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COMMUNICATION

One pot synthesis of phenanthridines using a palladium- catalyzed cyclization of aromatic ketoximes with aryl iodides via Beckmann rearrangement

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The catalytic reaction of ketoximes with aryl iodides via Beckmann rearrangement in the presence of catalytic amount of $Pd(OAc)_2$, Ag_2O and $ZnBr_2$ gave substituted phenanthridines in good to excellent yields. In the reaction aromatic ketoximes converted first into acetanilides in presence of $ZnBr_2$/TFA via Beckmann rearrangement then subsequent arylation in presence of palladium complex. Later, *ortho*-arylated acetanilides were converting into phenanthridine derivatives in presence of Hendrickson reagent.

Phenanthridines and its derivatives are the important core structures of many hetero cyclic naturally occurring and biologically active molecules. They have many clinical applications including antiprotozoal, antibacterial, anticancer agents, pharmaceutically and optoelectronic properties.[1] Several methods have been reported for the syntheses of phenanthridine skeleton such as radical,[2] one pot cascade,[3] benzyne-mediated,[4] photochemical,[5] hypervalent iodine-promoted,[6] photocyclized,[7] microwave assisted[8] and transition-metal-catalyzed.[9] Palladium-catalyzed C-C bond-forming reactions involving direct C-H bond activation has a powerful method for the synthesis of complex polycyclic heterocyclic structures.[10] In 2009, Fagnou group reporteda simple catalytic method for direct intramolecular arylation reaction for the synthesis of six- and five-membered ring biaryls.[11] Recently, Lautens described a palladium-catalyzed reaction involving ligand-mediated C-H activation and cross-coupling for the preperation of substituted phenanthridine derivatives (Fig 1).[12] Fensterbank et al. demonstrated a palladium catalyzed reaction for the most efficient synthesis of phenanthridines from benzylamines and aryl iodides through the oxidative dehydrogenative coupling by palladium and norbornene mediated domino reaction.[13]

More recently, Bin Li described a direct and efficient method for the synthesis of phenanthridines using a palladium-catalyzed C-H activation and C-C bond forming intramolecular reaction of *N*-(2-haloaryl)-imines.[14] Although a number of useful synthetic methods are available for the synthesis of phenanthridine core structures, there are remain many limitations such as multi step synthetic methods, limited substrate scope and in some cases harsh reaction conditions. Therefore, the development of more milder, general and convenient methods from easily available starting materials for the synthesis of the phenanthridine ring structures. Herein, we wish to report one pot synthesis of phenanthridines in the presence of palladium catalyst. The catalytic reaction was also compatible with various functional groups such as electron-rich, electron-deficient and halogen group substituted aromatic oximes and substituted iodo benzenes. Further, *ortho*-arylatedanilides were converted into useful heteroaromatics such as phenanthridines in presence of Ph_3PO and Tf_2O.[15]

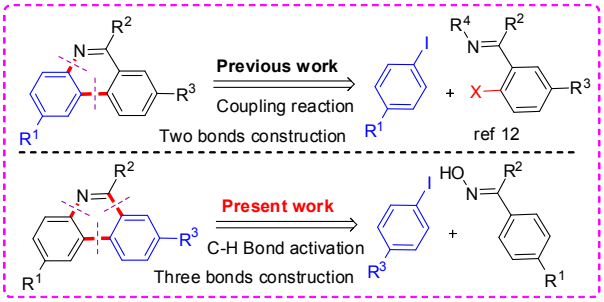
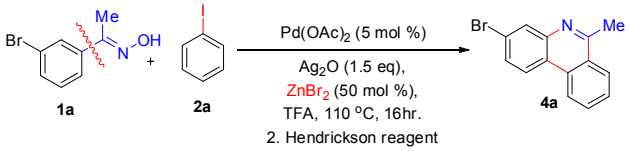


Fig 1. Synthesis of phenanthridines



Scheme 1. Phenanthridine synthesis of **4a**

The oxidative cyclization of 3-bromo acetophenone oxime **1a** with iodobenzene **2a** in the presence of $Pd(OAc)_2$ (5 mol %), Ag_2O (1.5 equiv), and $ZnBr_2$ (0.5 equiv) in TFA at 110 °C for 16 h gave 3-bromo-6-methylphenanthridine **4a** in 87% isolated yield (scheme 1). In the reaction, 3-bromo acetophenone oxime **1a** converted first into acetanilide via Beckmann rearrangement in presence of $ZnBr_2$ and TFA then subsequent *ortho*-arylation of acetanilide in presence of $Pd(OAc)_2$ and Ag_2O. Further, *ortho*-arylatedacetanilides **3a** were

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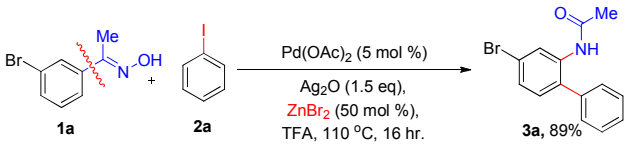
converted in to 3-bromo-6-methylphenanthridine **4a** 87% yield in presence of Hendrickson reagent.



In the beginning of the project, our aim was to synthesize phenanthridines from cyclization reaction of ketoximes with aryl iodides. For this strategy we have started our optimization studies. The cyclization reaction of 3-bromo acetophenone oxime **1a**, iodobenzene **2a** was examined in the presence of $Pd(OAc)_2$ (5 mol %) and AgOAc (1.5 eq) in AcOH at 110 °C for 16 h. However, in the reaction, no cyclization product **4a** was observed only a minor amount of *ortho*-arylatedanilide **3a** was observed. The catalytic reaction was also tested with various solvents such as TFA and TfOH provided *ortho*-arylatedanilide **3a** in 50%, 28% yields, surprisingly. In presence of acidic solvents ketoxime was converted in to acetanilide via Beckmann rearrangement followed by *ortho*-arylation in presence of palladium complex.

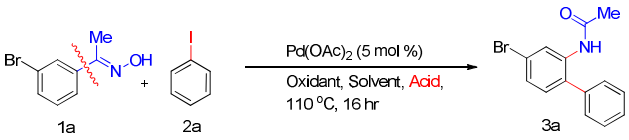
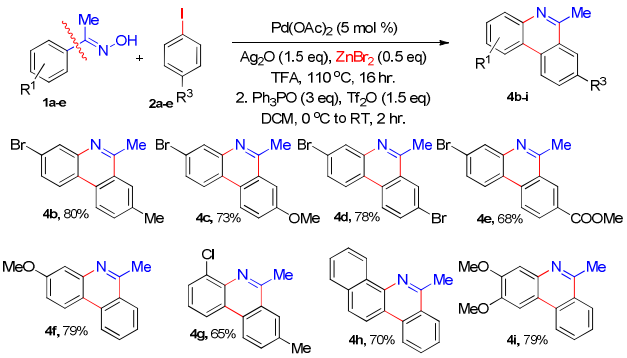


Table 1. Optimization studies[a]

Entry	Pd cat.	Oxidant	Acid	Solvent	Yield (%)[b]
1	Pd	AgOAc	-	AcOH	nr
2	Pd	AgOAc	-	TfOH	28
3	Pd	AgOAc	-	TFA	50
4	Pd	Ag_2O	-	TFA	65
5	Pd	AgOTf	-	TFA	30
6	Pd	$AgOCOCF_3$	-	TFA	10
7	Pd	AgF	-	TFA	5
8	Pd	Ag_2CO_3	-	TFA	3
9	Pd	-	-	TFA	nr
10	-	Ag_2O	-	TFA	nr
11	Pd	Ag_2O	TfOH	TFA	30
12	**Pd**	**Ag_2O**	**$ZnBr_2$**	**TFA**	**89**
13	Pd	Ag_2O	$ZnCl_2$	TFA	43
14	Pd	Ag_2O	*p*-TsCl	TFA	65
15	Pd	Ag_2O	$AlCl_3$	TFA	nr
16	Pd	Ag_2O	PCl_5	TFA	nr

[a]All reactions were carried out using **1a** (1.0 mmol), iodo benzene **2a** (3.0mmol), oxidant (1.5mmol), acid (0.5 mmol) and $Pd(OAc)_2$ (5 mol %) in solvent (2.0 mL) at 110 °C for 16h. [b]Yields were determined by the ^{1}H NMR integration method, using mesitylene as an internal standard.

In order to increase the yield of **3a**, initially reaction was studied with different type of solvents such as AcOH, TfOH and TFA with AgOAc (Table 1, entry 1-3). Among these TFA solvent is providing *ortho*-arylated anilide compound **3a** in 50% yield (entry 3) and TfOH solvent is less effective and it is giving 28% yield (entry 2). AcOH solvent is the totally inactive for the arylation reaction (entry 1). The catalytic reaction was also tested with various oxidants such as Ag_2O, AgOTf, $AgOCOCF_3$, AgF, and Ag_2CO_3 (Table 1, entry 4-8). The *ortho*-arylated anilide **3a** was observed in the presence of Ag_2O in 65% yield (entry 4), AgOTf, $AgOCOCF_3$, AgF, and Ag_2CO_3 were less effective for giving **3a** in 30%, 10%, 5%, 3% yields respectively (entry 5-8). The reaction was tested without palladium catalyst and just only in the presence of Ag_2O and TFA. In meantime the catalytic reaction was also tested without Ag_2O only with palladium and TFA. In both the reactions no *ortho*-arylated anilide product **3a** was observed (entry 9 and 10). The catalytic reaction was also studied with various acids such as TfOH, $ZnBr_2$, $ZnCl_2$ and *p*-TsCl (entry 11-14). Among them $ZnBr_2$ is the best for the Beckmann rearrangemant for providing the *ortho*-arylated anilide **3a** in excellent 89% yield (entry 12), TfOH, $ZnCl_2$, *p*-TsCl *ortho*-arylated anilide **3a** was observed in 30%, 43% and 65% yields (entry 11, 13 and 14). In meantime the catalytic reaction was also studied with Lewis acids such as $AlCl_3$ and PCl_5 under the same optimized conditions in the reaction no arylation compound **3a** was observed, only minor amount of 3-bromo acetanilide **7a** was obtained (entry 15 and 16). The yield of product **3a** was determined by the ^{1}H NMR integration methods using mesitylene as an internal standard. These results clearly revealed that both palladium and oxidant such as Ag_2O are crucial for the *ortho*-arylation reaction. In meanwhile, Intra-molecular cyclization reaction for the synthesis of phenanthridine was also tested with 3-bromo acetophenone oxime **1a** under the optimized reaction conditions and TFAA, in the reaction cyclization compound **4a** was observed only 35% yield. When the cyclization reaction was performed in the presence of Hendrickson reagent instead of TFAA in the reaction 3-bromo-6-methylphenanthridine **4a** was observed in 83% yield.



Scheme 2. Scope of the aromatic oximes

Under the similar reaction conditions, the catalytic reaction was examined with various substituted ketoximes **1a-e**. Thus, 3-bromo **1a**, 3-methoxy **1b**, 2-chloro **1c**, 1-naptho **1d**, 3,4-dimethoxy **1e** substituted ketoximes with aryl iodides **2a-e** underwent cyclization reaction selectively at the less hindered *ortho* C-H bond yielding the corresponding 6-methyl phenanthridines **4b-i** in good to excellent yields (scheme 2). The cyclization reaction of 3-bromo acetophenone oxime **1a** with 4-methyl **2b**, 4-methoxy **2c**, 4-bromo **2d**, 4-CO_2Me **2e** gave the corresponding 6-methyl phenanthridines **4b-e** in excellent 80%, 73%, 78% and 68% yields respectively. Next the cyclization reaction of 3-methoxy acetophenone oxime **1b** with iodo benzene **2a**, 2-chloro acetophenone oxime **1c** with 4-methyl

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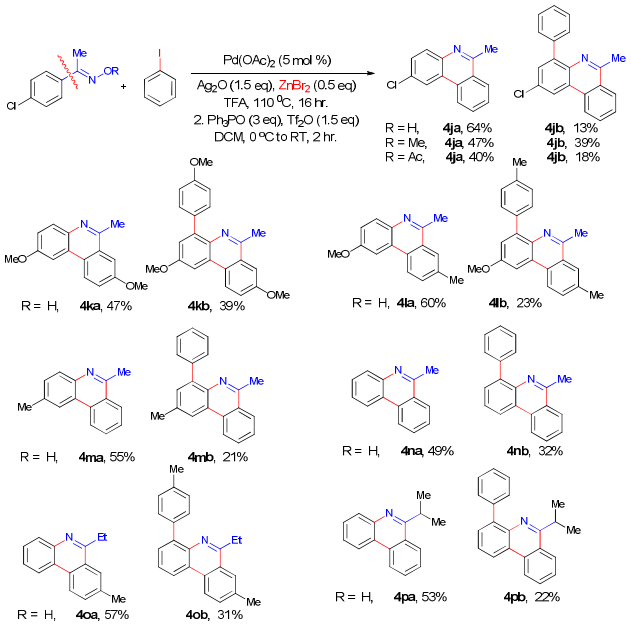
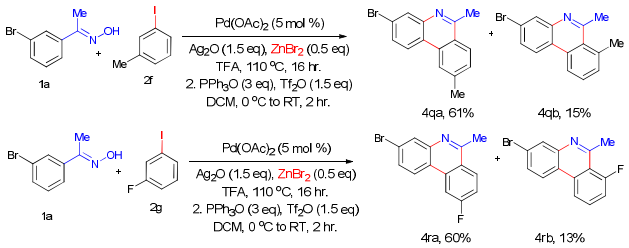
iodo benzene **2b** affording the corresponding 6-methylphenanthridines **4f** and **4g** in 79% and 65%, yields respectively. 1-naptho **1d**, 3,4-dimethoxy **1e** acetophenone oximes with iodo benzene **2a** also proceeded smoothly under similar reaction conditions providing the 6-methylphenanthridines **4h** and **4i** in 70% and 79% yields, respectively.

Next, the scope of the cyclization reaction of substituted symmetrical acetophenone oximes was examined under the optimized reaction conditions (scheme 3). Initially, the reaction was tested with 4-chloro acetophenone oxime **1f** with iodo benzene **2a** in the reaction two types of cyclization products were observed mono arylated **4ja** and di arylated **4jb** in 64% and 13% yields. The cyclization reaction was tested with *O*-methyl 4-chloro ketoxime **5a** and ido benzene **2a** under similar reaction conditions forming mono arylated **4ja** and di arylated **4jb** in 47% and 39% yields. The catalytic reaction was also tested with *O*-acyl 4-chloro ketoxime **6a**, cyclization with iodo benzene **2a**, under the optimezed reaction conditions providing mono arylated **4ja** and di arylated **4jb** in 40% and 18% yields. The cyclization of 4-methoxy ketoxime **1g**, with 4-methoxy iodo benzene **2c**, giving **4ka** and **4kb**, in 47% and 39% yields, 4-methoxy ketoxime **1g**, with 4-methyl iodo benzene **2b**, giving **4la** and **4lb**, in 60% and 23% yields. The cyclization of 4-methyl ketoxime **1h**, with iodo benzene **2a**, was also providing **4ma** and **4mb**, in 55% and 21% yields. The cyclization reaction of acetophenone oxime **1i** with iodo benzene **2a** in the raection 6-methylphenanthridine **4na** and **4nb** was observed in 49% and 32% yields. The reaction was tested with propiophenone oxime **1j,** with 4-methyl iodo benzene **2b**, 6-ethylphenanthridines **4oa** and **4ob** were observed in 57% and 31% yields. The reaction of Isobutero acetophenone oxime **1k,** with iodo benzene **2a**, was also giving 6-isopropyl phenanthridines **4pa** and **4pb** in 53% and 22% yields.



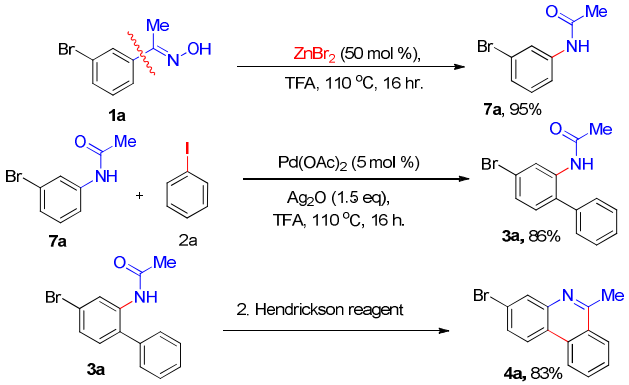
Scheme 3. Scope of the symmetrical oximes

The catalytic reaction was also tested with unsymmetrical iodo benzenes such as 3-methyl **2f**, 3-fluoro **2g,** iodo benzenes with 3-bromo acetophenone oxime **1a**, in this reaction, there are two *ortho* C-H bonds for cyclization. In both the reactions, two types of 3-bromo phenenthridines cyclization products were observed **4qa**, **4qb** in 61%, 15% and **4ra**, **4rb** in 60%, 13% yields (scheme 4).

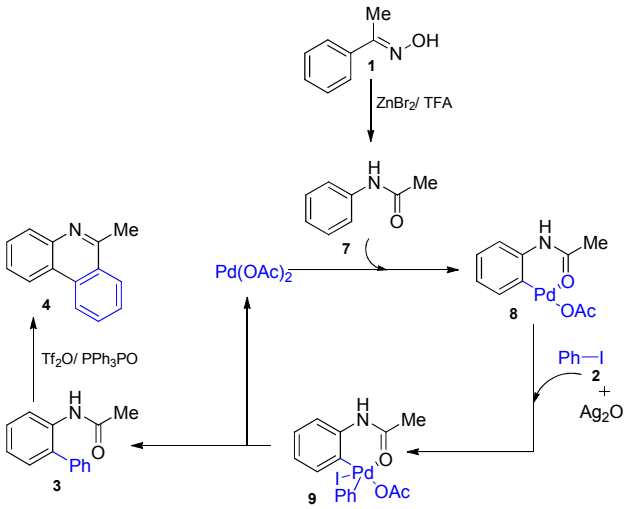


Scheme 4. Scope of the unsymmetrical iodo benzenes

The Beckmann rearrangement of 3-bromo acetophenone oxime **1a** in presence of $ZnBr_2$/TFA providing 3-bromo acetanilide **7a** in 95% yield. In meantime the catalytic reaction was also studied with 3-bromo acetanilide **7a** with iodo benzene **2a** in presence of palladium catalyst and Ag_2O gave ortho-arylated 3-bromo acetanilide **3a** in 86% yield. Further ortho-arylated 3-bromo acetanilide **3a** was converted in to phenenthridine derivatives by using Hendrickson reagent in 83% yield (scheme 5).



Scheme 5. Phenanthridine synthesis



Scheme 6. Proposed mechanism

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A possible reaction mechanism was explained for the catalytic reaction in Scheme 6.[9,16] The catalytic reaction first ketoxime **1** converting in to acetanilide **7** in presence of $ZnBr_2$/TFA via Beckman rearrangement. Acetanilide **7** oxygen chelating with palladium complex followed by *ortho* metallation of aromatics provided intermediate **8.** Trans metallation of palladium in to the aryl iodide **2** bond in presence of Ag_2O provided intermediate **9.** Next reductive elimination of intermediate **9** in presence of AcOH or TFA giving *ortho*-arylated acetanilide **3** and regenerate the active catalyst for next catalytic reaction. Later, *ortho*-arylated acetanilides **3** were coverted into phenanthridine derivatives **4** in presence of Hendrickson reagent (Ph_3PO and Tf_2O) (scheme 6).

Conclusions

In conclusion, we have developed a palladium-catalyzed synthesis of phenanthridine derivatives from the catalytic reaction of substituted aromatic ketoximes with aryl iodides. The present catalytic reaction is highly regioselective in case of unsymmetrical oximes, yielding substituted phenanthridines in good to excellent yields. In the reaction, *meta*- substituted ketoximes cyclization takes place very selectively at the less hindered aromatic C-H bond and also in the reaction oxime moiety is converting into the anilide moiety. Further, substituted arylated anilides were converted into phenanthridine derivatives in the presence of Hendrickson reagent.

Acknowledgements

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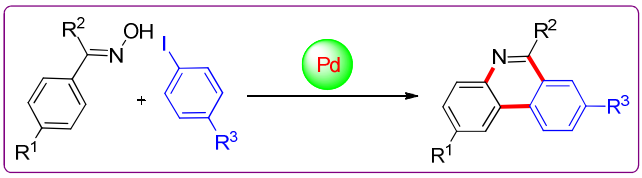
Graphical Abstract

One pot synthesis of phenanthridines using a palladium - catalyzed cyclization of aromatic ketoximes with aryl iodides via Beckmann rearrangement

Gajula Raju[a], Vijayacharan Guguloth[a] and Battu Satyanarayana[a]*



Abstract:

The catalytic reaction of ketoximes with aryl iodides via Beckmann rearrangement in the presence of catalytic amount of $Pd(OAc)_2$, Ag_2O and $ZnBr_2$ gave substituted phenanthidines in good to excellent yields. In the reaction aromatic ketoximes converted first into acetanilides in presence of $ZnBr_2$/TFA via Beckmann rearrangement then subsequent arylation in presence of palladium complex. Later, *ortho*-arylated acetanilides were converting into phenanthridine derivatives in presence of Hendrickson reagent.

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