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Exploration of copper and amine-free Sonogashira cross coupling reactions of 2-halo-3-alkyl imidazo[4,5-*b*]pyridines using tetrabutyl ammonium acetate as an activator under microwave enhanced conditions

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ABSTRACT

Enhancing the reactivity of the catalytic system by using palladium catalyst with sterically demanding and electron rich ligands attached to it has often been shown as an appropriate way of performing the copper-free Sonogashira reaction. In this paper, we report $PdCl_2(PCy_3)_2$ as an efficient catalyst for the copper and amine-free Sonogashira cross coupling reactions of 2-halo-3-alkyl imidazo[4,5-*b*]pyridines (I, Br, Cl) using tetrabutyl ammonium acetate as an activator under microwave enhanced conditions.

Purine derived structures, such as derivatives of imidazo[4,5-*b*]pyridine (Scheme 2) have caused considerable attention because of their significant bioactivities.[1] Their activity includes antibacterial,[2] antimicrobial,[3] mutagenic,[4] antipholigistic,[5] fungicidal,[6] antiviral,[7] anticancer,[8] antimitotic,[9] antituberculostatic,[10] antiallergic[11] and antihypertensive[12] actions. The alkynylation reaction of heterocyclic based halides using Sonogashira reaction conditions has been widely used for the preparations of many novel systems of potential interest. Examples are the alkynylation of halogenated pyrroles,[13] phthalimides,[14] benzofurans,[15] pyridines,[16] pyrimidines[17] etc. These wide range properties of imidazo[4,5-*b*]pyridine based structures prompted us to synthesise more diverse analogues which are potential to have medicinal relevance.

Nowadays, microwave assisted organic synthesis (MAOS)[18] plays a vital role in drug discovery laboratories. One of the most extensively studied reaction types in microwave mediated reactions is transition- metal catalysed reactions which usually takes hours and days for completion. Rapid lead generation and optimisation have recently been facilitated by the emergence of MAOS[18] and the technique is today one of the major tool for the medicinal chemist. MAOS can facilitate the discovery of new reactions and reduce the cycle time in optimisation of reactions. In addition, it serves to expand the chemical space in compound library synthesis.

Palladium chemistry involving nitrogen containing heteroaromatics has been a recent challenge in drug discovery due to the difference in the structural and electronic properties in comparison to the corresponding carbocyclic aryl compounds. 'The inability of these substrates to couple efficiently in metal catalysed cross coupling reactions has been attributed to the potential binding nature of these heteroaryl substrates to the metal centre resulting in the formation of inactive $(substrate)_n$—metal complexes'.[19] As a part of our research work aimed at microwave assisted palladium catalysed cross coupling reactions,[20] we were interested in the Sonogashira cross coupling reactions of 2-halo imidazo[4,5-*b*] pyridines. Despite the recent advancements, there still remains a need for an efficient protocol employing low catalyst loadings for the coupling of nitrogen containing heteroaromatics with terminal alkynes. The Sonogashira cross coupling reaction[21–23] of terminal acetylenes with aryl or vinyl halides has been proved as a versatile method for the creation of carbon-carbon bonds. To the best of our

Table 1
Effect of catalyst on the copper-free Sonogashira coupling[a] of **3a** and **4a**

Entry	Catalyst	Yield (%)
1	$Pd(PPh_3)_4$	Traces
2	$PdCl_2(PPh_3)_2$	40
3	$PdCl_2(CH_3CN)_2$	35
4	$Pd_2(dba)_3$	45
5	$PdCl_2(PCy_3)_2$	58

[a] Reagents and conditions: **3a** (0.5 mmol), **4a** (0.6 mmol), Cs_2CO_3 (3 mmol), Pd catalyst (5 mol %), NMP (0.5 mL), 120° microwave.

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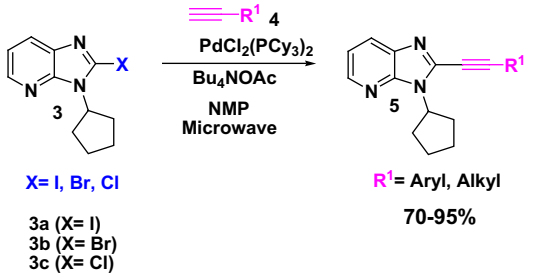
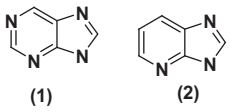
Table 2
Effect of base on the Sonogashira coupling[a] of **3a** and **4a**

Entry	Base	Base equivalents	Yield (%)
1	Na_2CO_3	2.0	30
2	K_2CO_3	1.5	40
3	KOAc	2.0	NR
4	Cs_2CO_3	2.5	60
5	Bu_4NOAc	2.5	93

[a] Reagents and conditions: **3a** (0.5 mmol), **4a** (0.6 mmol), base (1.5 mmol), $PdCl_2(PCy_3)_2$ (10 mol %), NMP (0.5 ml), microwave, 110°.



Scheme 1. Synthesis of 3-cyclopentyl-2-alkynyl-3*H*-imidazo[4,5-*b*]pyridine.



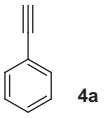
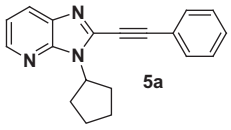
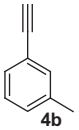
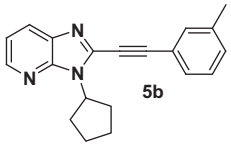
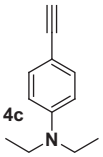
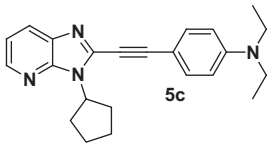
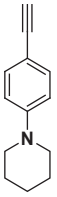
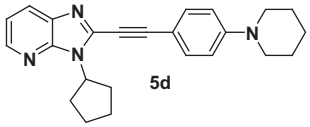
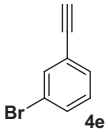
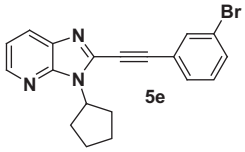
Scheme 2.

knowledge, this is the first report on Sonogashira cross-coupling reactions using 3-alkyl2-haloimidazo[4,5-*b*]pyridine as heteroaromatic substrate. The Sonogashira reaction process usually runs smoothly when the more expensive unstable aryl or vinyl iodides are used. The conditions are more favourable if the electron-poor organic halide system is 'activated'. Thus, strongly activated systems represent a real challenge for any cross coupling methodology.

The most commonly used catalytic systems for Sonogashira transformation include $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$ and $Pd(Ph_3)_4$ together with CuI as cocatalyst and large amounts of amines as the solvents or cosolvents. The use of copper in these reactions is believed to assist the reaction through the formation of an acetylide and then this group is transferred to Pd by a transmetalation step. However, the formation of copper acetylides[24] can also lead to homocoupling products, so modifications of these conditions, and in particular copper-free conditions,[25] have been continued to be investigated.

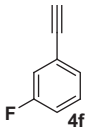
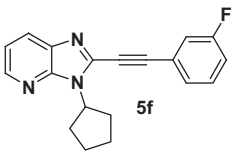
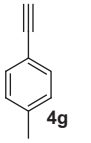
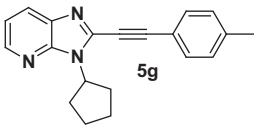
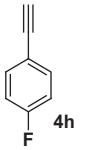
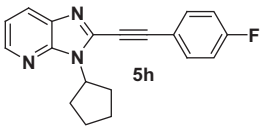
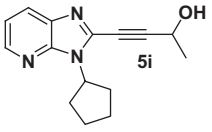
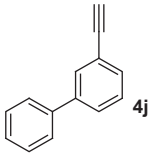
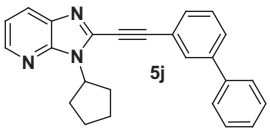
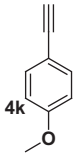
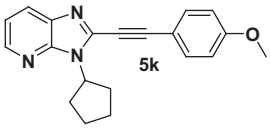
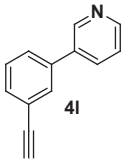
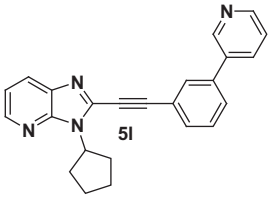
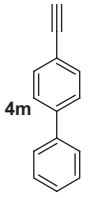
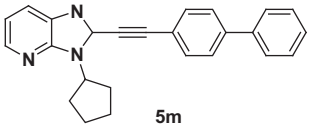
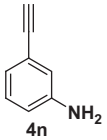
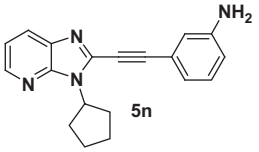
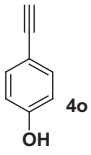
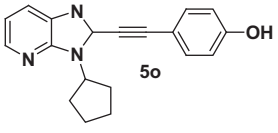
We chose the cross coupling of iodo intermediate, **3a** with phenyl acetylene as the model reaction to screen the catalyst and optimise the reaction conditions. First, the catalytic activities of some catalysts were tested in the presence of caesium carbonate at 110 °C in a microwave using NMP (*N*-methyl pyrolidinone) as a solvent under copper-free conditions. Fortunately, we were able to see 40% product formation as indicated by LCMS after 15 min using $PdCl_2(PCy_3)_2$, Table 1. $PdCl_2(PCy_3)_2$, which has more basic and bulky groups showing highest catalytic activity. These results encouraged us to further optimise the reaction conditions in the presence of $PdCl_2(PCy_3)_2$ using different bases and solvents, as well as changing the reaction temperatures. Different inorganic bases like Na_2CO_3, Cs_2CO_3, KOAc, Bu_4–NOAc were tried to find a suitable

Table 3
Sonogashira coupling[a] of **3a**, **3b**, **3c** with various terminal alkynes[b]

Entry	Halo intermediate, **3**	Alkynes, **4**	Product, **5**	Yield (%)
1	**3a** (**3b**) (**3c**)	 **4a**	 **5a**	93 (86) (79)
2	**3a** (**3b**)	 **4b**	 **5b**	89 (88)
3	**3a**	 **4c**	 **5c**	90
4	**3a** (**3b**)	 **4d**	 **5d**	85 (70)
5	**3a** (**3c**)	 Br **4e**	 Br **5e**	94 (82)

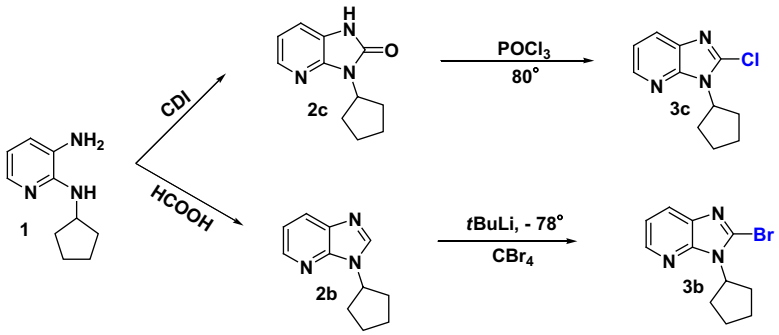
(*continued on next page*)

Table 3 (*continued*)

Entry	Halo intermediate, **3**	Alkynes, **4**	Product, **5**	Yield (%)
6	**3a** (**3c**)	 **4f**	 **5f**	92 (86)
7	**3a**	 **4g**	 **5g**	95
8	**3a** (**3c**)	 **4h**	 **5h**	88 (75)
9	**3a** (**3b**)	 **4i**	 **5i**	78 (35)
10	**3a** (**3b**)	 **4j**	 **5j**	92 (84)
11	**3a**	 **4k**	 **5k**	87
12	**3a**	 **4l**	 **5l**	91
13	**3a** (**3c**)	 **4m**	 **5m**	94 (88)
14	**3c**	 **4n**	 **5n**	72
15	**3b**	 **4o**	 **5o**	70

[a] Reagents and conditions: Catalyst $PdCl_2(PCy_3)_2$ (10 mol %), intermediate **3a**, (0.1 mmol), alkyne **4**, (0.13 mmol), Bu_4NOAc (0.3 mmol), NMP (0.5 mL) at 110° in microwave, 15 mts.

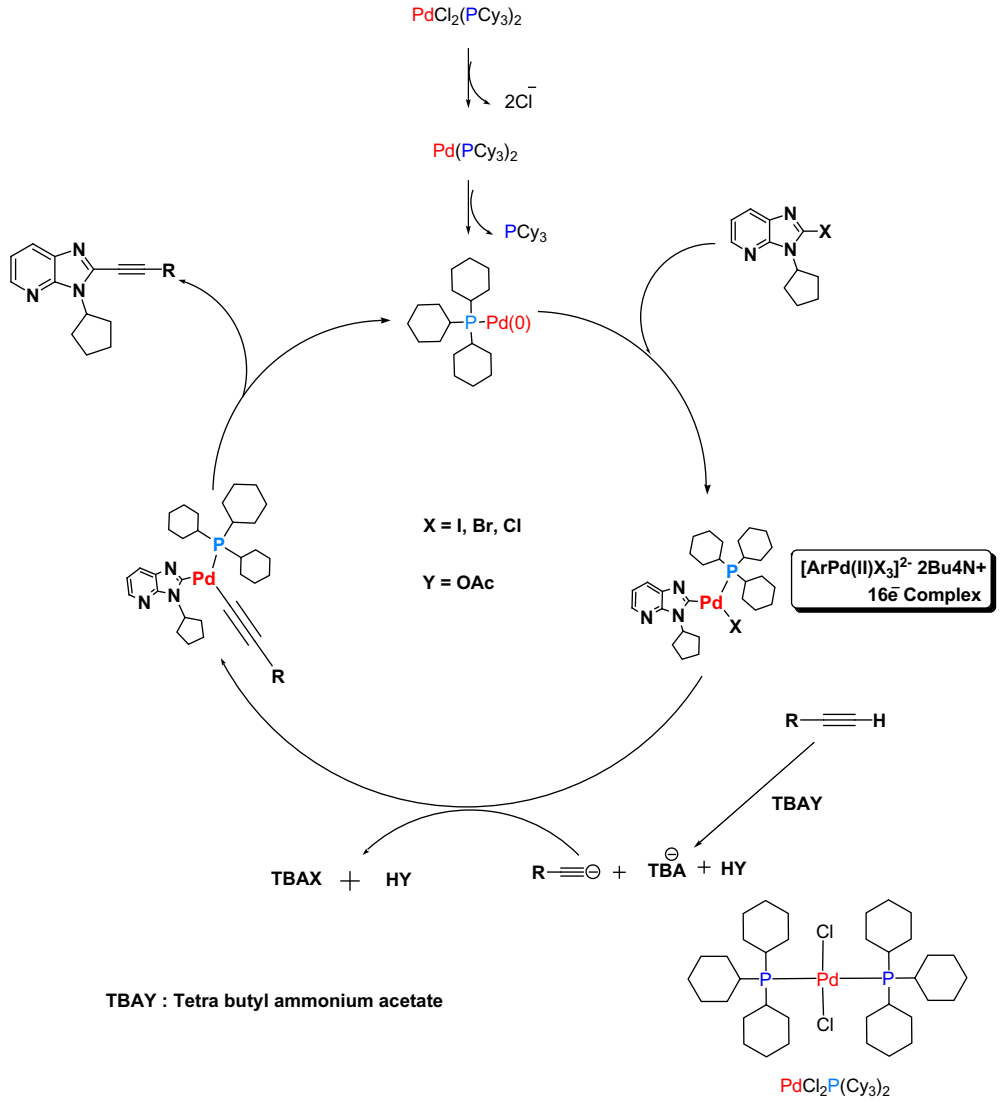
[b] When **3c** was used, catalytic loading of 20 mol % was used to push the reactions to completion and reaction was conducted at 150° in microwave for 45 mts. Yields mentioned correspond to isolated yields.



Scheme 3. Synthesis of 2-halo-3-cyclopentyl-3*H*-imidazo[4,5-*b*]pyridine.

base that would affect the desired reaction, Table 2. Both Cs_2CO_3 and Bu_4–NOAc were effective as bases, with Bu_4–NOAc being the more reactive, allowing the reaction to be completed in 30 min. Among the solvents screened (THF, toluene, dioxane, CH_3CN, DMF and NMP), NMP proved to be the most efficient.

Due to the electronegativity of the nitrogen atoms, the C-2 position of 3-alkyl-2-haloimidazo[4,5-*b*]pyridine (activated halo intermediate) should be easily susceptible to the oxidative addition to palladium complex. We have also investigated the influence of the nature of the halogen (I, Br, Cl) on the reactivity of 3-alkyl2-haloimidazo[4,5-*b*]pyridines (Scheme 1). The iodo intermediate reacted much faster (15 min) when compared to the bromo intermediate which took 30 min in microwave conditions for complete conversion to products. The chloro intermediate, **3c** reacted



Scheme 4. Proposed mechanism for Sonogashira coupling.

much slowly and also required higher temperatures for complete conversions to products. Having demonstrated that phenyl acetylene can be efficiently cross coupled with both **3a** and **3b**, we investigated the scope of this methodology[28] using various terminal alkynes Table 3. The results described in table shows that much slower reactions were observed using 3-butyn-2-ol instead of phenyl acetylene. With this alkyne the iodo intermediate was coupled more efficiently compared to the bromo derivative which reacted very sluggishly. In the case of **3c** higher mol% of the catalyst was required to drive the reactions for completion. Compound **3a** was synthesised according to the procedure described in Ref. 20. The synthesis of **3b** and **3c**[27] is shown in Scheme 3.

The outstanding activity of this catalyst employed for Sonogashira coupling of 3-alkyl-2-haloimidazo[4,5-*b*]pyridines has been attributed to a combination of electronic and steric properties that enhance the rates of oxidative addition, transmetalation, and reductive elimination steps in the catalytic cycle. The rates of all the three steps in the catalytic cycle are believed to be maximised by employing the conditions that favour the formation of intermediates bearing a singlet phosphine ligand, (Scheme 4). This can be explained as follows: (a) In the catalytic cycle, monoligated species are believed to be formed which are stabilised by electron rich and sterically demanding ligands attached to the palladium centre. (b) The oxidative addition of halides is faster with $L_1Pd(0)$ (monoligated) species than with other highly ligated complexes. (Due to the smaller size of a $L_1Pd(0)$, substrate can approach the latter more closely and, hence, react at a faster rate). $L_1Pd(Ar)X$ undergoes faster transmetalation than $L_2Pd(Ar)X$ complex. (c) Literature survey indicates that rate of reductive elimination from LPd(Ar)R (R= aryl, NR_2, OR) is faster than that for the same process for an analogous $L_2Pd(Ar)R$ complex[26] due to steric reasons.

Bu_4NOAc is thought to act as a mild base to deprotonate the most acidic hydrogen in the alkyne. Moreover, the formation of Pd(0) species in these reactions may be facilitated by the use of Bu_4NOAc.

In summary, we have established that $PdCl_2(PCy_3)_2$ catalytic system catalyses the Sonogashira coupling reaction of 3-cyclopentyl-2-halo imidazo[4,5-*b*]pyridines (I, Br, Cl) to yield various 2-alkynyl imidazo[4,5-*b*]pyridines in excellent yields. The choice of tetrabutyammoniumacetate as the base was important for the high yields of the cross coupled products. Work aimed at further synthetic utility of the halo intermediate is being pursued.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.028.

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28. *General procedure for coupling of 2-halo imidazo[4,5-b] pyridine derivative with different terminal acetylenes.* (Sonogashira coupling)
To a solution of 3-substituted-2-haloimidazo[4,5-*b*]pyridine derivative (1 equiv) in NMP, were added terminal acetylene (1.5 equiv) and tetrabutyl ammonium acetate (1.5 equiv). The solution was purged with nitrogen and stirred at room temperature for 0.15 h, at that time $PdCl_2(PCy_3)_2$ was added. The reaction solution was purged again with nitrogen and then placed in the microwave and heated for 10 to 30 min at 110 °C (for iodide and bromide intermediates). When chloro intermediate was used, the reaction contents were heated at 150 °C. When TLC and LCMS showed full consumption of starting materials, the reaction mixture was diluted with ethyl acetate, separated the ethyl acetate layer, given water wash, brine wash and was dried over anhydrous sodium sulphate and concentrated to get the crude material. The crude product was directly purified by column chromatography (0–15% hexane/EtOAc) to isolate the 3-alkyl-2-akynyl imidao[4,5-*b*] pyridine derivatives. The characterisation details of compounds **5a** and **5e** are given below.
2-(2-(3-Bromophenyl)ethynyl)-3-cyclopentyl-3*H*-imidazo[4,5-*b*]pyridine
Brown solid, Yield 94%, mp (102.6–102.4 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80–1.81 (m, 2H), 2.06–2.22 (m, 4H), 2.46–2.59 (m, 2H), 5.27–5.33 (m, 1H), 7.23–7.25 (m, 2H), 7.27–7.32 (m, 2H), 7.57–7.59 (m, 1H), 8.01–8.04 (m, 1H), 8.42–8.43 (m, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 24.82, 30.97, 56.56, 93.90, 118.65, 122.22, 125.84, 127.36, 129.89, 130.44, 132.46, 134.37, 135.30, 144.76; IR (KBr) 3425, 3054, 2950, 2868, 2221, 2157, 1942, 1724, 1592, 1552, 1492, 1424, 1399, 1370, 1276, 1243, 1069, 771, 705, 676, 653, 620 cm^{-1}; LCMS 368.12 (M+H); Anal. Calcd for $C_{19}H_{16}BrN_3$: C, 62.31; H, 4.40; N, 11.47%. Found: C, 62.34; H, 4.37; N, 11.35%.