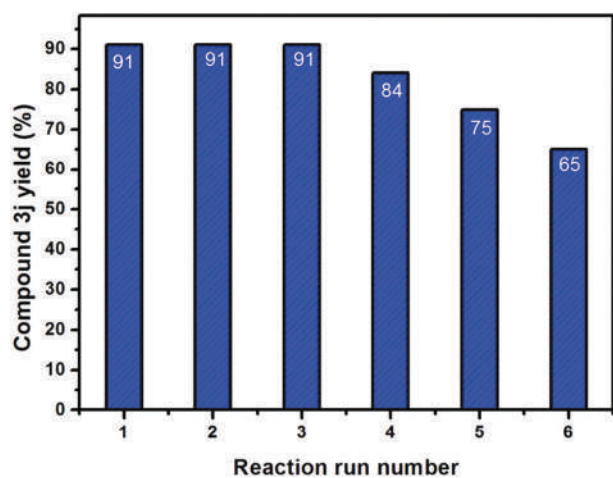


Fig. 3 Recyclability test of the catalyst Pd-PEPPSI-IPent^C. Reaction conditions: 2-bromo aniline (3 mmol), phenyl acetylene (3 mmol), Cs₂CO₃ (6 mmol), Pd-PEPPSI-IPent^{Cl} (0.1 mol%) in an EtOH:H₂O (1:1, 10 mL) medium at 60 °C for 50 min.

To clarify the catalytic role, reaction pathway and rate of the reaction in the one-pot synthesis, we analysed the crude samples obtained at various time intervals of 20, 30, 40 and 50 min using ^1H NMR (DMSO- d_6 , 500 MHz) and the spectra are shown in Fig. 4. The ^1H NMR spectrum (a) showed that our catalyst promoted the conversion of aryl bromide and acetylene to the Sonogashira coupled product within 20 min and the corresponding peaks due to the $-\text{NH}_2$ group and aryl group were

observed at 5.5 ppm and at 7.4 ppm, respectively. The cyclization reaction is also confirmed by the peak observed at 11.5 ppm due to an indole $-\text{NH}$ group. The ^1H NMR spectra of the crude product obtained at 30 and 40 min showed a decrease in peak intensity at 5.5 and 7.4 ppm and the corresponding increase in peak intensity at 11.5 ppm with increase in reaction time. This clearly indicates the conversion of the Sonogashira product into the desired product. The ^1H NMR spectrum shows

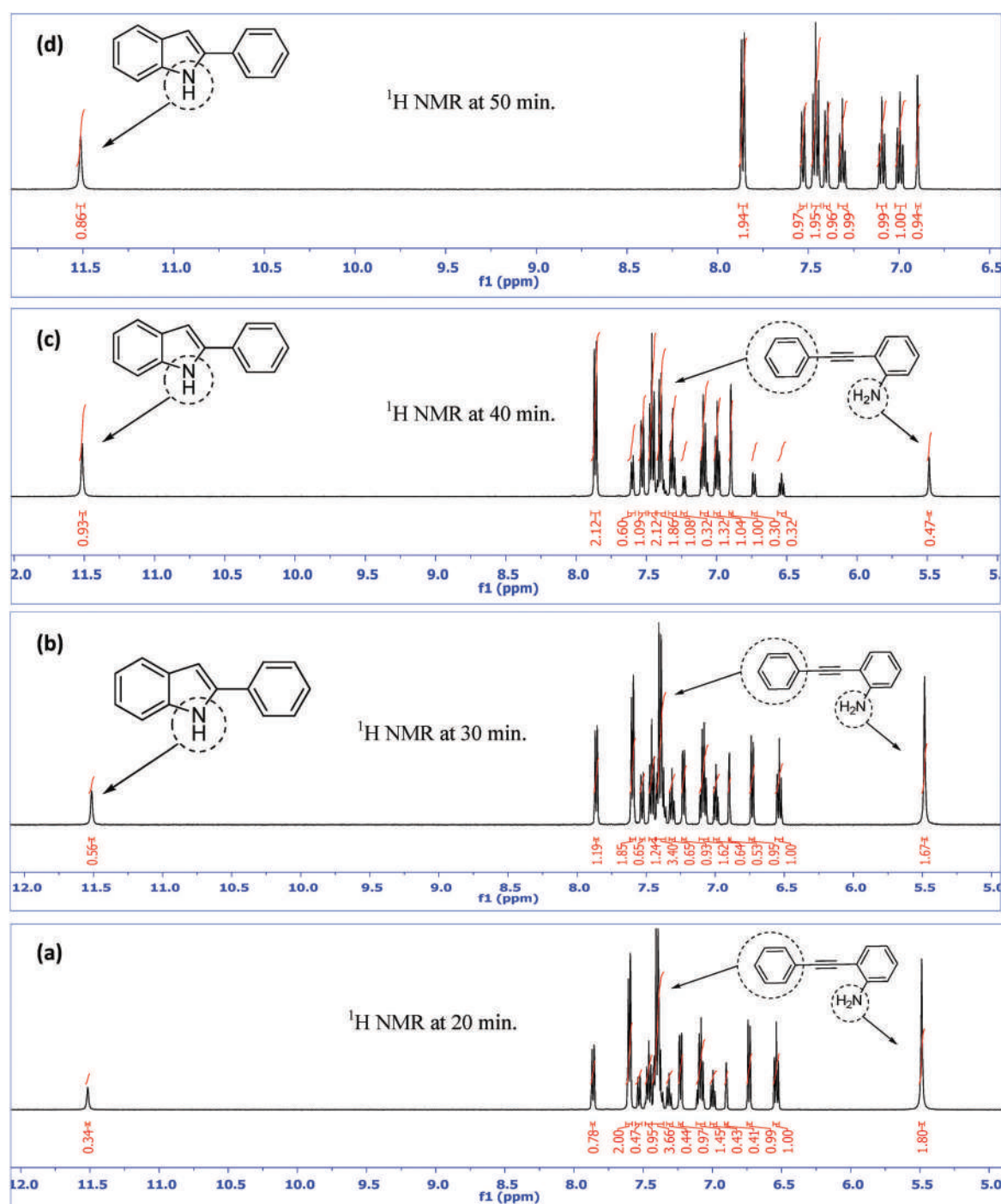


Fig. 4 ^1H NMR spectra (crude) at various time intervals of (a) 20 min, (b) 30 min, (c) 40 min and (d) 50 min. Reaction conditions: 2-bromo aniline (10 mol), phenyl acetylene (10 mol), Cs_2CO_3 (20 mol), Pd-PEPPSI-IPent^{Cl} (0.1%), EtOH:H₂O (2 mL, 1:1), 60 °C and 50 min.

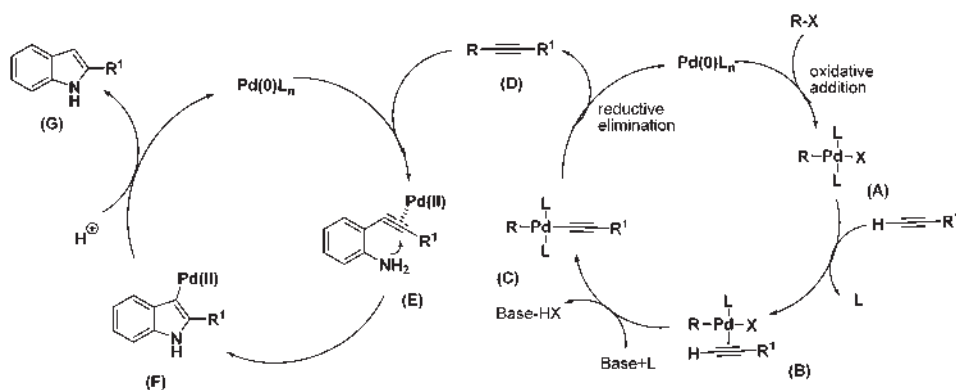


Fig. 5 Plausible mechanistic pathway for the one-pot synthesis.

the complete conversion and formation of 2-phenyl indole after 50 min. This study also proves that the reaction pathway goes *via* the Sonogashira coupled product followed by cyclization and also provides evidence with respect to the rate of the reaction, with the Sonogashira coupled product formed within 20 min and cyclization taking a slightly longer time of ~30 min.

In accordance with previous literature reports,³⁷ a plausible reaction mechanism is proposed (Fig. 5). Initially the oxidative addition of aryl bromide to Pd(0) leads to the formation of a Pd-complex (A) followed by insertion of alkyne to form a π -bond mediated new Pd-complex (B). Deprotonation of the alkyne groups of Pd-complex B and bromine displacement lead to the formation of complex C followed by reductive elimination to give the Sonogashira coupled product (D). Then a π -bond mediated new Pd(II)-complex (E) is formed, followed by deprotonation to give the cyclized Pd(II)-complex (F). Then protonation of the Pd(II)-complex (F) gives the desired compound (G).

Conclusions

In summary, we have demonstrated the use of catalyst Pd-PEPPSI-IPent^{Cl} as a highly active Pd-NHC catalytic system for the one pot synthesis of 2-substituted indoles *via* Sonogashira coupling (without copper catalyst) followed by cyclization with an unprecedented reactivity and stability. A variety of aromatic/hetero aromatic acetylenes including activated, deactivated and sterically hindered moieties and both simple and substituted aryl acetylenes were coupled with various substituted 2-bromo anilines using Pd-PEPPSI-IPent^{Cl} under mild reaction conditions in a greener reaction medium of ethanol:water (1:1) without a ligand and an inert atmosphere. To the best of our knowledge, Pd-PEPPSI-IPent^{Cl} is used for the first time in these couplings to afford excellent yields. Moreover 0.1 mol% of the catalyst is sufficient to carry-out both Sonogashira reactions followed by cyclizations even in the absence of any ligand. Our approach, hence offers an important and environmentally beneficial alternative recyclable catalytic system for the synthesis of various 2-substituted indoles.

Experimental section

A typical procedure for the one pot synthesis of 2-substituted indoles

A 25 ml round bottomed flask was charged with compounds **1a–1h** (3 mmol), terminal alkynes **2a–2m** (3 mmol) and Cs₂CO₃ (6 mmol) in ethanol:water (1:1, 10 mL) and the reaction mixture was stirred for 5 minutes under ambient conditions. Then Pd-PEPPSI-IPent^{Cl} (0.1 mol%) is added and stirring is continued for another 5 minutes. The reaction mixture was stirred at 60 °C for 45–70 min. The reaction progress and completion were monitored by TLC, and the reaction mixture was cooled to room temperature, and filtered using Whatman filter paper followed by hexane washing (3 mL). About 5 mL of water was added to the filtrate and extracted twice with ethyl acetate (2 × 10 mL). The organic layers were combined together and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure. The residue was purified by flash column chromatography by eluting with 2% MeOH-DCM affording the title compounds **3a–3t** (yield: 75–91%).

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