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Hydrophilic Pd-phosphines catalyzed one-pot synthesis of substituted isoquinolines, furopyridines and thienopyridines in aqueous medium

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ABSTRACT

A first example of simple and efficient hydrophilic Pd-phosphine complexes catalyzed one-pot three-component reaction of *ortho*-bromo aldehydes, terminal alkynes and ammonium acetate proceeds through the tandem coupling-imination-annulation path for the synthesis of substituted isoquinolines, furopyridines and thienopyridines in good to excellent yields in green aqueous medium at mild temperature was described.

Isoquinolines and their derivatives are one of the most significant class of fused-heterocyclic compounds and play a substantial responsibility in huge number of pharmacological activities.[1-2] Therefore, the great efforts have been devoted, to develop effective methodologies for their synthesis. The classical synthesis of isoquinoline derivatives viz., Pictet-Spengler[3] Pomeranz-Fritsch[4] and Bischler-Napieralski [5] reactions usually proceed through some typical conditions. To overcome the demerits of traditional methods, few Pd-Cu[6] and Cu[7-9] catalysed one-pot protocols involving tandem conversions to achieve isoquinoline derivatives were well described. However, all the above catalytic systems require toxic organic solvents and high reaction temperatures[6-9] for their greater proficiency. Hence, the development of suitable metal catalysts for the one-pot synthesis of substituted isoquinolines in environmentally benign solvents under mild temperature is still remains a motivating and highly necessary goal.

The implementation of sustainable chemical synthesis, as per green chemistry protocols, reactions conducting in aqueous solvent system have become special interest to scientific commune as well as industry[10]. As well, water could influence on the reaction rates and selectivities, because of hydrophobic interactions. In response to the above stated features, our group have long been working on the development of some new water soluble polar phosphine ligands[11] and their corresponding Rh and Ru-catalysts were successively utilized for hydroformylation[12] and hydrothialation[13] reactions in eco-friendly aqueous media. In continuation of our group work, we herein, first time report the catalytic efficacy of some new Pd-complexes composed with polar phosphine ligands for the one-pot three-component reaction of *ortho*-bromo aldehdyes, terminal alkynes and ammonium acetate to afford substituted isoquinolines, furopyridines and thienopyridines in green aqueous medium under mild temperature.

To choose the suitable catalytic conditions, at first, we have studied the one-pot reaction of 2-bromobenzaldehyde (**1a**), phenyl acetylene (**2a**) and ammonium acetate **(3a)** in the presence of K_2CO_3 and using different types of catalysts including (Cu, Pd and Pd/Cu) in (1: 4) in THF-water media. The particulars of reaction conditions and results were shown in table 1. From the table 1, no desired product **4a** was observed, when we used both Cu(I) alone and Pd(II) alone as catalysts at 65 °C even after 12 hours (Table 1, entries 1-3). The same reaction was also sluggish in the case of $Pd(OAc)_2$/CuI combination (Table 1, entry 4). On the other hand, the moderate yield of **4a** was obtained using $PdCl_2(PPh_3)_2$/CuI as catalyst at 50 °C after 6 hours (Table 1, entry 5). Encouraged by this result, we further intended to examine the efficacy of our aqueous stable 3 mol% of Pd-polar phosphines (Pd-(L_1-L_7) [*generated in-situ from the reaction of 1 : 2 ratio of* $Pd(OAc)_2$ *& polar phosphine ligands* (L_1-L_7) *as shown in figure 1*] + 5 mol% of CuI catalytic systems.

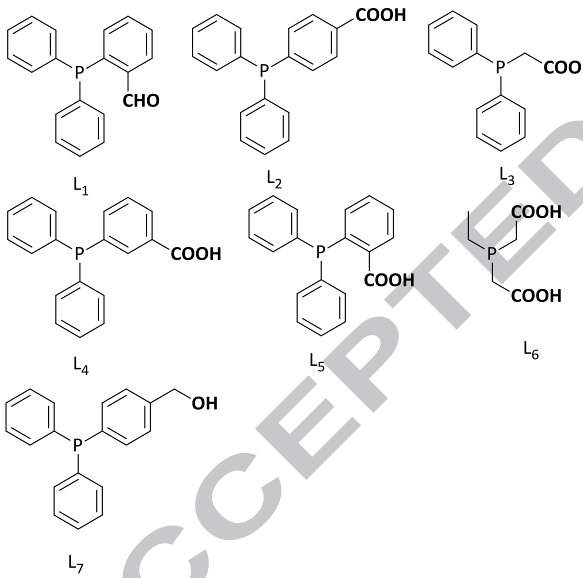
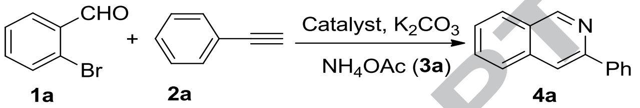


Figure 1. Hydrophilic phosphine ligands used in the present study.

Remarkably, all the Pd-(L_1-L_7) complexes have allowed the fast accomplishment of the one-pot reaction and provided the product **4a** with good to excellent yields in the range of 74-87% at 50 °C (Table 1, entries 6-12). Among them, the best result was observed in the case of Pd-L_4 complex (Table 1, entry 9). The different catalyst concentration and temperature studies revealed that the 2 mol % of Pd-L_4 at 50 °C was the suitable choice for the present approach (Table 1, entry 13). The reaction of **1a**, **2a** and **3a** using 2mol % of Pd-L_4 in the absence of CuI was also none, which indicated that the use of Cu as a co-catalyst is necessary for the synthesis of **4a** (Table 1, entry 16). The effects of various bases were also investigated (Table S1, ESI).

Table 1. Optimization of the reaction conditions.

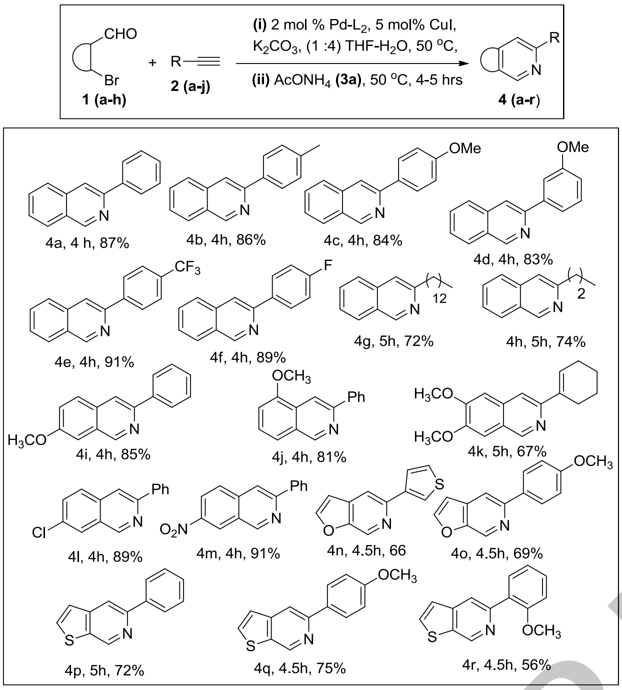


Entry	Catalyst (mol %)	Temp (°C)	Time(h)	Yield (%)^b
1	CuI (6)	65	12	NR
2	$Pd(OAc)_2$ (4)	65	12	NR
3	$PdCl_2(PPh_3)_2$ (4)	65	12	NR
4	$Pd(OAc)_2$(4)/CuI(5)	65	12	trace
5	$PdCl_2(PPh_3)_2$(4)/CuI(5)	50	6	54
6	Pd-L_1(3)/CuI (5)	50	4	74
7	Pd-L_2(3)/CuI (5)	50	4	83
8	Pd-L_3(3)/CuI (5)	50	4	82
9	Pd-L_4(3)/CuI (5)	50	4	87
10	Pd-L_5(3)/CuI (5)	50	4	84
11	Pd-L_6(3)/CuI (5)	50	4	76
12	Pd-L_7(3)/CuI (5)	50	4	84
13	Pd-L_4(2)/CuI (5)	50	4	87
14	Pd-L_4(1)/CuI (5)	50	5	59
15	Pd-L_4(2)/CuI (5)	RT	8	51
16	Pd-L_4 (3)	50	10	NR

Reaction conditions: ^{a}Reaction was carried out with 1mmol of **1a**, 1.2mmol of **2a**, 1.5mmol of **3a** using 2mmol of K_2CO_3 in 2 mL of (1:4) THF-H_2O.^{b} Isolated yields after coloumn chromatography. NR = no reaction.

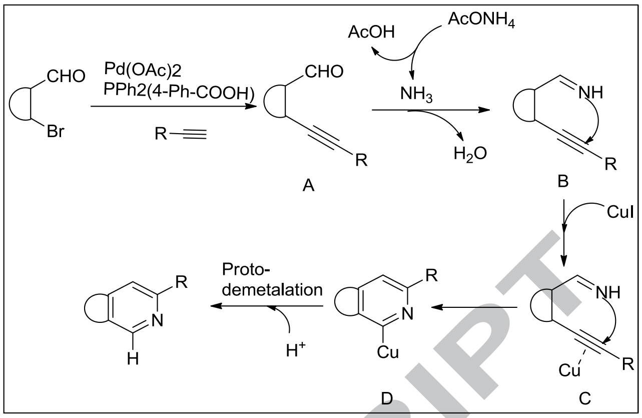
The above optimized conditions in our hand, we further explored our one-pot three component methodology to synthesize various substituted isoquinolines, furopyridines & thienopyridines and their results were depicted in table 2. From the table 2, it is found that all the used 2-bromobenzaldehyde and phenylacetylene derivatives were compatible to furnish substituted isoquinolines in good to excellent yields (Table 2, entries **4a-4m**). However, the yields of corresponding isoquinolines were high in the case of 2-bromobenzaldehydes and phenylacetylenes bearing electron-withdrawing groups (Table 2, entries **4e-4f**) and **4l-4m**). On the other hand, the aliphatic alkynes were less reactive and decrease in the yields of desired product was observed as compared to aromatic alkynes (Table 2, entries **4g-4h and 4k**). In addition, the present one-pot approach was also well-suited to synthesize furopyridines and thienopyridines derivatives in moderate to good yields (Table 1, entries **4n-4r**). The formation of all the compounds was confirmed by ^{1}H-NMR, ^{13}C-NMR and mass spectral data, which are reliable with the reported data previously.[6-9]

Table 2. Substrate scope



[a] All products were characterized by ^{1}H and ^{13}C NMR spectroscopy.
[b] Isolated yields after column chromatography.

Based on our present results (**Table 1**) and from the literature support[6,9], a plausible catalytic cycle for the above one pot three-component reaction was proposed. As shown in **scheme 1**, initially, the Pd-catalyzed coupling of o-bromo aldehydes with terminal alkynes occur to form o-alkynyl aldehyde intermediate A, which on further condensation reaction with reaction with ammonia to give imine intermediate B. Later, the π-coordination between CuI and alkyne of intermediate B generate active intermediate C in which intramolecular nucleophilic attack of imine nitrogen species towards alknye functionality was enhanced. Accordingly, the formed copper intermediate D further undergo protodemetalation process to achieve the desired cyclized products.



Scheme 1. A plausible reaction mechanism

In conclusion, we have first time established the simple and efficient hydrophilic Pd-phosphine catalytic system for the one-pot three-component synthesis of isoquinoline, furopyridine and thienopyridine derivatives in good to excellent yields in environmentally benign aqueous medium under mild temperature.

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A Supplementary data

Experimental details, characterization data of **4a-4r** products can be found, in the online version, at http://dx.doi.org/

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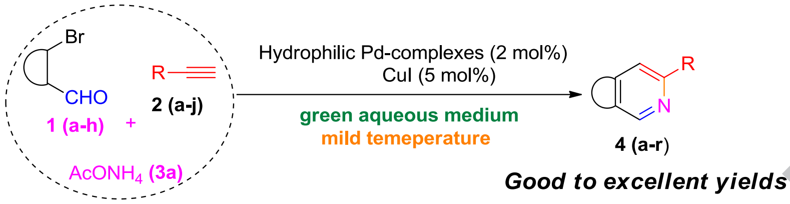
Graphical abstract



Good to excellent yields

Highlights

- Hydrophilic Pd-phosphine/CuI catalysed one-pot three component approach
- Synthesis of isoquinolines, furopyridines and thienopyridines in aqueous medium
- Relatively better results compared to previous reports