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Rapid Synthesis of Polysubstituted Phenanthridines from Simple Aliphatic/Aromatic Nitriles and Iodo Arenes *via* Pd(II) Catalyzed Domino C-C/C-C/C-N Bonds Formation

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An efficient and straightforward method has been developed for the synthesis of polysubstituted phenanthridines from simple aryl iodides and alkyl/aryl nitriles *via* the palladium-catalyzed nucleophilic addition of aryl iodides to nitriles followed by cascade formation of C-C and C-N bonds *viz* in-situ generated imine directed sequential two fold C-H activation.

Carbon-carbon and carbon-nitrogen bonds are ubiquitously present in most of the natural and synthetic made organic molecules, particularly in heterocyclic frameworks. The constructions of these bonds are arguably the most challenging and important aspect for organic chemists. Hence, the designing of catalytic strategies for multiple bonds (C-C/C-C/C-N) formation in a one-pot manner *viz* domino approach using an inexpensive substrate with the simple catalytic system is a highly desirable and continuous effort in contemporary organic synthesis.[1,2] Functionalized heterocyclic compounds, for instance, substituted phenanthridines are the key structural motif that found in many natural products and biologically relevant compounds (Figure 1).[3,4] As a consequence of their diverse applications, several classical[5] and new synthetic methods such as radical mediated reaction,[6] metal catalyzed cross coupling[7] and photochemical approaches[8] have been developed for the synthesis of phenanthridine motifs. Although a number of protocols are available for their preparation, a majority of the strategy relies on radical mediated chemical or photochemical reactions, which essentially requires pre-functionalized starting materials. Therefore, decreasing the overall efficacy of the developed methods and not satisfying the green and sustainability aspect of chemistry.

With this understanding and our research interest in the development of a new synthetic methodology for the

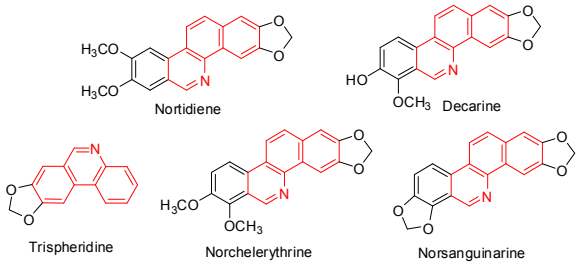
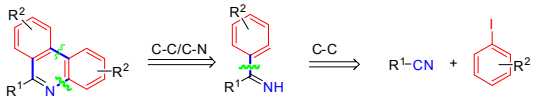


Figure 1. Bio-active compounds containing a phenanthridine core.

construction of important heterocyclic molecules from readily available starting materials.[10] We envisioned that the rapid synthesis of biologically relevant phenanthridine derivatives could be achieved in a *one-pot* manner from aryl iodides and alkyl/aryl nitriles *viz* palladium catalyzed nucleophilic addition of aryl iodides to nitriles, which would eventually generate imine *in-situ* followed by cascade formation of C-C and C-N bonds *via* imine directed sequential two fold C-H activation (Scheme 1). To the best of our knowledge, this is the first report in describing the synthesis of polysubstituted phenanthridines involving the Pd-catalyzed insertion of nitrile with dual C-H functionalization.



Scheme 1: Working Hypothesis

Nitriles represent an important class of organic molecules which have been extensively utilized for the synthesis of nitrogen-containing heterocyclic frameworks[11] and have a broad range of applications in polymer chemistry and pharmaceutical industry owing to their diverse variations.[12] Transition metal- catalyzed nucleophilic addition on nitriles was elegantly demonstrated by Larock *et al.* for the synthesis of acyclic aryl ketone products.[13] Since then, a remarkable advance in this field has been achieved. In 2013, Hsieh and co-

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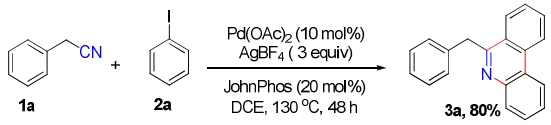
workers reported a method for the synthesis of fluorenones from aryl iodides and aryl nitriles under palladium catalyzed conditions with limited substrate scope.[14] Considering these facts and for validating our hypothesis, we began our investigation by selecting 2-phenylacetonitrile **1a** and phenyliodide **2a** as model substrates. In a general procedure, **1a** and **2a** were treated with $Pd(OAc)_2$ (10 mol%), $AgBF_4$ (3.0 equiv.) and TFA (20 mol%) in toluene at 130 °C for 48 h afforded the phenanthridine **3a**, in 17% yield. However, the outcome of this results was quite opposite from the previously described method.[14] We further optimized the reaction for this particular substrate by carrying out extensive screening of solvent, oxidant, ligand, time and temperature to obtain the optimum yield (for detailed optimization studies, see Supporting Information, Table S1-S5). After judicious optimization, we concluded that reaction of **1a** with iodobenzene **2a** in presence of $Pd(OAc)_2$ (10 mol%), $AgBF_4$ (3.0 equiv.), JohnPhos (20 mol%), in DCE at 130 °C for 48 h afforded the product **3a** in 80% yield (Scheme 2). Surprisingly, under the optimized reaction conditions, there was no evidence of α-arylation, which was some concern due to the presence of active C-H bond adjacent to nitrile group.[15]

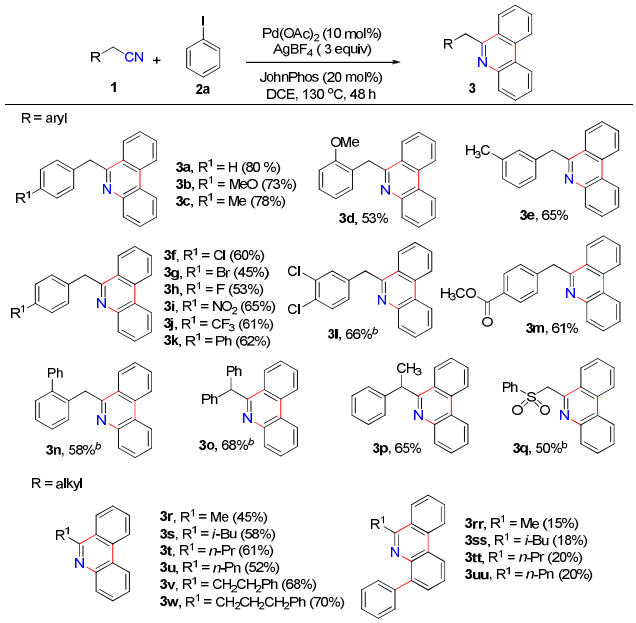


Scheme 2. Synthesis of phananthridiene from 1a and 2a

Having obtained optimal reaction conditions, we set out to explore the scope of this unique approach with different aliphatic nitriles with respect to iodobenzene and the results are listed in Table 1. Initially, aryl-acetonitriles **1a-e** bearing electron donating groups at different positions (*ortho*, *meta,* and *para)* were tested under optimized reaction conditions and furnished the desired product **3a-e** in good yields(53-80%). Furthermore, when moderate electron withdrawing groups such as bromine, chlorine, fluorine were introduced at *para*-position of an aryl ring, expected products **3f-h** also procured in moderate to good yields (45-60%).

Pleasingly, aryl nitriles carrying strong electron withdrawing group on phenyl ring such as *-NO_2* and *-CF_3*, afforded the phenanthridine derivatives **3i-j** in a reasonably good yields (61-65%). Similarly, the presence of ester group at the *para* position does not affect the overall outcome of the transformation (**3m,** 61%) and there was no evidence of *ortho-arylated* product formation, which was a primary concern as ester group might act as a directing group. The reaction condition is also tolerant with sterically hindered nitriles such as diphenylacetonitrile **1o** and α-methyl phenylacetonitrile **1p** to produce the corresponding phenanthridines (65-68%, **3o-p**). Similarly, phenylsulphonylacetonitirle was also compatible under the optimized reaction condition, affording sulfonylatedphenanthridine **3q** albeit in moderate yield (50%), which is otherwise difficult to synthesize in one step. Next, linear chain aliphatic nitriles such as *methyl*, *iso-butyl*, *propyl* and *pentyl* nitriles were reacted well with iodobenzene under standard conditions to afford the corresponding products in moderate to good yields (**3r-u,** 45-62%). It is worthy to note that in case of short-chain aliphatic nitriles **1r-1u**, further arylation occurred at the 4th position of the phenanthridine ring and providing 4/6- substituted phenanthridine derivatives in low yields (**3rr-uu,** 15-20%).

Table 1. Scope of Aliphatic Nitriles for the Synthesis of Phenanthridiene Derivatives[a]



[a]Reaction Conditions: **1** (0.25 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (10 mol%), $AgBF_4$ (0.75 mmol), JohnPhos (20 mol%) in 2.5 mL of DCE at 130 °C for 48 h. [b]72 h.

We next examined the generality and limitation of this tandem approach for the synthesis of 6-aryl substituted phenanthridines by employing arylnitriles **4** with aryliodides **2** as the coupling partner. To our delight, when arylnitriles **4a-g** containing the electron donating groups such as *methyl*, *methoxy,* and *3,4-dioxy* at various positions of the aromatic ring were subjected under similar reaction conditions, the desired products **5a-g** isolated in a good yields (65-75%) with control of regioselectivity. The ambiguity of structure was eventually confirmed by the single-crystal X-ray diffraction analysis of **5c** (CCDC no. and other details, see SI)[16] in addition to the spectroscopic evidence. This high-level selectivity is an attractive feature of this reaction. Fortunately, when the reaction was carried out with 4 mmol of benzonitrile **4a** under standard reaction conditions, the desired phenanthridine **5a** was isolated in 56% yield along with some uncharacterized compounds and starting materials (15%). Reaction condition is also tolerant towards various *halo* functional groups at *meta* and *para* positions in the aryl nitriles component (**5h-k,** 58-66%). Remarkably, the presence of strong electron-withdrawing group such as trifluoromethyl at the *para* position did not hamper the overall efficiency of the product yield (**5l,** 72%). To further diversify the scope of this transformation, another reaction partner, aryliodides containing either

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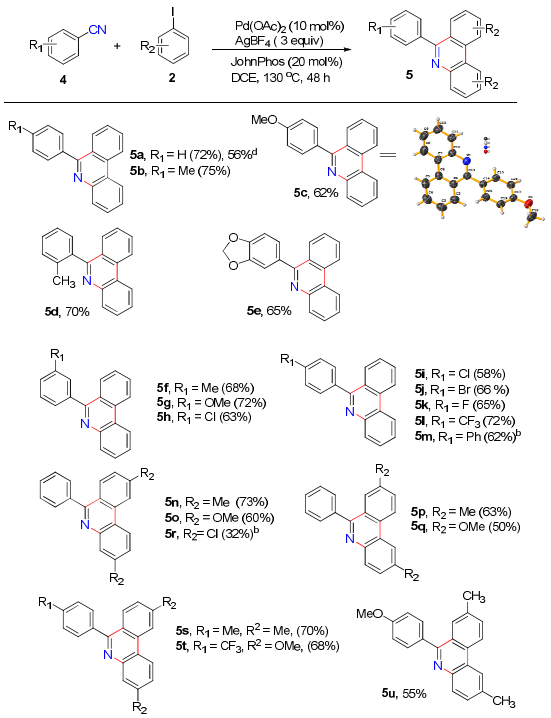
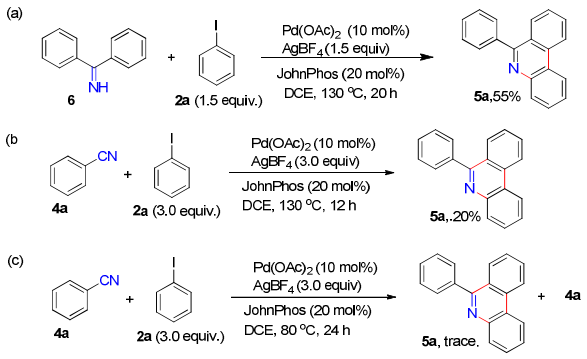
electron-donating or electron withdrawing groups were also tested under similar conditions. Aryiodide containing an electron donating group **(2n-o)** at *para* position reacted well to afford desired product in good yields (**5n-o**, 60-73%). The reaction of *meta*-substituted aryl iodides **2p-q** containing two possible sites for C-H bond activation proceeded with high regioselectivity to give the less-hindered regioisomeric products (**5p-q,** 50-63%).

Table 2. Scope of Arylnitriles with Aryliodide for the Synthesis of Phenanthridine Derivatives.[a]



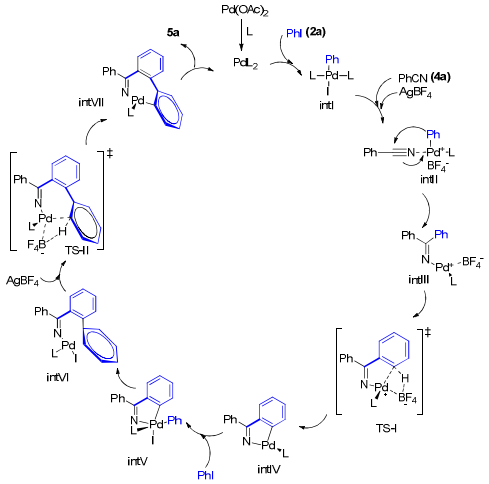
[a]Reaction Conditions: **4** (0.25 mmol), **2** (0.75 mmol), $Pd(OAc)_2$ (10 mol%), $AgBF_4$ (0.75 mmol), JohnPhos (20 mol%) in 2.5 mL of DCE at 130 °C for 48 h. [b]72 h. [d]Reaction was carried out at 4.0 mmol scale.



Scheme 3. Control Experiments.

Importantly, we observed that electron-rich aryl iodides were more reactive and gave better yields than those possessing electron withdrawing groups such as *ester* and *nitro* groups. Of note, moderate electron withdrawing group survived well under reaction conditions. Further, tri-substituted phenanthridine derivatives were synthesized in good yield (**5s-u,** 55-70%).

In order to understand the mechanistic aspect of this unprecedented transformation, some control experiments were performed (Scheme 3). Based on the outcome of this transformation, we believe that imine (*in-situ* generated) might be the potential reaction intermediate.[13,14] To confirm our hypothesis imine **6** was treated with iodobenzene **2a** under optimized conditions (Scheme 3a), and the desired product **5a** was isolated in 55% yield. These results justify our hypothesis and *in-situ* generated pallada-imine species eventually direct the sequential formation of C-C and C-N bonds in a *one-pot* manner. Similarly, we proceeded the reaction with a short period (12 h) and at a lower temperature (80 °C) and found that the desired product formed in meager yield (Scheme 3b and c) and rest starting materials was recovered.



Scheme 4. The catalytic cycle of phenanthridine synthesis.

Guided with these supporting evidence and literature reports,[17] a plausible reaction mechanism of this transformation is outlined in Scheme 4. First, aryl palladium species **intI** is generated by oxidative addition with phenyl iodide **2a**. Subsequently, nitrile **4a** coordinate with the vacant site of Pd and further undergoes for halide exchange in the presence of $AgBF_4$ to form intermediate **intII** and followed by intramolecular 1,3 migration of the aryl group from the Pd center to carbon to form pallada-imine species **intIII**. Subsequently, *in-situ* generated pallada-imine species **intIII** form a five-membered Pd complex **intIV** *via* an agostic C-H interaction (TS-I). Then, species **intIV** undergoes oxidative addition/reductive elimination to deliver the intermediate **intVI**. Further, intermediate **intVI** form seven-membered cyclometalated species **intVII** *via ortho* C-H bond activation through base assisted concerted palladation/deprotonation (TS-II). Finally, a reductive elimination leads to the desired phenanthridine **5a** and regenerate palladium which goes on to the catalytic cycle.

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In summary, we have developed an efficient and unprecedented route for the direct synthesis of valuable phenanthridine derivatives from simple and readily available starting materials. The overall reaction proceeds *via* palladium-catalyzed nucleophilic addition reaction followed by cascade formation of carbon-carbon (*ortho*-arylation) and carbon-nitrogen bonds through sequential two fold C-H activation. Some of the noteworthy features of the present study are: a) use of commercial and nontoxic starting materials, b) straightforward and practical reaction conditions, c) atom and step economical, d) highly regioselective, d) cascade formation of C-C/C-C and C-N bonds, e) broad substrate scope, and f) gram scale synthesis. The developed synthetic methods hold great potential and will stimulate further research in the synthesis of diverse heterocycles.

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Conflicts of interest

The authors declare no conflict of interest.

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