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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

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Murali Krishna Kolli[a,c,#], Nagul Meera Shaik[b,c,#], Govindasamy Chandrasekar[a,*], Sridhar Chidara[b,c] and Ragu Babu Korupolu[b]

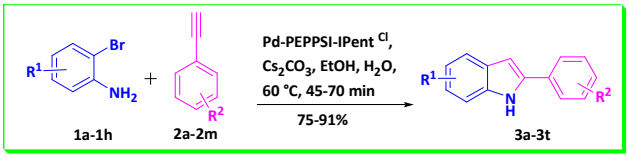
Pyridine containing decidedly resourceful Pd-*N*-heterocyclic carbene complex, Pd-PEPPSI-IPent^{Cl} (PEPPSI=pyridine enhanced precatalyst preparation, stabilization, and initiation) is being used as a first class recyclable catalytic system for the synthesis of 2-substituted indoles via domino copper-free 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 copper catalyst and inert atmosphere. The catalyst is used for the first time in these reactions. The findings suggest that 0.1 mol% of catalyst is sufficient, recyclable and can be reused 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 the 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 a 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 structure flexibility and thereby enabling the steric requirements of each individual step of the catalytic cycle in these reactions.[14]

Sonogashira reaction attained a greater degree of importance in the synthetic organic chemistry for synthesizing industrially important compounds of heterocycles, arylated compounds, natural products, polymers and organic nanostructured materials. Sonogashira reaction offers a simple and straight forward coupling of aryl halides with terminal acetylenes using palladium catalyst and copper cocatalyst in basic medium. The utility of the reaction required inert atmosphere and moisture free conditions, since trace amounts of oxygen could lead to homo-coupled products by Glaser coupling[15] as the copper–acetylide intermediate is extremely sensitive to aerobic conditions.[16a-g] Therefore, achieving copper-free conditions that would provide a tolerance in 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]



R^1, R^2: Various aryl/hetero aryl groups and electron-donating/ withdrawing groups

Scheme 1. Synthesis of 2-substituted indoles using Pd-PEPPSI-IPent^{Cl} catalyst

Bolm and co-workers explained the significance of copper catalysed Sonogashira reactions in the presence of chelating diamines.[18] Surprisingly in 2014, Lu *et al.*,[19] synthesized a new Pd-*NHC*(II) catalyst for Sonogashira coupling reaction in aerobic and copper-free conditions. Organ *et al.*,[20a-c] developed a versatile Pd-*NHC* complexes through PEPPSI (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) method with Pd(II) species bearing an *NHC* ligand, two halides and 3-chloro pyridyl group[20d].

[a.] *Department of Chemistry, SAS Division, VIT University, Chennai-600127, Tamilnadu, India. Tel.: +91 44 39931237; fax: +91 44 3993 2555; E-mail: gc_sekar78@yahoo.co.in, chandrasekar.g@vit.ac.in (G. Chandrasekar)*
[b.] *Department of Engineering Chemistry, Andhra University, Visakhapatnam, A.P., India-530003*
[c.] *Department of Medicinal Chemistry, GVK Biosciences Pvt. Ltd, IDA Nacharam, Hyderabad, Telangana, India-500076*
[#.] *Equal contribution*
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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 one pot synthesis of 2-substituted indoles via Sonogashira coupling (without copper catalyst) followed by cyclization under green approach. Sonogashira coupling under copper/amine free conditions were first reported by the Ghosh et.,[21] and 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 mixed-aqueous medium is reported.[14] Specifically, the PEPPSI themed (NHC)PdCl_2(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 mixed aqueous medium.

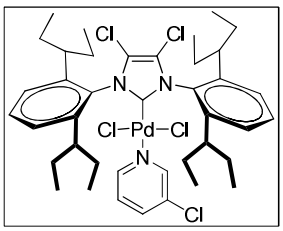

Fig. 1 Pd-PEPPSI-IPent^{Cl}

Hence a remarkable challenge is faced in Sonogashira coupling reaction was overcome and it has been carried out in copper-free, amine-free and air atmosphere conditions. 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 literature[24] with some modifications in order to improve the yields. So far solvents such as, acetone, toluene, tetrahydrofuran, acetonitrile, 1, 4-dioxane and dimethylformamide[25] are most frequently used for Sonogashira coupling reactions. But these are expensive, toxic, and difficult to recycle. Development of inexpensive and environmentally acceptable method for the synthesis of 2-substitued indoles is therefore highly desirable.

As part of our interest taking into consideration the immense biological importance, synthesis, separation and purification of compounds, expensiveness and recyclability of catalyst and also looking into environmentally friendly reaction conditions, we now report ligand-free one pot synthesis of 2-substituted indoles via Sonogashira coupling (copper/amine free) followed by cyclization using Pd-PEPPSI-IPent^{Cl} catalyst in ethanol : water as the 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-bromo anilines (**1a-1h**) and terminal acetylenes (**2a-2m**) are shown in Table 3 as outlined in **scheme 1**. There are 20 compounds (**3a-3t)** were prepared by 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.

Table 1. Screening on the effect of various palladium catalysts for the synthesis of 2-phenyl indole

1j 2j 3j

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	$Pd(Ph_3P)_4$	None	12 h	<5
8	$PdCl_2(dppf)_2$	None	12 h	5
9	$PdCl_2(TPP)_2$	None	12 h	11
10	$PdCl_2(CH_3CN)_2$	None	12 h	14
11	$Pd_2(dba)_3$	Binap	12 h	18
12	$Pd(H_2NCH_2CH_2NH_2)Cl_2$	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]

Reaction conditions : 2-bromo aniline (3 mmol), Phenyl acetylene (3 mmol), Cs_2CO_3 (6 mmol), PEPPSI-IPent^{Cl} (0.5 mol%) in EtOH : H_2O (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.

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In order to establish the optimal condition for Sonogashira coupling reaction, we have selected the model reaction between 2-bromoaniline and phenyl acetylene in the presence of various palladium based catalysts, ligand, Cs_2CO_3 in EtOH : H_2O (1 : 1) medium at 60 °C and the products yield are depicted in Table 1. It is very clear from the experimental results that the reaction did not proceed with $PdCl_2$ 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 $Pd(PPh_3)_4$ in the absence of ligand, the product obtained was less than 5% in yield (Table 1, entry 7). Very less amount of product yield was observed in the reactions catalyzed by various palladium catalysts (Table 1, entry 8-12). However, interestingly a competitive product yield of 62% was observed using Pd-PEPPSI-iPr (Table 1, entry 13) and this triggered us to screen various Pd-PEPPSI catalysts to enhance the product yield for the convenient catalytic use. Catalysts such as Pd-PEPPSI- iPent, SIPr, SONO-SP[2], IPent[Cl] are used for this reaction and observed increasing product yields accordingly (Table 1, entry 14-17). On the other hand increase in temperature from 60 to 100 ˚C did not contribute to any increase in yield (Table 1, entry 18). Therefore, 60 ˚C was opted as an optimal temperature for further experiments. Moderate yields were observed when reaction was carried out under Microwave and in sealed tube (Table 1, entry 19-20). Note worthily, Pd-PEPPSI-IPent[Cl] was found to give superior results among other catalysts studied at this temperature even in the absence of ligand and without copper catalyst (Table 1, entry 17).

Table 2. Screening on effect of various solvents

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

Reaction conditions: 2-bromo aniline (3 mmol), Phenyl acetylene (3 mmol), Cs_2CO_3 (6 mmol), PEPPSI-IPent[Cl] (0.5 mol%) in EtOH : H_2O (1:1, 10 mL) medium at 60 ˚C for 50 min. a = isolated yield after column purification.

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 percentage of Pd-PEPPSI-IPent[Cl] catalyst on the above model reaction. **Fig. 2** Represents the product yield of **3j** with different reaction time on different mole percentage of Pd-PEPPSI-IPent[Cl]. The increase in product yield with respect to the reaction time was observed in different mole percentage of Pd-PEPPSI-IPent[Cl] catalysts used from 0.05 and 0.5. The reaction completes after 70 min with the product yield of 65 % and 75 % using 0.05 mol% and 0.08 mol% of Pd-PEPPSI-IPent[Cl] catalyst, respectively. When the catalyst amount is increased to 0.1, 0.3 and 0.5 mol%, the reaction completes at 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 catalyst is adequate to complete the reaction within 50 min.

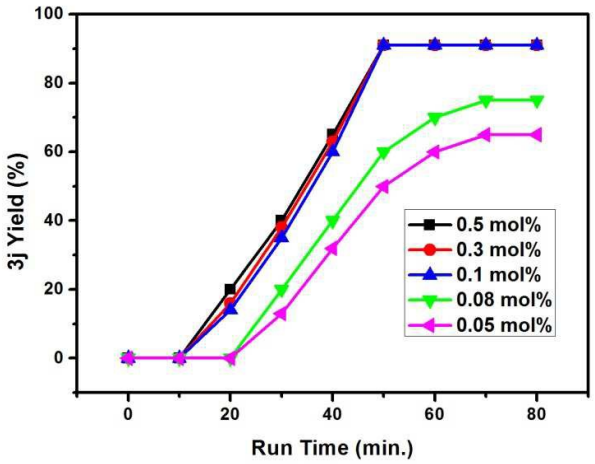

Fig. 2 Time course for the formation of compound **3j**[a] at variable concentrations of Pd-PEPPSI-IPent[Cl]
Reaction conditions: 2-bromo aniline (3 mmol), Phenyl acetylene (3 mmol), Cs_2CO_3 (6 mmol), Pd-PEPPSI-IPent[Cl] in EtOH : H_2O (1 : 1, 10 mL) medium at 60 ˚C for 50 min. a = isolated yield after column purification

The scope and the limitations of this reaction methodology were studied using various electron-donating and electron-withdrawing substituted 2-bromoaniline and aryl/heterocyclic acetylene and found that all compounds were successfully 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 on amine/acetylene facilitate the reaction to complete at a shorter reaction time compared to the electron-withdrawing groups present on amine/acetylene compounds. The rate determining step of cyclization (Fig. 5) is based on the nucleophilicity 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 the electron-withdrawing group is present on the amine, it decreases the nucleophilicity of the amine, thereby decreasing the rate of cyclization that 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 scale 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 R&D scale and scale up process.

Optimized conditions in hand, we endeavoured to catalyze the Sonogashira coupling reactions followed by cyclization for compounds (**1a-1h)** with terminal acetylenes (**2a-2m**). All the

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reactions were carried out under the non-inert atmosphere and without 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, (^{1}H, ^{1}H-D_2O Ex. & ^{13}C) NMR, LCMS, HRMS and IR spectra.

In the next study, we have examined the recovery of catalyst for the Sonogashira coupling reaction followed by cyclization of compound **3j** with phenyl acetylene over six consecutive reaction cycles. After completion of 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 by ^{1}H NMR spectroscopic method. The ^{1}H 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 fourth, fifth and sixth run cycle to the product yield of 84 %, 75 % and 65 %, respectively (Fig. 3).

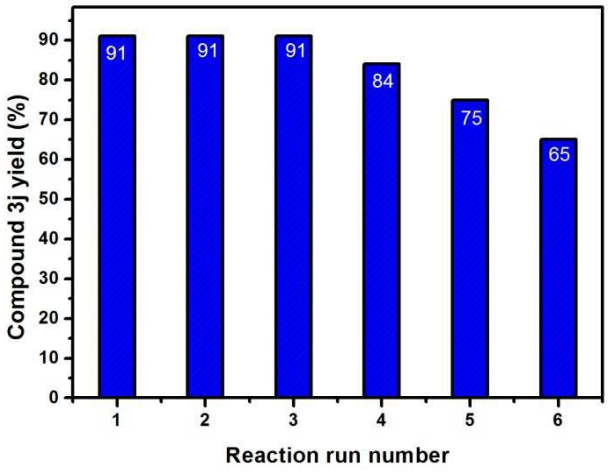

Fig. 3 Recyclability test of the catalyst Pd-PEPPSI-IPent^{C}
Reaction conditions: 2-bromo aniline (3 mmol), Phenyl acetylene (3 mmol), Cs_2CO_3 (6 mmol), Pd-PEPPSI-IPent^{Cl} (0.1 mol %) in EtOH : H_2O (1 : 1, 10 mL) medium at 60 ˚C for 50 min

To clarify the catalytic role, reaction pathway and rate of the reaction in one-pot synthesis, we analysed the crude samples obtained at various time intervals of 20, 30, 40 and 50 min using ^{1}H NMR (DMSO-d_6, 500 MHz) and the spectra are shown in Fig 4. The ^{1}H NMR spectrum (a) showed that our catalyst promoted the conversion of aryl bromide and acetylene to the Sonogashira coupled product within 20 min and corresponding peaks due to –NH_2 group and aryl group were observed peaks 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 indole –NH group. The ^{1}H NMR spectra of crude 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 that the conversion of Sonogashira product in to the desired product formation. The ^{1}H NMR spectrum is showing the complete conversion and formation of 2-phenyl indole after 50 min. This study also proves that the reaction path way going via Sonogashira coupled product followed by cyclization and also evidence with respect to the rate of the reaction, the Sonogashira coupled product formed within 20 min and cyclization taking little longer time ~30 min.

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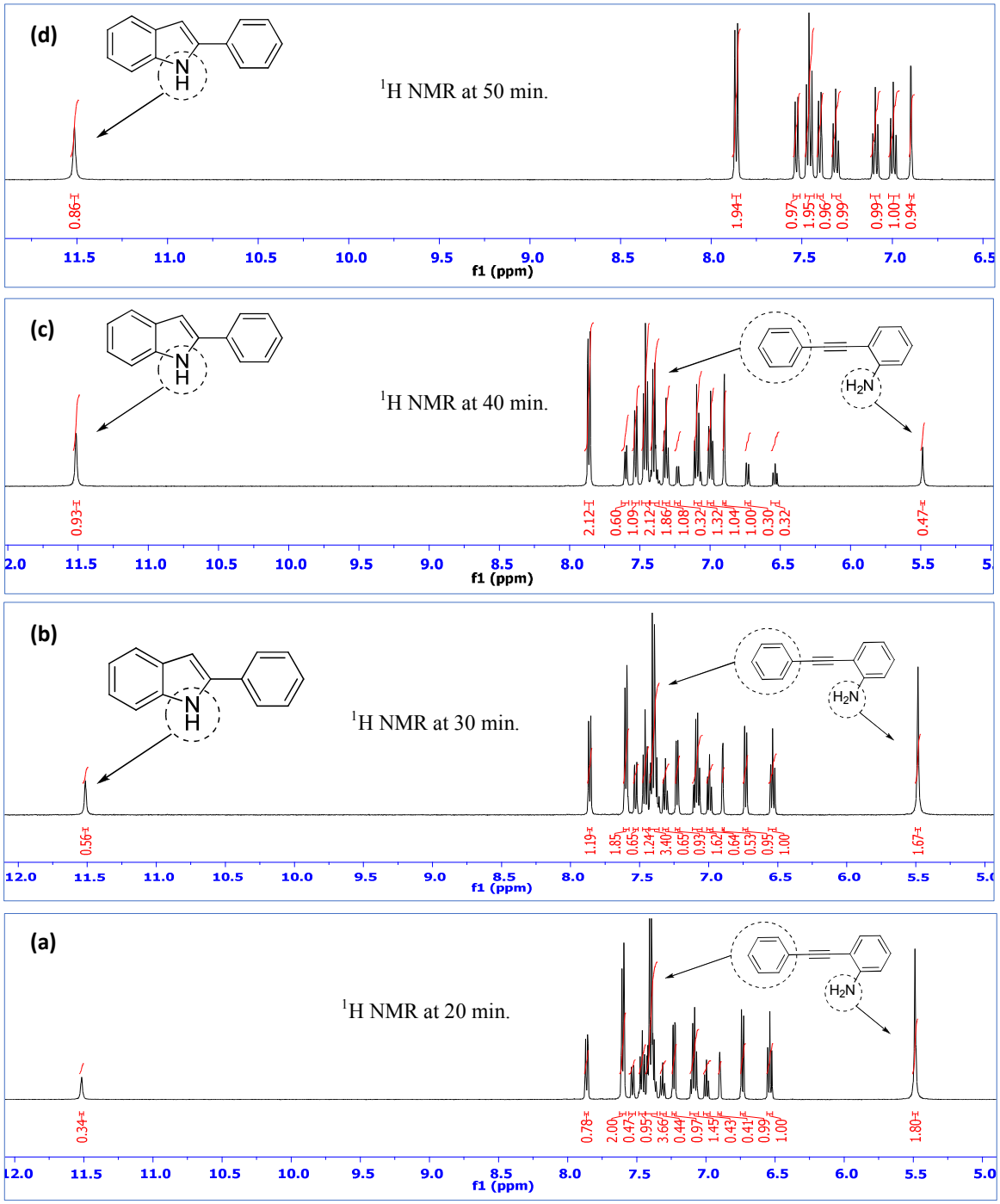

Fig. 4 ^{1}H NMR spectrums (crude) at various time intervals of (a) 20 min, (b) 30 min, (c) 40 min and (d) 50 min
Reaction condition: 2-Bromo aniline (10 mol), phenyl acetylene (10 mol), Cs_2CO_3 (20 mol), Pd-PEPPSI-IPent^{Cl} (0.1 %), EtOH : H_2O (2 mL, 1:1), 60 ˚C and 50 min

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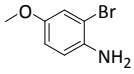
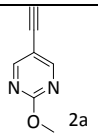
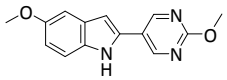
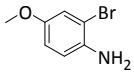
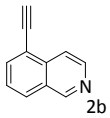
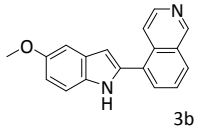
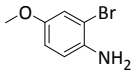
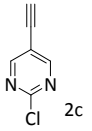
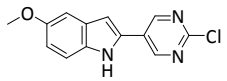
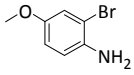
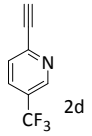
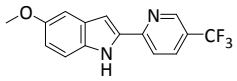
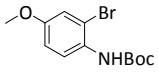
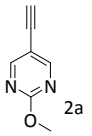
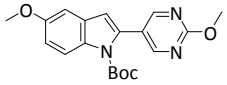
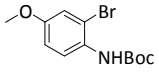
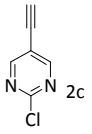
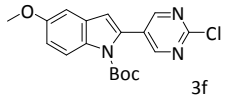
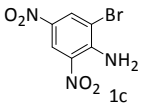
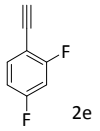
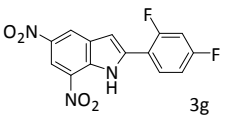
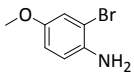
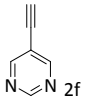
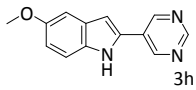
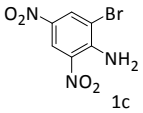
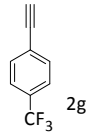
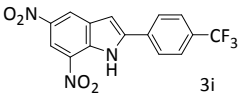
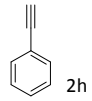
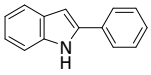
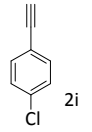
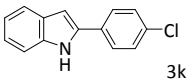
Table 3. Synthesis of various 2-substituted indoles using Pd-PEPPSI-IPent^{Cl} catalyst

Entry	Bromo aniline	acetylene	Product	Time (Min)	Yield[a] (%)	Mp (°C)
1.	 1a	 2a	 3a	45	90%	215-217
2.	 1a	 2b	 3b	45	85%	176-180
3.	 1a	 2c	 3c	50	86%	234-238
4.	 1a	 2d	 3d	50	90%	168-172
5.	 1b	 2a	 3e	45	85%	130-133
6.	 1b	 2c	 3f	70	80%	162-164
7.	 1c	 2e	 3g	70	90%	202-206
8.	 1a	 2f	 3h	50	88%	134-138
9.	 1c	 2g	 3i	70	86%	202-206
10.	 1d	 2h	 3j	50	91%	186-187[26,b]
11.	 1d	 2i	 3k	50	83%	195-196[27,b]

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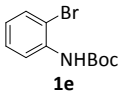
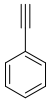
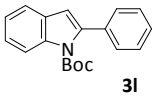
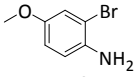
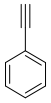
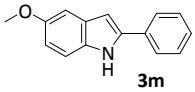
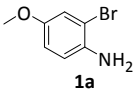
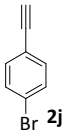
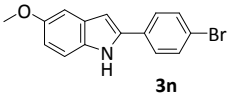
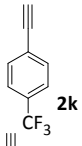
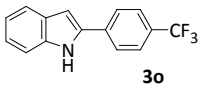
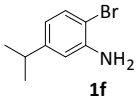
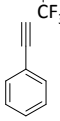
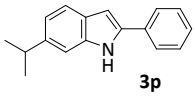
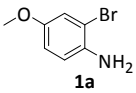
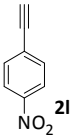
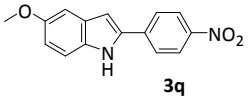
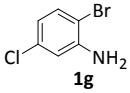
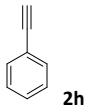
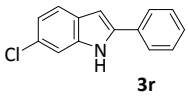
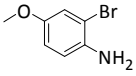
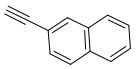
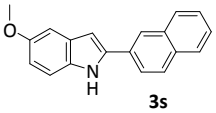
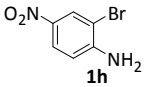
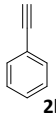
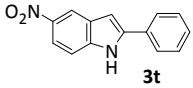
12.	 **1e**	 **2h**	 **3l**	70	80%	76-78[28,b]
13.	 **1a**	 **2h**	 **3m**	45	83%	160-162[29,b]
14.	 **1a**	 **2j**	 **3n**	45	84%	201-202[30,b]
15.	 **1d**	 **2k**	 **3o**	50	82%	240-241[31,b]
16.	 **1f**	 **2h**	 **3p**	50	82%	100-101[32,b]
17.	 **1a**	 **2l**	 **3q**	50	75%	200-201[33,b]
18.	 **1g**	 **2h**	 **3r**	50	83%	180-181[34,b]
19.	 **1a**	 **2m**	 **3s**	50	79%	213-214[35,b]
20.	 **1h**	 **2h**	 **3t**	70	86%	234-235[36,b]

a = Isolated yield.

b = Spectral data (^{1}H, ^{13}C NMR) of known compounds (3j-3t) were found to be identical with those reported in the literature.

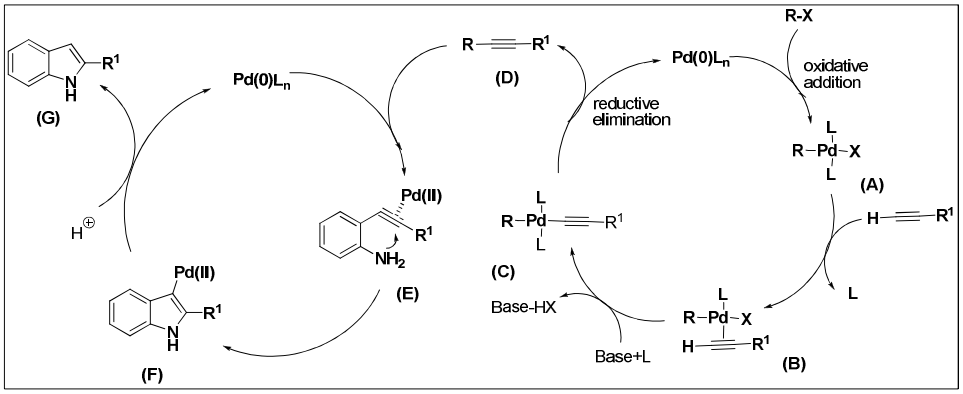


Fig. 5 Plausible mechanistic pathway for the one-pot synthesis

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In accordance with previous literature report,[37] a plausible reaction mechanism is proposed (Fig. 5). Initially the oxidative addition of aryl bromide to Pd(0) leads to formation of Pd-complex (A) followed by insertion of alkyne to form π-bond mediated new Pd-complex (B). Deprotonation of alkyne groups of Pd-complex B and bromine displacement leads to formation of complex (C) followed by reductive elimination to give the Sonogashira coupled product (D). Then formation of π-bond mediated new Pd(II)-complex (E), followed by deprotanation to give the cyclized Pd(II)-complex (F). Then protonation of 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 greener reaction medium ethanol : water (1 : 1) without ligand and 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 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

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 Cs_2CO_3 (6 mmol) in ethanol:water (1 : 1, 10 mL) and the reaction mixture was stirred for 5 minutes at 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 completions were monitored by TLC, reaction mixture was cooled to room temperature, filtered through 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 x 10 mL). The organic layers 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 afforded the title compounds **3a-3t** (yield: 75%-91%).

Acknowledgments

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References

1. a) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules* 2013, **18**, 6620–6662; b) T. C. Barden, Top. *Heterocycl. Chem.*, 2011, **26**, 31–46; c) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.,* 2013, **30**, 694–752; d) S. Hibino and T. Choshi, *Nat. Prod. Rep.,* 2002, **19**, 148–180; e) M. Lounasmaa, A. Tolvanen*.,* 2000, **17**, 175-191.
2. a) B. Robinson, **Chem. Rev.,** 1969, **69**, 227-250; b) W. E. Noland and F. J. Baude, *Org. Synth.,* 1973, **5**, 567-571; c) A. D. Batcho and W. Leimgruber, *Org. Synth.,* 1985, **63**, 214; d) G. Gassman and T. J. Van Bergen, *Org. Synth.*, 1988, **6**, 601-605; (e) F. Liu and D. Ma. *J. Org. Chem*., 2007, **72**, 4844-4850; (f) T. Guo, F. Huang, L. Yu, Z. Yu. *Tetrahedron Lett.,* 2015, **56**, 296-302; (g) A. Varela-Fernandez, J. A. Varela and C. Saa. *Synthesis,* 2012, **44**, 3285-3295; (h) T. Wang, S. Shi, D. Pflasterer, E. Rettenmeier, M. Rudolph, F. Rominger and A. S. K. Hashmi. *Eur. J. Org. Chem*., 2014, **20**, 292-296; (i) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger, and A. S. K. Hashmi*. Angew. Chem. Int. Ed.*, 2016, **55**, 794-797; (j) A. S. K. Hashmi, T. D. Ramamurthi and F. Rominger. *Adv. Synth. Catal.,* 2010, **352**, 971-975; (k) M. Michalska and K. Grela. *Synlett.,* 2016, **27**, 599-603; (l) A. Arcadi, G. Bianchi and F. Marinelli, *Synthesis,* 2004, **4**, 610-618; (m) B.Z. Lu, H. Wei, Y. Zhang, W. Zhao, M. Dufour, G. Li, V. Farina and C.H. Senanayake. *J. Org. Chem.,* 2013, **78**, 4558-4562.
3. Z. Y. Wang, G. Q. Chen and L. X. Shao, *J. Org. Chem*., 2012, **77**, 6608-6614.
4. T. Brenstrum, D. A. Gerritma, G. M. Adjabeng, C. S. Frampton, J. Britten, A. J. Robertson, J. Mc Nutty and A. Capretta, *J. Org. Chem.,* 2004, **69**, 7635-7639.
5. (a) K. Ofele, *J. Organomet. Chem*., 1968, **12**, 42-43; (b) H. W. Wanzlick and H. J. Schonherr, *Angew. Chem. Int. Ed*., 1968, **7**, 141-142; (c) J. H. kim, J. W. Kim, M. Shokouhimehr and Y. S. Lee, *J. Org. Chem.,* 2005, **70**, 6714-6720; (d) B. Karimi and P. F. Akhavan, *Chem. Commun.,* 2009, 25, 3750-3752; (e) H. V. Huynh, C. H. Yeo and Y. X. Chew, *Organometallics*, 2010, **29**, 1479-1486; (f) A. Kapdi, D. Prajapati, C. Schulzke and M. K. Kindermann, *RSC Adv*., 2015, **5**, 53073-53085.
6. (a) G. A. Grassa, M.S. Viciu, J. K. Huang, C. M. Zhang, M. L. Trundell and and S. P. Nolan, *Organometallics*, 2002, **21**, 2866-2873; (b) R. Singh, M. S. Viciu, N. Kramareva, O. Navarro and S. P. Nolan, *Org. Lett*., 2005, **7**, 1829-1832; (c) J. Nasielski, N. Hadei, G. Achonduh, E. A. B. Kantchev, C. J. O'Brien, A. Lough and M. G. Organ, *Chem. Eur. J*., 2010, **16**, 10844-10853; (d) S. Dastagir, K. S. J. Coleman, A. R. Cowley and M. L. H. Green, *Organometallics*, 2010, **29**, 4858-4870; (e) Y. Q. Tang, M. Lu and L. X. Shao, *J. Organomet. Chem*., 2011, **696**, 3741-3744.
7. (a) W. A. Hermann, V. P. W. Bohm, C. W. K. Gstottmayr, M. Grosche, C. P. Reisinger and T. Weskamp, *J. Organomet. Chem*., 2001, **617**, 616-628; (b) O. Navarro, H. Kaur, P. Mahjoor

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DOI: 10.1039/C7NJ01544E

and S. P. Nolan, *J. Org. Chem*., 2004, **69**, 3173-3180; (c) C. Burstein, C. W. Lehmann and F. Glorius, *Tetrahedron,* 2005, **61**, 6207-6217; (d) N. Hadei, E. A. B. Kantchev, and M. G. Organ, *Org. Lett*., 2005, **7**, 1991-1994; (e) N. Marion, O. Navarro, J. G. Mei, E. D. Stevens, N. M. Scott and S. P. Nolan, *J. Am. Chem. Soc*., 2006, **128**, 4101-4111; (f) C. Fleckenstein, S. Roy, S. Costa, P. Leuthausser and H. Plenio, *Chem. Commun*., 2007, 2870-2872; (g) O. Diebolt, V. Jurik, R. C. da Braunstein, L. Cavallo, S. P. Nolan, A. M. Z. Slawin and C. S. J. Cazin, *Organometallics*, 2010, **29**, 1443-1450; (h) M. T. Chen, D. A. Vicic, M. L. Turner and O. Navarro, *Organometallics*, 2011, **30**, 5052-5056; (i) T. Tu, Z. M. Sun, W. W. Fang, M. Z. Xu and Y. F. Zhou, *Org. Lett*., 2012, **14**, 4250-4253; (j) Z. Y. Wang, Q. N. Ma, R. H. Li and L. X. Shao, *Org. Biol. Chem*., 2013, **11,** 7899-7906.

8. M. G. Organ, S. Calimsiz, M. Sayah, K. H. Hoi and A. J. Lough, *Angew. Chem. Int. Ed.*, 2009, **48**, 2383-2387.
9. M. Kuriyama, S. Mastuo, M. Shinozawa and O. Onomura, *Org. Lett*., 2013, **15**, 2716-2719.
10. E. Brenner, D. Matt, M. Henrion, M. Teci and L. Toupet, *Dalton Trans*., 2011, **40**, 9889-9898.
11. (a) H. E. Moll, D. Semeril, D. Matt, L. Toupet and J. Harrowfield, *Org. Biomol. Chem*., 2012, **10**, 372-382; (b) N. Sahin, D. Semeril, E. Brenner, D. Matt, I. Ozdemir, C. Kaya and L. Toupet, *Chem. Cat. Chem.*, 2013, **5**, 1116-1125.
12. (a) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C.S. J. Cazin and S. P. Nolan, *Chem. Eur. J*., 2012, **18**, 4517-4521; (b) G. Bastug and S. P. Nolan, *Organometallics*, 2014, **33**, 1253-1258; (c) A. S. K. Hashmi, C. Lothschutz, C. Bçhling, T. Hengst, C. Hubbert and F. Rominger. *Adv. Synth. Catal.,* 2010, **352**, 3001 – 3012; (d) A. S. K. Hashmi, C. Lothschutz, K. Graf, T. Haffner, A. Schuster and F. Rominger, *Adv. Synth. Catal.,* 2011, **353**, 1407 – 1412; (e) D. Riedel, T. Wurm, K. Graf, M. Rudolph, F. Rominger, and A. S. K. Hashmi, *Adv. Synth. Catal.,* 2015, **357**, 1515 – 1523; (f) A. S. K. Hashmi, C. Lothschutz, C. Bohling and F. Rominger, *Organometallics,* 2011, **30**, 2411–2417.
13. (a) G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *Angew. Chem. Int. Ed*., 2003, **42**, 3690-3693; (b) G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *J. Am. Chem. Soc.*, 2004, **126**, 15195-15201.
14. M. V. Krishna Reddy, P. V. G. Reddy and C. Suresh Reddy, *New J. Chem*., 2016, **01**, 1-8.
15. P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem. Int. Ed.*, 2000, **39**, 2632–2657.
16. (*a*) M. Bakherad, A. Keivanloo, B. Bahramian and M. Hashemi, *Tetrahedron Lett.*, 2009, **50**, 1557–1559; (*b*) S. Mori, T. Yanase, S. Aoyagi, Y. Monguchi, T. Maegawa and H. Sajiki, *Chem. Eur. J.*, 2008, **14**, 6994–6999; (*c*) F. Cataldo and C. S. Casari, *J. Inorg. Organomet. Polym.*, 2007, **17**, 641–651; (*d*) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874–922; (*e*) B. Liang, M. Dai, J. Chen and Z. Yang, *J. Org. Chem.*, 2005, **70**, 391–393; (*f*) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46–49; (*g*) S. Thorand and N. Krause, *J. Org. Chem.*, 1998, **63**, 8551–8553.
17. H. Greim, D. Bury, H.-J. Klimisch, M. Oeben-Negele and K. Ziegler-Skylakakis, *Chemosphere*, 1998, **36**, 271–295.
18. L. H. Zou, A. J. Johansson, E. Zuidema and C. Bolm, *Chem. Eur. J.,* 2013, **19**, 8144-8152.
19. C. H. Lu, L. Wang, F. Yang, R. Wu and W. Shen, *RSC Adv*., 2014, **4**, 30447-30452.
20. (a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson and M. G. Organ, *Chem. Eur. J.*, 2006, **12**, 4743-4748; (b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J .O'Brien and C. Valente, *Chem. Eur. J.*, 2006, **12**, 4749 – 4755; (c) A. Zeiler, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Chem. Eur. J.,* 2015, **21**, 11065 – 11071; (d) C. Valente, M. E. Belowich, N. Hadei and M. G. Organ, *Eur. J. Org. Chem.,* 2010, **23**, 4343–4354.
21. A. John, M. M. Shaikh and P. Ghosh; *Dalton Trans.*, 2009, 47, 10581–10591.
22. L. Ray, S. Barman, M. M. Shaikh and P. Ghosh, *Chem. Eur. J.*, 2008, **14**, 6646–6655.
23. C. M. Le, T. Sperger, R. Fu, X. Hou, Y. H. Lim, F. Schoenebeck, and M. Lautens, J. *A. Chem. Soc.,* 2016, **138**, 14441-14448; b) L. Kong, R. Ganguly, Y. Li and R. Kinjo, *Chem. Sci.,* 2015, **6**, 2893-2902.
24. S. Sharif, R. P. Rucker, N. Chandrasoma, D. Mitchell, M. J. Rodriguez., R. D. J. Froese, and M. G. Organ, *Angew. Chem. Int. Ed.*, 2015, **54**, 9507 –9511.
25. L. F. Liu, W. D. Wang and C. Y. Xiao, *J. Organomet. Chem.*, 2014, **749**, 83-87.
26. J. Kwon, J. Chung, S. Byun and B. M. A. Kim, *J. Org. Chem.,* 2016, **5**, 470-476.
27. P. Li, L. Wang, M. Wang and F. You, *Eur. J. Org. Chem.,* 2008, 5946–5951.
28. C. Rossy, E. Fouquet and X-F. Felpin, *Beilstein J. Org. Chem.* 2013**, *9,*** 1426–1431.
29. M. -Z. Lu, P. Lu, Y-H. Xu and T. -P. Loh, *Org. Lett.* 2014, **16**, 2614–2617.
30. W. W. Tan, X. Hou and N. Yoshikai, *Synthesis,* 2014, **46**, 2727-2733.
31. M. Shen, E. B. Leslie and G. T. Driver, *Angew. Chem. Int. Ed.* 2008, **47**, 5056 –5059.
32. H. Lee and S. C. Yi, *Organometallics,* 2016, **35**, 1973-1977.
33. Y. Wei, I. Deb and N. Yoshikai, *J. Am. Chem. Soc.,* 2012, **134**, 9098-9101.
34. K. Okuma, I. -J. Seto, I.-K. Sakaguchi, S. Ozaki, N. Nagahora and K. Shioji, *Tetrahedron Lett.,* 2009, **50**, 2943-2945.
35. Y. Wei, I. Deb and N. Yoshikai, *J. Am. Chem. Soc.,* 2012, **134** (22), 9098-9101.
36. N. Sakai, K. Annaka, A. Fujita, A. Sato and T. J. Konakahara, *Org. Chem.,* 2008, **73**, 11-15.
37. S. Elavarasan, B. Baskar, C. Senthil., P. Bhanja, A. Bhaumik, P. Selvam and M. Sasidharan, *RSC Adv.,* 2016, **6**, 49376–49386.

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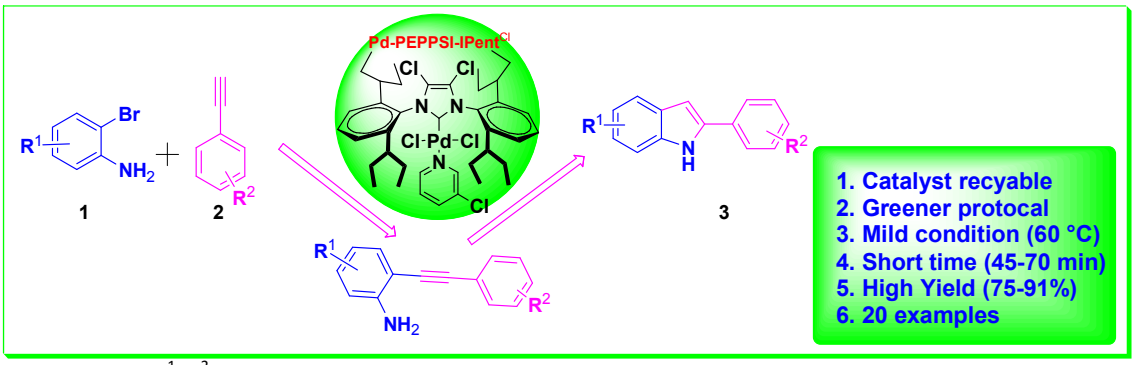
Graphical Abstract

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[a,c,#], Nagul Meera Shaik[b,c,#], Govindasamy Chandrasekar[a,*], Sridhar Chidara[b,c] and Ragu Babu Korupolu[b]

One pot synthesis of 2-substituted indoles via sonogashira coupling (without copper catalyst) followed by intermolecular cyclization using new competent palladium catalyst Pd-PEPPSI-IPent^{Cl} under mild and greener approach



R^1, R^2 = Varies aryl/hetero aryl groups and electron donating/withdrawing groups