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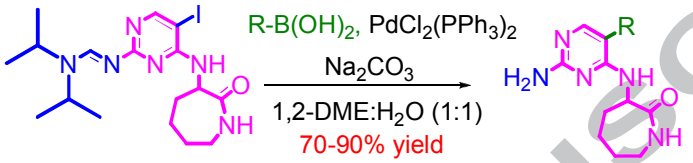

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A concise Pd catalyzed cross coupling reaction along with deprotection for the synthesis of a new series of pyrimidine derivatives

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ABSTRACT

A new series of 2-amino, 4-azepanone, 5-aryl substituted derivatives of pyrimidine compounds were synthesized for the first time from the commercially available 2-amino-4-hydroxypyrimidine. The key step in the reaction is a conceptually new single step palladium catalyzed cross coupling along with the deprotection of *N,N*-diisopropylformimidamide using bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$).

Pyrimidine is one of the prime motif in a large variety of compounds that exhibit important biological and pharmaceutical activities[1,2] including antimicrobial[3] antiinflammatory,[4] cytotoxic,[5] anticonvulsant activity,[6] antitumor agent,[7] antimalarial[8] and anticancer.[9] Further, the structure activity relationship revealed substitution of the electron donating group at the 2,4-position and the substitution of aromatic ring at 5-position of pyrimidine were found to increase the biological activity.[10,11] 3-amino-2-azepanone has good electron donating ability with additional binding sites. Moreover, compounds with 3-amino-2-azepanone are enzyme beneficial for potent antitumor activity,[12] anti-inflammatory activity,[13] cysteine protease cathepsine K inhibition[14] and migraine head ache.[15] Hence, a new series of pyrimidine derivatives with 3-amino-2-azepanone at 4-position were tried. The development of cross coupling with various substituted benzene ring and heterocyclic compounds at 5-position of pyrimidine, keeping the amino group intact at 2-position is challenging. Hence, the amino group at 2-position was protected with *N,N*-diisopropyl formamide and then catalytic cross coupling by Suzuki reaction using $PdCl_2(PPh_3)_2$ was tried. Interestingly the coupling along with the deprotection of *N,N*-diisopropylformamidine was achieved in a single step.

This work incorporates the synthesis of 2-amino-4-azepanone-5-aryl substituted pyrimidine compounds **5 (a-h)** from commercially available 2-amino-4-hydroxypyrimidine **1**. The reaction of 2-amino-4-hydroxypyrimidine with iodine in aqueous sodium hydroxide solution afforded the 2-amino-5-iodopyrimidin-4-ol **2**.[16] The regioselective chlorination of the hydroxy group with the combination of *N,N*-diisopropylfomamide and oxalyl chloride[16,17] gave 4-chloro-2-diisopropylaminomethyleneamino-5-iodopyrimidine **3**. Further, the reaction of compound **3** with 3-amino-2-azepanone in the presence of potassium carbonate in DMF resulted in *N'*-(5-iodo-4-(2-oxoazepan-3-ylamino)pyrimidin-2-yl)-*N,N*-diisopropyl formimidamide **4** with 80% yield. The cross coupling reaction of compound **4** by various substituted aryl carbocycles and heterocycles through Suzuki reaction using various boronic acid in the presence of $PdCl_2(PPh_3)_2$ and sodium carbonate in 1,2-DME and water (1:1) led to the formation of compounds **5 (a-h)** with 70-90% yield (Scheme 1, Table 1). The absence of imine CH carbon at δ 158 in Distortionless enhancement by polarization transfer (DEPT) added evidence to the deprotection.

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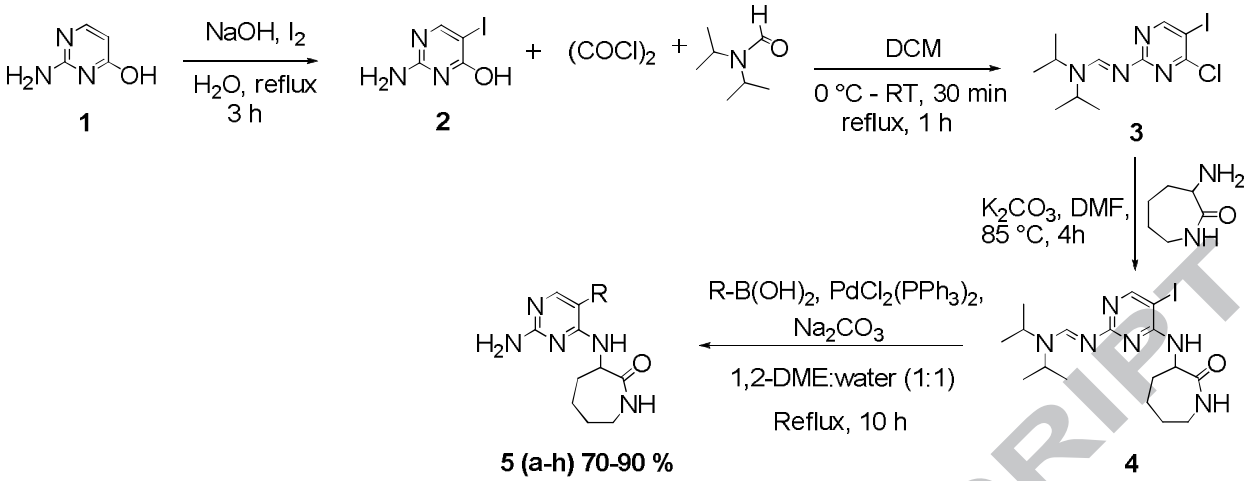


Scheme 1. New strategy for palladium catalyzed cross coupling of 5-substituted 2-amino-4-amino azepan-2-one derivatives.

Table 1 Synthesized compounds **5 (a-h)** with yield[a]

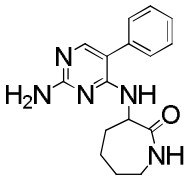
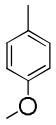
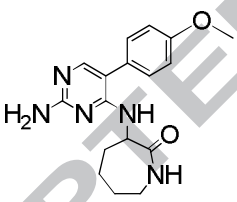
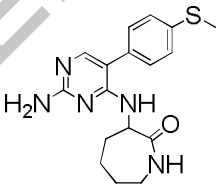
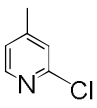
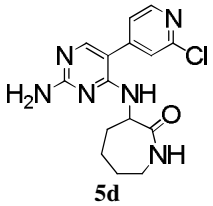
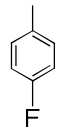
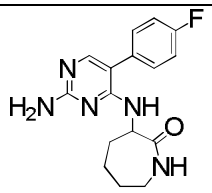
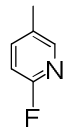
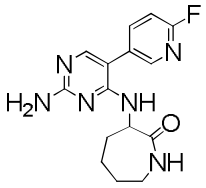
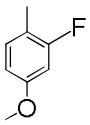
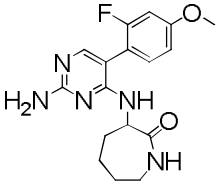
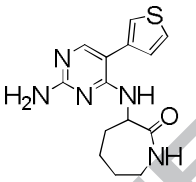
Entry	R-B(OH)$_2$ (R)	Product **5**	IUPAC Name	Yield[b] (%)
1		 **5a**	3-(2-amino-5-phenylpyrimidin-4-ylamino)azepan-2-one	80
2		 **5b**	3-(2-amino-5-(4-methoxyphenyl)pyrimidin-4-ylamino)azepan-2-one	75
3		 **5c**	3-(2-amino-5-(4-(methylthio)phenyl)pyrimidin-4-ylamino)azepan-2-one	75
4		 **5d**	3-(2-amino-5-(2-chloropyridin-4-yl)pyrimidin-4-ylamino)azepan-2-one	70

Table 1 (Continue)

Entry	R-B(OH)$_2$ (R)	Product **5**	IUPAC Name	Yield[b] (%)
5		 **5e**	3-(2-amino-5-(4-fluorophenyl)pyrimidin-4-ylamino)azepan-2-one	75
6		 **5f**	3-(2-amino-5-(6-fluoropyridin-3-yl)pyrimidin-4-ylamino)azepan-2-one	70
7		 **5g**	3-(2-amino-5-(2-fluoro-4-methoxyphenyl)pyrimidin-4-ylamino)azepan-2-one	75
8		 **5h**	3-(2-amino-5-(thiophen-3-yl)pyrimidin-4-ylamino)azepan-2-one	90

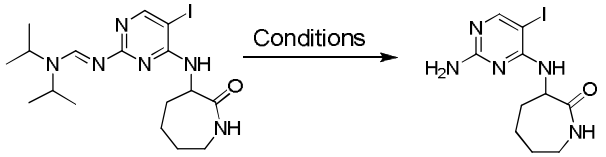
[a] Reaction condition: compound **4** (0.32 mmol)**,** Na_2CO_3 (0.98 mmol), boronic acid (0.39 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol) in 1,2-DME and water (1:1) reflux for 10 h under nitrogen atmosphere. Reaction completion at 10 h was monitored by TLC.

[b] Isolated Yield

Common deprotection strategies for amine required strongly acidic or basic media under room temperature or heating to give necessary cleavage.[16-19] There are also reports on deprotection of *N,N*-diisopropylformimidamide by neutral or base hydrolysis in literature,[16-17, 20] but the base hydrolysis tried in this experiment, with sodium hydroxide and ethanol, was not successful under various conditions (Table 2). This was confirmed by TLC and GCMS. Two-step reaction to achieve similar target molecules as that of the proposed with cross coupling using tetrakis(triphenylphosphine)palladium(0) followed by acid hydrolyzed deprotection of *N,N*-diisopropylformimidamide are reported in the literature,[19] but when the deprotection of *N,N*-diisopropylformimidamide **4** was tried by acid hydrolysis with 4 M aq. HCl in ethanol under reflux for 5 h, the compound **4a** was obtained with a moderate yield of 40% (Table 2, entry 9). Further, the desired product **5 (a-h)** could also be obtained when the deprotected compound **4a** was subjected to cross coupling using $PdCl_2(PPh_3)_2$ and sodium carbonate in 1,2-DME and water (1:1) in 40% yield (Scheme 2, step i & iii).

The deprotection with $PdCl_2(PPh_3)_2$ and phenyl boronic acid in the presence of water without any base gave **4a** in 50% yield (Table 2, entry 10, Scheme 2, step ii) but the cross coupling at 5-position did not take place. When cross coupling was tried in non aqueous condition using $PdCl_2(PPh_3)_2$, phenyl boronic acid with base sodium carbonate and 1,2-DME, cross coupling did not occur (Table 3), this may be due to lower solubility of base in 1,2-DME. Hence, the reaction was tried with $PdCl_2(PPh_3)_2$, phenyl boronic acid in presence of potassium carbonate in DMF. The cross coupled product **4b** was obtained (Table 3) and confirmed by LCMS. DMF was used instead of 1,2-DME because of the higher boiling point and better dissolution of K_2CO_3. K_2CO_3 was used instead of Na_2CO_3 because of better solubility.

Table 2 Optimization of reaction condition for deprotection of *N,N*-diisopropylformimidamide without cross coupling

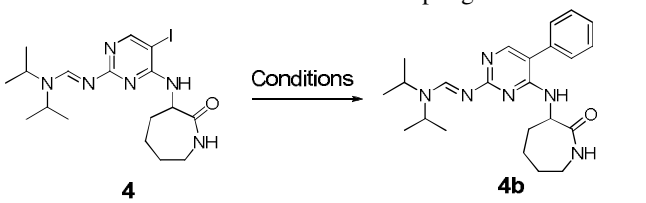


4 **4a**

Entry	Base/Acid/Catalyst/Solvent	Condition	Result
1	Ethanol/H_2O(1:1)	rt, 24 h	N.R. [a]
2	Ethanol/H_2O(1:1)	Reflux, 4 h	N.R. [a]
3	4% aq.Na_2CO_3/ Ethanol	rt, 5 h	N.R. [a,b]
4	4% aq.Na_2CO_3/ Ethanol	Reflux, 5h	N.R. [a,b]
5	4% aq.NaOH/ Ethanol	rt, 5 h	N.R. [a,b]
6	4% aq.NaOH/ Ethanol	Reflux, 1h	N.R. [a,b]
7	4% aq.NaOH/ Ethanol	Reflux, 5h	N.R. [a,b]
8	4M aq.HCl/Ethanol	rt, 24 h	N.R. [a,c]
9	4M aq.HCl/Ethanol	Reflux, 5h	40% [c,d]
10	$PdCl_2(PPh_3)_2$/without base /1,2 DME/Water(1:1)	Reflux, 5 h	50% [d,e]

[a] No reaction. TLC, GCMS and LCMS indicated that the deprotection did not proceed.
[b] Compound **4** (0.15g) in 4 mL each of ethanol and 4% aq. base.
[c] 0.15 g compound **4** in 5 mL of 4 M aq. HCl in ethanol.
[d] Deprotection was confirmed by LCMS , GCMS and NMR.
[e] Compound **4** (0.32 mmol), Phenyl boronic acid (0.39 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol) in 1,2-DME and water (1:1) under nitrogen atmosphere.

Table 3 Reaction conditions for cross coupling[a]

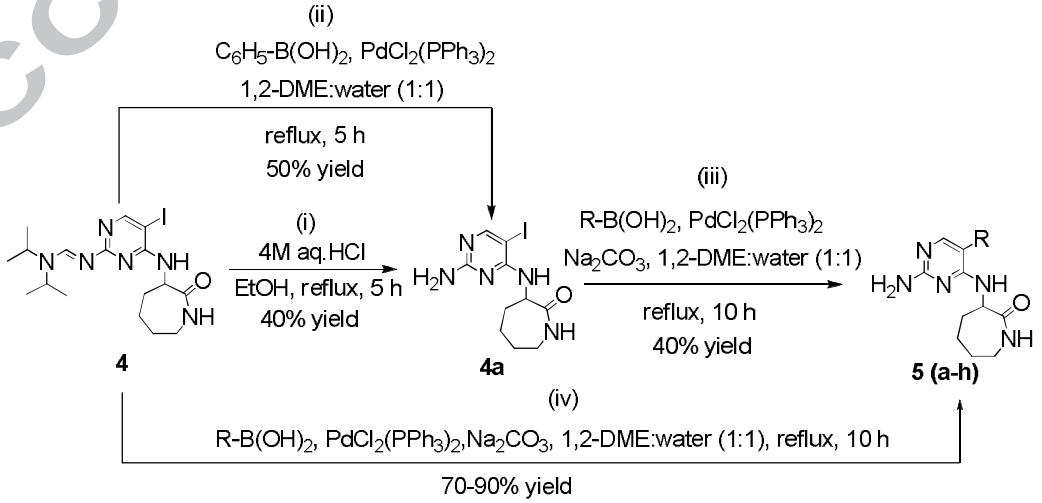


4 **4b**

Entry	Reagent/Catalyst/base/Solvent	Condition	Result
1	C_6H_5-$B(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, 1,2-DME	reflux, 10 h	N.R. [b]
2	C_6H_5-$B(OH)_2$, $PdCl_2(PPh_3)_2$, K_2CO_3, DMF	100 ° C, 10 h	Less stable [c]

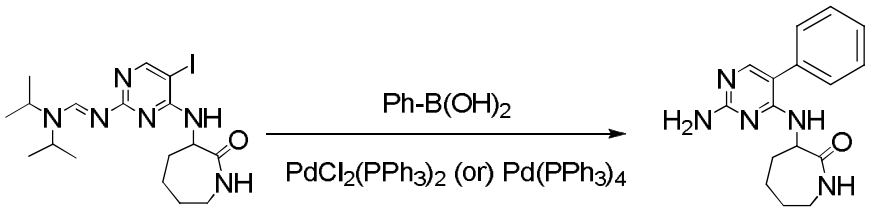
[a] Compound **4** (0.22 mmol), base (0.43 mmol), phenyl boronic acid (0.22 mmol) and $PdCl_2(PPh_3)_2$ (0.02 mmol) in 1,2-DME/ DMF without water, under nitrogen atmosphere.
[b] No reaction, compound 4 was recovered and confirmed by LCMS.
[c] Confirmed by LCMS

Optimization of single step deprotection along with cross coupling was tried with regard to catalyst, base, solvent, temperature and time. When the Optimization was tried by treating compound **4** with phenyl boronic acid as a sample using different reaction conditions (Table 4) to give **5a**., $PdCl_2(PPh_3)_2$ was found to give better yield (80 %) in 1,2-DME and water (1:1) solvent with Na_2CO_3 as base (Table 4, entry 7). Further, when the compound **4** was checked by TLC, there was no compound **4** left over at 10 h. This confirmed the optimum time as 10 h. When the same reaction was tried with $Pd(PPh_3)_4$ under identical conditions only 50% yield was obtained. Furthermore, when the base was changed to K_2CO_3 and $CsCO_3$ the yield got reduced to 70% and 58% respectively. The same reaction when performed with $PdCl_2(PPh_3)_2$ as catalyst, Na_2CO_3 as base and the solvent DMF and water (1:1) heated at 100 °C for 10 h resulted in a reduced yield of 58%. From these observations the conditions (Table 4, entry 7) has been taken as the optimum condition and followed for all the derivatives. $Pd(PPh_3)_4$ was used because of the earlier report on cross coupling[20] but $PdCl_2(PPh_3)_2$ gave better results than $Pd(PPh_3)_4$. Moreover, $PdCl_2(PPh_3)_2$ has a better shelf life and cheaper compared to $Pd(PPh_3)_4$. Hence, the synthetic route with $PdCl_2(PPh_3)_2$ proved to be beneficial both in terms of reagent stability and the cost.



Scheme 2 Optimization for deprotection of *N,N*-diisopropylformimidamide and cross coupling using $PdCl_2(PPh_3)_2$

Table 4. Optimization of reaction conditions for deprotection along with cross coupling using phenyl boronic acid[a]



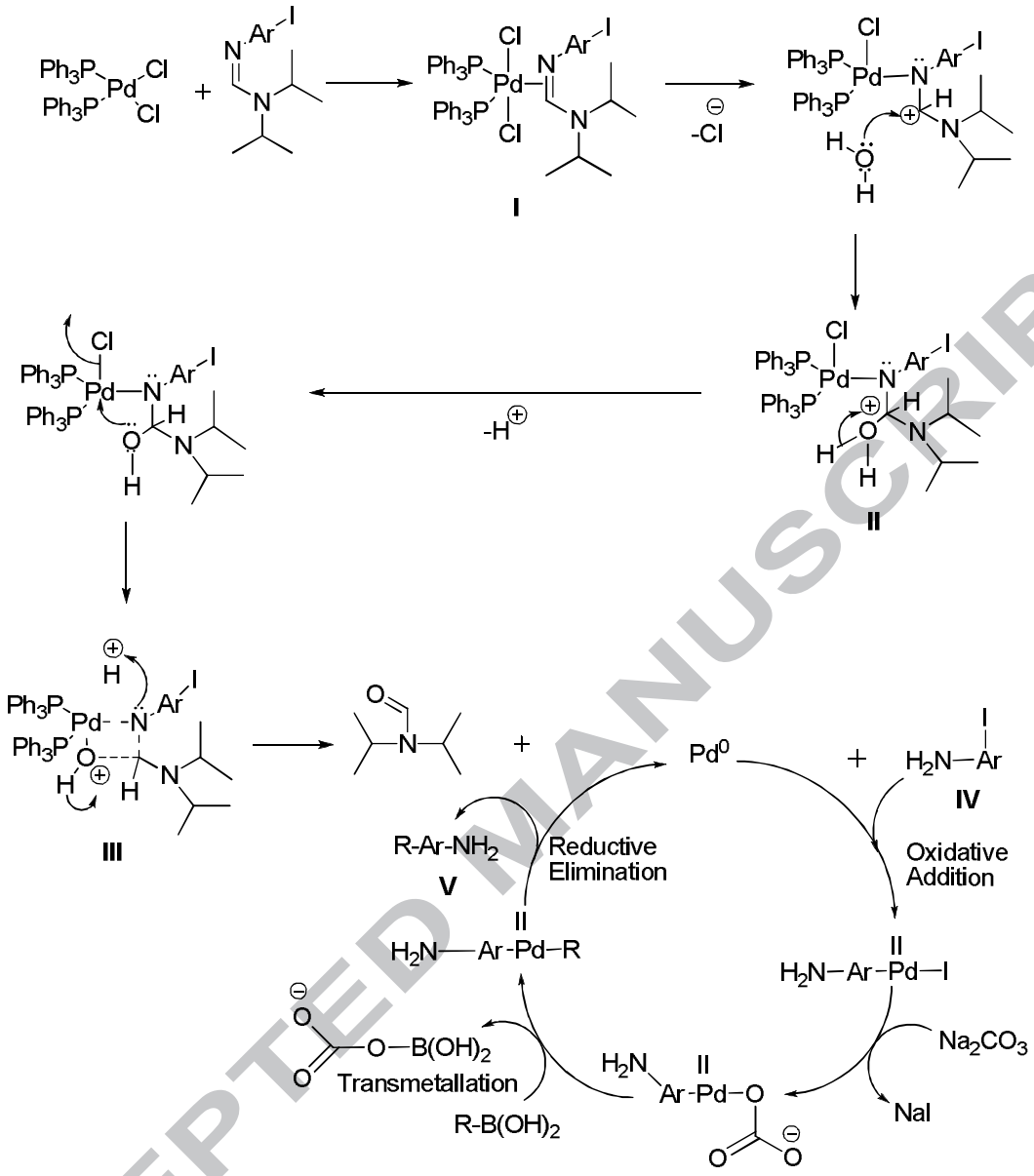
4 **5a**

Entry	Catalyst	Base	Solvent	T/°C	Results (yield[c] %) Time (h) 2	5	10
1	$Pd(PPh_3)_4$	Na_2CO_3	1,2-DME/H_2O (1:1)	reflux	N.R.[b]	24	50
2	$Pd(PPh_3)_4$	K_2CO_3	1,2-DME/H_2O (1:1)	reflux	N.R.[b]	22	46
3	$Pd(PPh_3)_4$	Cs_2CO_3	1,2-DME/H_2O (1:1)	reflux	N.R.[b]	18	38
4	$Pd(PPh_3)_4$	Na_2CO_3	DMF/H_2O (1:1)	100	N.R.[b]	20	45
5	$Pd(PPh_3)_4$	K_2CO_3	DMF/H_2O (1:1)	100	N.R.[b]	15	36
6	$Pd(PPh_3)_4$	Cs_2CO_3	DMF/H_2O (1:1)	100	N.R.[b]	15	28
7	**$PdCl_2(PPh_3)_2$**	**Na_2CO_3**	**1,2-DME/H_2O (1:1)**	**reflux**	N.R.[b]	**37**	**80**
8	$PdCl_2(PPh_3)_2$	K_2CO_3	1,2-DME/H_2O (1:1)	reflux	N.R.[b]	30	70
9	$PdCl_2(PPh_3)_2$	Cs_2CO_3	1,2-DME/H_2O (1:1)	reflux	N.R.[b]	28	58
10	$PdCl_2(PPh_3)_2$	Na_2CO_3	DMF/H_2O (1:1)	100	N.R.[b]	30	58
11	$PdCl_2(PPh_3)_2$	K_2CO_3	DMF/H_2O (1:1)	100	N.R.[b]	30	55
12	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DMF/H_2O (1:1)	100	N.R.[b]	22	48

[a] Compound 4 (0.15 mmol), base (0.45 mmol), phenyl boronic acid (0.17 mmol), Pd catalyst (0.015 mmol) in 5 mL solvent under nitrogen atmosphere.

[b] No reaction, monitored by TLC and LCMS (compound **4** mass was observed).

[c] Isolated yield.



Scheme 3 Proposed mechanism for deprotection and cross coupling reaction using $PdCl_2(PPh_3)_2$

The mechanism can be proposed as follows: A typical role of the transition metal catalyst such as $PdCl_2(PPh_3)_2$ to enhance the reactivity of a substrate is the formation of a complex with π-electrons of imine multiple bonds, which facilitate the attack of Nu- to an electron-deficient carbon to give an organo-palladium intermediate having a C-Nu bond (Scheme 3).[21] Although it is known that a combination of a Lewis acid (MXn)and a transition-metal catalyst (M′X) is useful for enhancing certain organic transformations. To the best of our knowledge, there is no precedent in which a single-metal complex (MXn = M′Xn) exhibits dual roles in a transformation. The initial step would be the formation of π-imine-palladium complex **I**. This complex would activate the imine by enhancing the partial positive charge on the carbon atom. Addition of oxygen nucleophile to imine tends to occur from the face opposite to that occupied by palladium, and would lead to the formation of **II**. The oxonium ion **II** formed in the intermediate may be stabilized by the deprotonation, which may lead to the formation of HCl combining with the Cl- cleaved from the palladium. The lone pair on oxygen may then attack the palladium forming cyclic intermediate **III**, which may further undergo reductive

elimination to give palladium(0) with amine and *N,N*-diisopropylformamide. Further the palladium(0) and the amine **IV** formed undergo cross coupling reaction by the well established Suzuki coupling mechanism to give the product **V** (Scheme 3).

In conclusion, a new series of pyrimidine-azepan-2-one derivatives **5 (a-h)** were synthesized for the first time by a single step cross coupling of carbocylic or heterocylic ring at 5-position along with deprotection of *N,N*-diisopropylformimidamide using bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$) in good yield

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Supplementary Material

Experimental procedures and full spectroscopic data for all the synthesized compounds are made available.

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