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Palladium catalyzed one-pot synthesis of 2-(pyridin-4-yl) quinolines *via* a multicomponent unprecedented reaction of pyridine-4-carbaldehyde, 2-iodoaniline and triethylamine †

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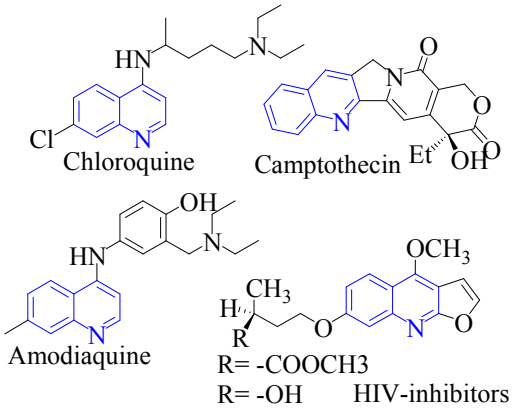
Palladium catalyzed synthesis of 2-(pyridin-4-yl) quinolines with an unprecedented participation of Et_3N in moderate to high yields was achieved in a novel multicomponent one-pot cyclization reaction of readily available pyridine-4-carbaldehyde, 2-iodoaniline and triethylamine in refluxing toluene.

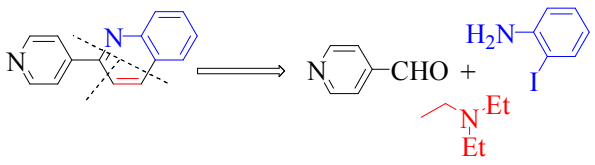
Quinolines are essential structural motif, found in plethora classes of antifungal agents such as 8-hydroxy quinolines, 2-aryl or styryl-quinolines which showed potent antifungal activities.[1-2] This moiety is also found as prominent substructure in a numerous number of natural and unnatural compounds having biological activities, such as antibacterial,[3] HIV-1 replication inhibitors [4] and most importantly within anti malarial agents[5] shown in Figure 1. C-2 pyridinyl substituted quinolines are best MIC_{80} and MIC_{50} against the clinically important fungi *Candida albicans* and *non- albicans Candida* species and have shown activities against dermatophytes.[6] Hence, the development of alternative approaches for the preparation of quinolines, have gained great interest.[7-9]

Multicomponent reactions (MCRs) have emerged in recent times as popular, powerful and useful tools in synthetic, combinatorial, and medicinal chemistry.[10] The significant advantages such as greater efficiency, facileness, atom economy, convergent and structural complexity compared to the conventional linear -type syntheses have made MCRs as prominent strategies for the diverse construction of heterocyclic scaffolds.[11] Moreover, MCRs have also been extensively exploited in the synthesis of quinolines.[12] Et_3N is an exceptionally versatile compound in organic chemistry by providing several roles such as base,[13] reducing agent[14] and catalyst.[15] In this context, we have demonstrated a straightforward synthesis of 2-(pyridin-4-yl) quinolines, some of which have already been characterized with prominent biological activities,[1-2] *via* a three-component reaction of pyridine-4-carbaldehyde, 2-iodoaniline and triethylamine, involving an unprecedented double C-H insertion reactions of Et_3N with the assembling of the quinoline core from [3+2+1] atom fragments and the formation of three new bonds (scheme 1).

Figure 1 Quinoline based natural products.



We preliminary aimed the synthesis of benzo[*c*][2,6]naph-thyridine **4a** from pyridine-4-carbaldehyde **1** and 2-iodoaniline **2**. In this regard, when the reaction was conducted with **1a** and **2a** in the presence of Et_3N (7 equiv), $Pd_2(dba)_3$ (5 mol %) and PPh_3 (10 mol%) in dry DMF at 110 °C for 24 h, instead of **4a**, 2-(pyridin-



Scheme 1 Multicomponent approach to quinoline.

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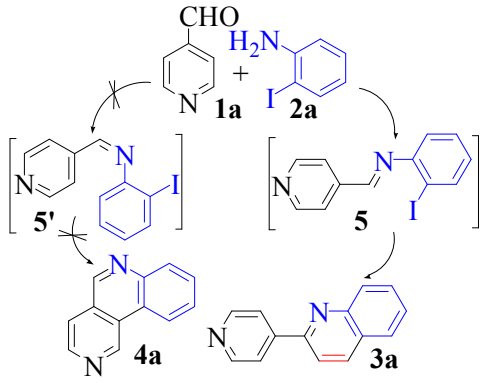
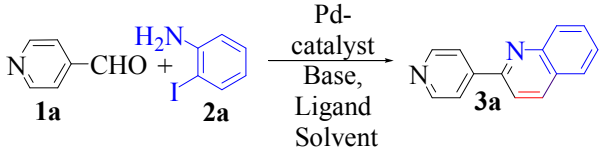
† Electronic Supplementary Information (ESI) available: Experimental details and characterization for all final compounds. For ESI see DOI: 10.1039/c000000x/

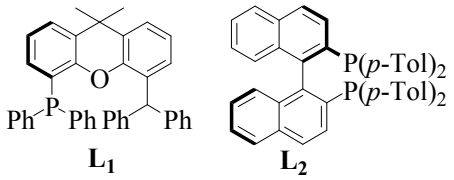


Scheme 2 Palladium-catalyzed cyclization reaction.

4-yl) quinoline **3a** was produced solely in 42% yield (Table 1, entry 1). The structure of **3a** was confirmed by matching the ^{1}H, ^{13}C NMR spectra and HRMS with the reported data.[2a, 16] The cascade reaction herein was unambiguously progressed through the initial formation of more stable E-imine isomer which offered **3a** rather than **4a** that would be obtained from less stable Z-imine (Scheme 2). Now since **3a** is a biologically prominent compound as per reports, [1, 2] we moved on to the synthesis of 2-(pyridin-4-yl) quinolines. Then, exhaustive studies of the reaction conditions for the synthesis of **3a** by employing an array of catalytic systems, bases, ligands, temperatures, additives and solvents were conducted (Table 1). It was found that the presence of combined additives of 4 Å MS with $MgSO_4$ fabricated $Pd_2(dba)_3$ as the most suitable catalyst for the reaction among others, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $PdCl_2$, $Pd(MeCN)_2Cl_2$ and $Pd(OAc)_2$ (entries 1-9). Use of toluene as the solvent led the reaction most effectively compared to other solvents like DMF, DMA, DMSO, xylene and mesitylene (entries 10-14).

Table 1 Optimization of the reaction conditions.[a]





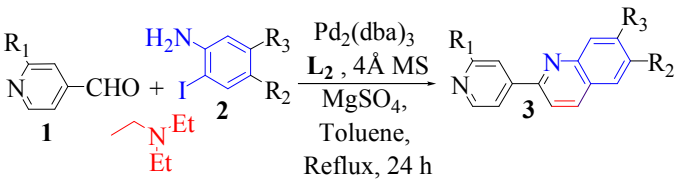
Entry	Catalyst	Solvent	Ligand	Additive I	Additive II	T/ ^{0}C	Base (equiv)	Time/h	Yield (%)[b]
1	$Pd_2(dba)_3$	DMF	PPh_3	—	—	110	Et_3N (7)	24	42
2	$Pd_2(dba)_3$	DMF	PPh_3	4 Å MS	—	110	Et_3N (7)	24	49
3	$Pd_2(dba)_3$	DMF	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	58
4	$Pd_2(dba)_3$	DMF	PPh_3	4 Å MS	Na_2SO_4	110	Et_3N (7)	24	53
5	$Pd(PPh_3)_4$	DMF	—	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	49
6	$Pd(PPh_3)_2Cl_2$	DMF	—	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	48
7	$PdCl_2$	DMF	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	45
8	$Pd(MeCN)_2Cl_2$	DMF	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	47
9	$Pd(OAc)_2$	DMF	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	51
10	$Pd_2(dba)_3$	DMA	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	53
11	$Pd_2(dba)_3$	DMSO	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	50
12	$Pd_2(dba)_3$	Toluene	PPh_3	4 Å MS	$MgSO_4$	Reflux	Et_3N (7)	24	67
13	$Pd_2(dba)_3$	Xylene	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	60
14	$Pd_2(dba)_3$	Mesitylene	PPh_3	4 Å MS	$MgSO_4$	110	Et_3N (7)	24	58
15	$Pd_2(dba)_3$	Toluene	PCy_3	4 Å MS	$MgSO_4$	Reflux	Et_3N (7)	24	59
16	$Pd_2(dba)_3$	Toluene	dppp	4 Å MS	$MgSO_4$	Reflux	Et_3N (7)	24	64
17	$Pd_2(dba)_3$	Toluene	L_1	4 Å MS	$MgSO_4$	Reflux	Et_3N (7)	24	68
18	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Et_3N (7)	24	75
19	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	90	Et_3N (7)	24	52
20	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	100	Et_3N (7)	24	62
21	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	120	Et_3N (7)	24	72
22	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Et_3N (3)	24	73
23	**$Pd_2(dba)_3$**	**Toluene**	L_2	**4 Å MS**	**$MgSO_4$**	**Reflux**	**Et_3N (2)**	**24**	**75**
24	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Et_3N (1)	24	56
25	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Et_3N (2)	12	0
26	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Et_3N (2)	18	47
27	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	$(Me_2CH)_2NEt$	24	49
28	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Me_3N (2)	24	0
29	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	K_2CO_3	24	0
30	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Cs_2CO_3	24	0
31	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Na_2CO_3	24	0
32	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	Li_2CO_3	24	0
33	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	NaOAc	24	0
34	$Pd_2(dba)_3$	Toluene	L_2	4 Å MS	$MgSO_4$	Reflux	KOAc	24	0

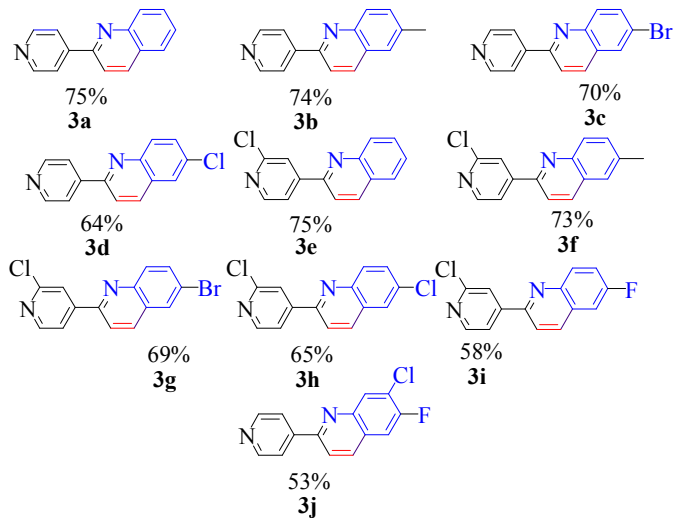
[a]Reactions were carried out with **1a** (0.654 mmol), **2a** (0.687 mmol), Pd-catalyst (5 mol %), ligand (10 mol%), base in 5 mL of solvent. 65 mg of 4 Å MS and additive II (6 equiv.) were used. [b] Isolated yields .

Then, various phosphine ligands, including PCy_3, dppp and xantphos **L_1** were tested but all produced **3a** in lower yields (entries 15-17). When (R)-(+)-Tol-BINAP **L_2** was used, **3a** was obtained in increased yield of 75% (entry 18). It was observed that the reaction afforded **3a** in lower yields on decreasing the temperature below 110 ^{0}C (entries 19, 20) and the elevation of temperature was also failed to improve the yield of the product (entry 21). The yield was found to be unbiased till 2 equiv. of triethylamine, below of which led to a decreased yield (entries 22-24). The formation of **3a** was initiated after 12h of reaction time (entries 25, 26). When *N, N*-Diisopropylethylamine (Hunig's base) was used as base, product **3a** was obtained in reduced yield of 49% solely (entry 27). In contrast, when bases having lack of ethylene source like Me_3N, K_2CO_3, Cs_2CO_3, Na_2CO_3, Li_2CO_3, NaOAc or KOAc were used, no formations of **3a** were found (entries 28-34). Hence, the initial base choice as triethylamine and the arbitrary set of reaction time at 24h favoured our luck to display an unexpected and unmatched result.

To extend the scope and general applicability of the protocol, a range of reactions was conducted with various 2-iodoanilines **2a-f** and pyridine-4-carbaldehydes **1a-b** (Table 2), under the optimized conditions constructed above (Table 1, entry 23). They reacted smoothly to produce corresponding quinolines **3** in moderate to high yields with tolerating of electron-donating as well as electron-withdrawing groups on aromatic rings. However, a reduced trend of yields was noticed with stronger withdrawal substitution on 2-iodoaniline ring (Table 2). On the other hand 2-iodo-4, 6-dimethylaniline **2g**, 2- bromoaniline **2h** and benzaldehyde **6** failed to afford quinolines **3**, although corresponding imines were isolated solely (compounds **5a-b** and **7** in Table 3). Similar results were observed on carrying out the reaction for 12 h or in the absence of Pd-catalyst for 24 h (Table 3, **5c-d**). It is clear that pyridinyl nucleus assisted the double C-H insertions of Et_3N (compare the formations of **3a-j** and **7**), which was not obeyed because of the presence of extra ortho methyl group forcing **5a** not to achieve appropriate geometry for cyclization. It is also elucidated that stronger withdrawal substitution on **2** reduced the yields of the imines **5**, from which corresponding quinolines **3** were obtained in lower yields (compare yields for **5a** and 5**d**). Moreover, 2-iodo-4-nitro-aniline **2i** failed to afford **3** or **5**.

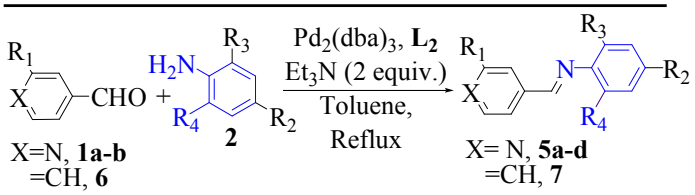
Table 2 Pd-Catalyzed multicomponent synthesis of quinolines.[a,b]

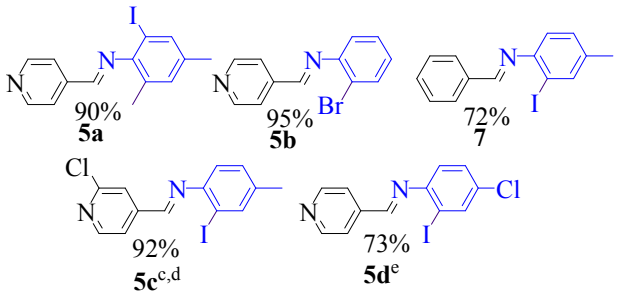




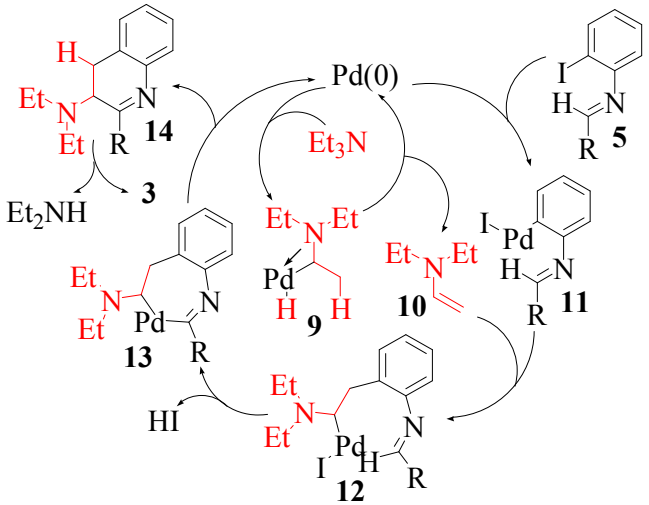
[a]All reactions were carried out with 1 (0.654 mmol), 2 (0.687 mmol), $Pd_2(dba)_3$ (5 mol %), **L_2** (10 mol %), Et_3N (2 equiv.), 65 mg of 4 Å MS and $MgSO_4$ (6 equiv.) in toluene (5 mL). [b]Isolated yields.

Table 3 Isolation of intermediate imine.[a,b]





[a]Reactions were carried out with **1** (0.654 mmol), **2** (0.687 mmol), $Pd_2(dba)_3$ (5 mol %), **L_2** (10 mol %), Et_3N (2 equiv.), 65 mg of 4 Å MS and $MgSO_4$ (6 equiv.) in toluene (5 mL). [b]Isolated yields. [c]Reaction time 12 h. [d,e] Absence of $Pd_2(dba)_3$.



Scheme 3 Proposed mechanism for the synthesis of 2-(pyridin-4-yl) quinolines **3**.

A proposed catalytic cycle for the synthesis of quinoline **3** is depicted in Scheme 3. In this mechanism, palladium undergoes oxidative addition to the carbon-iodine bond of imine **5** to form **11**. Both the olefinic C-H bonds of vinyl (diethyl) amine **10**, produced from triethylamine as per report, [17] can participate in insertion reactions *via* π -complex. However, majority of that could proceed by the involvement of the C-H bond β to the nitrogen atom [18] to produce primary alkylpalladium complex **12**. Reaction at the highlighted C-H bond produces seven-membered palladacycle **13**. Reductive elimination delivers **14**, and subsequent 1,2-elimination of Et_2NH provides 2-(pyridin-4-yl) quinoline **3.** There is no direct evidence for the formation of **10** at present, however it is clear that triethylamine is the solely source of the ethylene moiety required for the complete cyclization to afford **3** (compare entries 1-26 and 28-34 in Table 1).

In conclusion, we have developed a straightforward synthesis of 2-(pyridin-4-yl) quinolines in one-pot *via* multicomponent reaction of pyridine-4-carbaldehyde, 2-iodoaniline and triethylamine. In this reaction, three new bonds are formed with the assembling of [3+2+1] atom fragments. The reactions deal with longer reaction time. The starting materials are cheap and readily available. The unprecedented double C-H insertions of Et_3N have made this approach novel.

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