**Synthesis of Azalurenone Alkaloids by Pd- mediated Intramolecular Oxidative Cyclisation Protocol**

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## Introduction

The formation of C-C bonds remains the major synthetic challenge in organic chemistry. The use of transition metals in forming the C-C bonds was probably the most studied area of research in organic synthesis in the last half of the century.[1]Among the transition metals palladium was the most relied one to be used in organic synthesis. This reliance made it to award the Nobel Prize in 2010 in chemistry on transition metal catalysed cross-coupling reactions.[2] The palladium sometimes prove to be superior to the others owing to 1) compatible with different functional groups 2) it can functionalize all three types $sp^3$, $sp^2$ and sp carbon atoms 3) most of the palladium catalyst can tolerate air and moisture, and produces desired compounds in reasonably milder reaction conditions.[3] Furthermore, palladium shows low toxicity and easy to separate from the reaction mixture after the reaction is complete.

Fluorenone (**2.1**) is a cyclopentenone derivatives containing a five-member ketone fused with two benzene rings. When one of the fused benzene ring is substituted by pyridine ring compound referred to as azafluorenone (**2.2)** (Fig. 2.1).

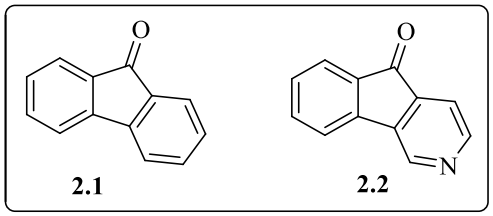



**Fig. 2.1** Fluorenone and azafluorenone

The Azafluorenones constitute a growing class of alkaloids. The representative alkaloids of this kind having potential bioactivity include the compounds **2.3-2.5** as shown in Fig. 2.2.[4] Onychine (**2.3**) showed activity against *C. albicans* B311 and also exhibited antimicrobial activity against *S. aureus* NCTC8530, *B subtitles* IFO 3007, *Escherichia coli* IFO 3545 and *Saccharomyces cerevisiae* IFO 0203.[5, 6] Polyfothine (**2.4**) shows DNA-damaging activity.[7]

Isoursuline (**2.5**) showed anti-malarial activity against *Plasmodium falciparum* at micromolar concentrations.[8] Considering the importance of azafluorenones, a general and convenient synthetic methodology still is ongoing research. Several such compounds and their derivatives are important for biomedical applications[9-31].

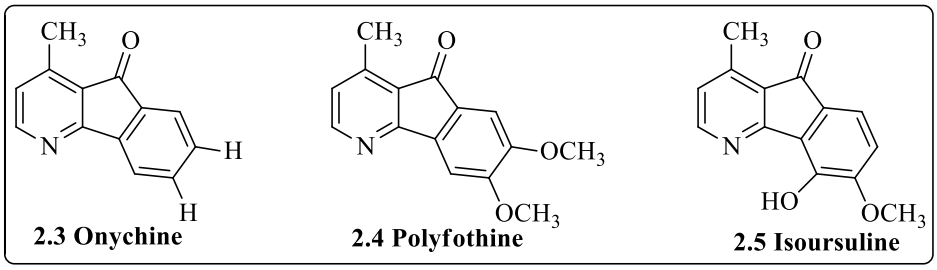
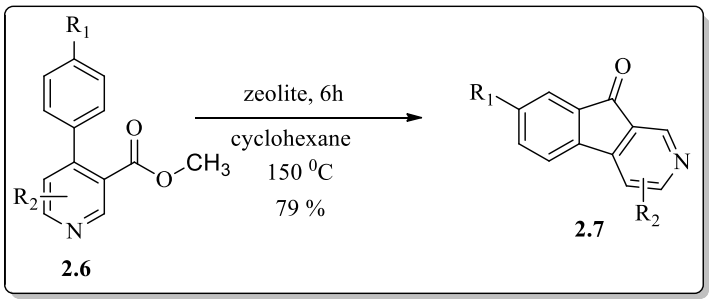


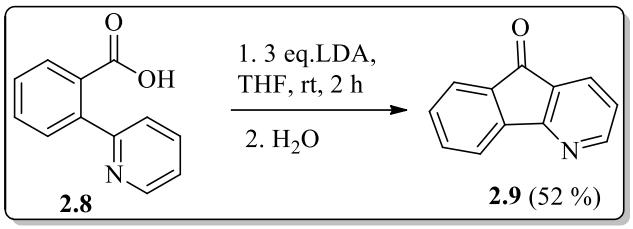

**Fig. 2.2**: Some bioactive azafluorenone alkaloids

Nitrogen containing heterocyclic compounds is prevalent in a wide range of naturally occurring bioactive molecules and clinical medicines.[32]The azafluorenone represent a major portion of these types. Construction of azafluorenone ring system is an emerging field of research for the last few decades. Several attempted syntheses have been reported in literature. Different group of chemists have accomplished the synthesis of azafluorenones *via* both the catalytic and non-catalytic ways. But, still development of new synthetic strategies is needed to meet the structural diversity and synthetic challenges. Among the reported procedures, Sreekumar *et al.*[33] have synthesized substituted azafluorenone **2.7** by zeolite catalyzed cyclization of appropriately substituted arylpyridines **2.6** (Scheme 2.1).



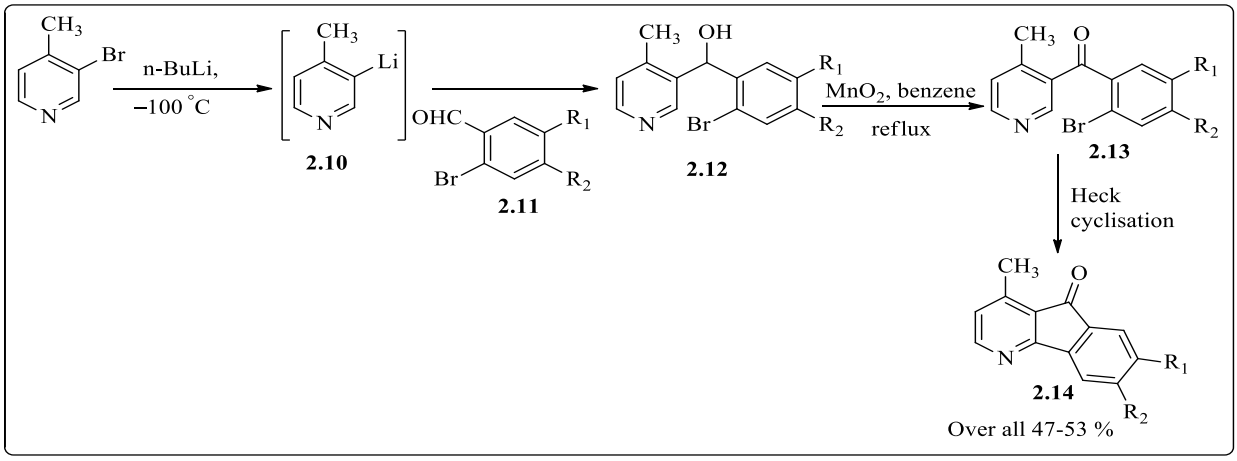

**Scheme 2.1:** zeolite catalysed synthesis of azafluorenone

In alternative approach a LDA mediated ring closing of 2-(2 and 4-pyridyl)-benzoic acids **2.8** has been reported by Mongin *et al.*[34] to synthesize azafluorenone **2.9** (Scheme 2.2). At room temperature LDA abstracts the remote hydrogen in the pyridine ring, and this lithiated intermediate undergos an intra-molecular cyclization to afford the azafluorenone in 52 % yields.



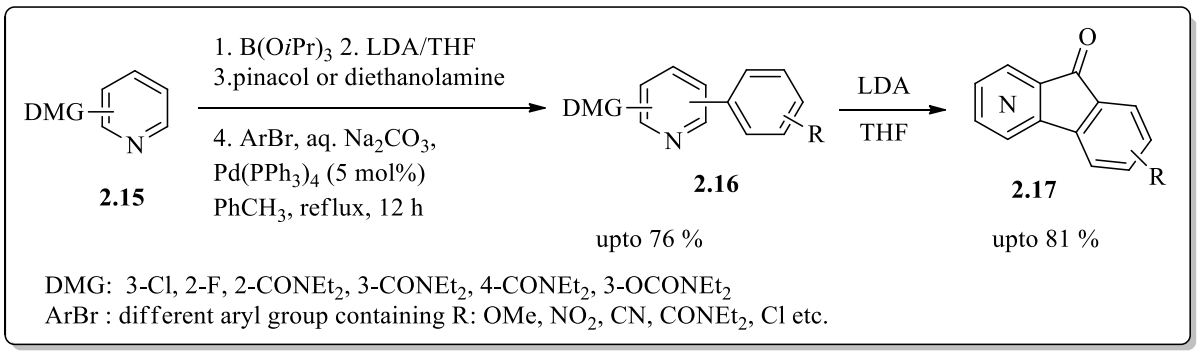

**Scheme 2.2:** LDA mediated synthesis.

Kraus *et al.*[4] devised a three step protocol for the formation of azafluorenone **2.14** *via* nucleophilic attack of 3-lithio-4-methylpyridine **2.10** on suitably substituted 2-bromobenzaldehyde **2.11** followed by successive steps of $MnO_2$ oxidation of resulting alcohols **2.12** and the Heck cyclization of keto compounds **2.13** to afford **2.14** in 53% yield (Scheme 2.3).



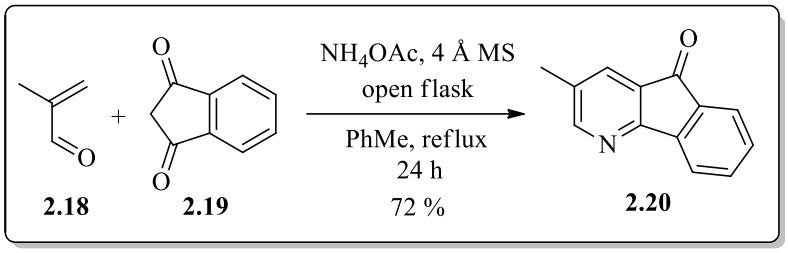

**Scheme 2.3:** Three step synthesis azafluorenone

A one pot synthesis of azabiaryls has been achieved by Snieckus *et al. via* Pd-catalysed Suzuki-Miyaura cross-coupling of **2.15** and arylhalide to form the biaryl intermediate **2.16**. The resulting biaryl **2.16** were condensed to azafluorenone **2.17** *via* LDA mediated cyclization in 81 % of yields (Scheme 2.4).[35]



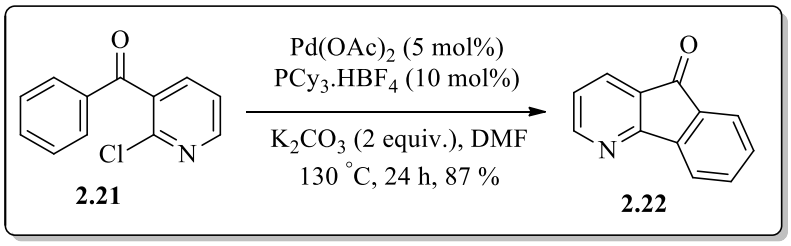

**Scheme 2.4**: One pot synthesis of azabiaryls

A three-component reaction strategy has been adopted by Constantieux and co-workers to synthesize azafluoreone and substituted pyridine derivatives (Scheme 2.5). Metal free Michael-addition mediated three component reaction between suitable acceptor **2.18**, donor **2.19** and ammonium acetate results the formation of 3-methylazafluorenone **2.20** in good yields.[36]




**Scheme 2.5**: Three component reaction for the synthesis of azafluorenone

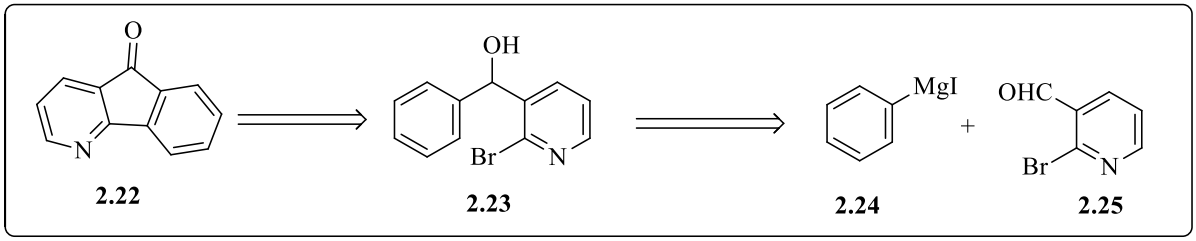
In another report Mongin groups described a Pd-catalyzed intramolecular arylation of diaryl ketone to synthesize azafluorenone. Different diaryl ketone **2.21** containing chlorine at the 2-position undergoes a Pd-catalyzed CH- activation type intramolecular arylation to afford the azafluorenone **2.22** in good to excellent yields (Scheme 2.6).[13]




**Scheme 2.6**: Pd-catalysed synthesis of azafluorenone

In continuation of our search for the Pd-catalyzed new reactions methodologies, we mainly focused on development of newer synthetic routes for the construction of carbocycles and heterocycles involving Heck type coupling reactions. Recently in our lab, cyclopentenone has been efficiently synthesized *via* Pd-catalysed intramolecular *5-exo-trig* oxidative Heck cyclization.[26, 37-59]In the extension, we aimed to explore the intramolecular oxidative Heck cyclization in synthesizing azafluorenone. Consequently, we have developed a short and efficient method for formation of azafluorenone *via* intramolecular oxidative Heck cyclization. We envisioned that intramolecular oxidative Heck cyclisation of alcohol **2.23** can be used for the synthesis of azafluorenone **2.22** in two step process (Scheme 2.4). Alcohol

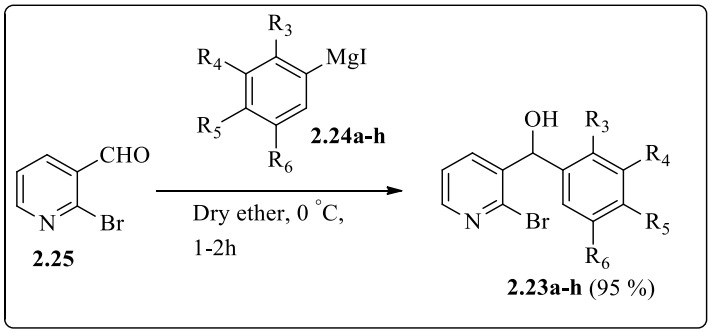
**2.23** can be obtained from reaction of 2-bromopyidine-3-carboxaldehyde **2.25** and corresponding Grignard reagent **2.24** of the iodobenzene.




**Scheme 2.4:** Retrosynthetic analysis

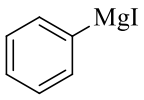
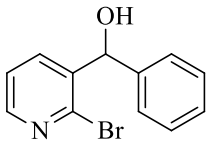
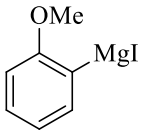
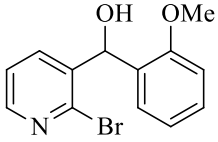
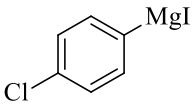
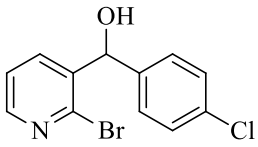
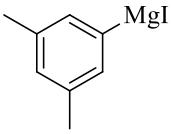
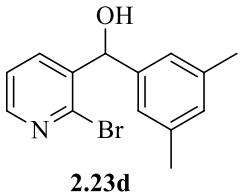
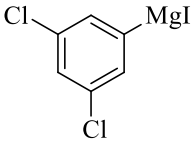
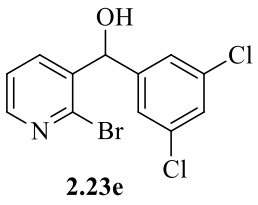
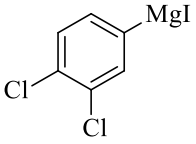
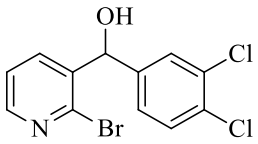
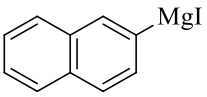
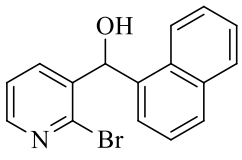
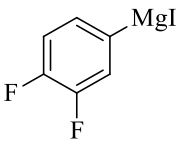
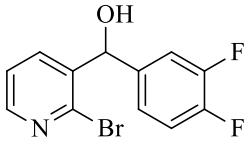
**Results and discussion**

In this paper we present the synthesis of different substituted azafluorenone *via* oxidative intra-molecular Heck cyclization protocol. The Heck precursor alcohols **2.23a-h** were synthesised *via* reaction of the Grignard reagents **2.24a-h** of corresponding iodides upon 2-bromopyridine-3-carboxaldehyde **2.25**. The Grignard reagents were easily prepared from fresh magnesium turnings activated by pinch of iodine and their corresponding halides (iodide or bromide) in refluxing dry ether medium. Then these freshly prepared Grignard reagents were added drop wise into an ice-cold ethereal solution of 2-bromoprydine-3-carboxaldehyde **2.25**, which gave our desired Heck precursor alcohols **2.23a-h** in quantitative yields (Scheme 2.5). The results are shown in the Table 2.1. And finally these alcohols **2.23a-h** when subjected to the Heck reaction conditions afforded different substituted azafluorenones (Scheme 2.6).




**Scheme 2.5:** Synthesis of alcohol precursors

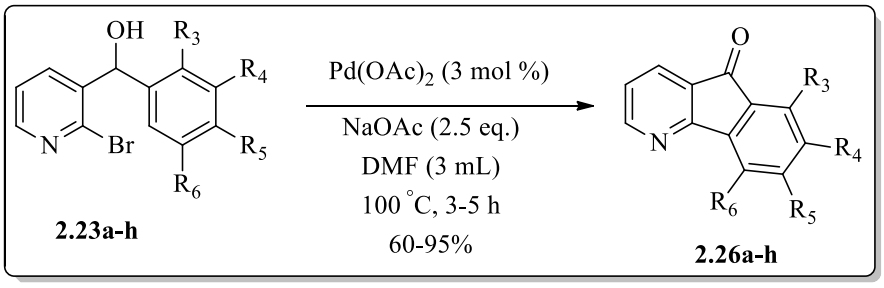
**Table 2.1:** Synthesis of the cyclization precursor alcohol[a]

| Entry | Grignard | Alcohols | Yields (%)[b] |
|---|---|---|---|
| 1 |  **2.24a** |  **2.23a** | 95 |
| 2 |  **2.24b** |  **2.23b** | 70 |
| 3 |  **2.24c** |  **2.23c** | 93 |
| 4 |  **2.24d** |  **2.23d** | 70 |
| 5 |  **2.24e** |  **2.23e** | 95 |
| 6 |  **2.24f** |  **2.23f** | 92 |
| 7 |  **2.24g** |  **2.23g** | 89 |
| 8 |  **2.24h** |  **2.23h** | 73 |

a) Fresh Mg turnings (3 equiv. w. r. to iodocompounds), pinch of iodine, flame heating for activation Mg, 2-3 mL of dry $Et_2O$, iodo compound (1.5 equiv. w. r. to aldehyde substrate), room temperature, 1 h.

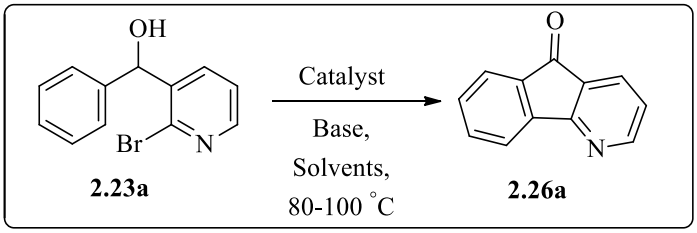
b) Isolated yields after purification.

Initially we started our journey for the oxidative cyclization with the alcohol **2.23a**.When representative alcohol **2.23a** was reacted with the catalytic system of $Pd(OAc)_2$, $Cs_2CO_3$ and $PPh_3$ it gave **2.26a** in 50 % yields at 80 ˚C temperature. Changing the base $Cs_2CO_3$ to $Na_2CO_3$ increase the product formation upto 83 %. A further increment of formation of azafluorenone to 95 % was obtained while using NaOAc and, with increasing the reaction temperature from 80 ˚C to 100 ˚C. During the search of finding a standard cyclization reaction conditions it was observed that absence of the ligand did not hampered the product formation. Among the sources of palladium (0) catalysts, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ gave the formation of only 50 % and 52 % of **2.26a** respectively (entry 7,9 ; Table 2.2). The formation of 40 % to 86 % of **2.26a** was obtained at the elevated temperature of 100 °C using other palladium(II) source, such as $PdCl_2$, $Pd(PPh_3)_2Cl_2$ etc. The $Pd(OAc)_2$ (5 mol%) and NaOAc (2.5 equiv.) was found to be the most high yielding catalytic system during this study. The azafluorenone **2.26a** was obtained in 50 to 87 % yields while using acetonitrile and DMA as solvent. The solvent DMF was proved to be most effective solvent system at 100 °C. During the screening, the optimal reaction conditions was set to be the Pd $(OAc)_2$ (3 mol%), NaOAc (2.5 equiv.), DMF (3 mL) and, 100 ˚C (entry 5 , Table 2).




**Scheme 2.6:** Intramolecular oxidative Heck cyclisation

**Table 2.2:** Optimisation of intramolecular Heck cyclization[b]




| Entry | Catalyst | Ligand | Base | Solvent | Temp (˚C) | Yields(%)[c] |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DMF | 80 | 50 |
| 2 | $Pd(OAc)_2$ | $PPh_3$ | $K_2CO_3$ | DMF | 80 | 70 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | $Na_2CO_3$ | DMF | 80 | 83 |
| 4 | $Pd(OAc)_2$ | $PPh_3$ | NaOAc | DMF | 100 | 90 |
| 5 | $Pd(OAc)_2$ | - | NaOAc | DMF | 100 | 95 |
| 6 | $Pd(CH_3CN)_2Cl_2$ | - | NaOAc | DMF | 100 | 40 |
| 7 | $Pd_2(dba)_3$ | - | NaOAc | DMF | 100 | 50 |
| 8 | $PdCl_2$ | - | NaOAc | DMF | 100 | 86 |
| 9 | $Pd(PPh_3)_4$ | - | NaOAc | DMF | 100 | 52 |
| 10 | $Pd(PPh_3)_2Cl_2$ | - | NaOAc | DMF | 100 | 62 |
| 11 | $Pd(OAc)_2$ | - | NaOAc | $CH_3CN$ | 100 | 80 |
| 12 | $Pd(OAc)_2$ | - | NaOAc | DMA | 100 | 87 |
| 13 | $Pd(OAc)_2$ | - | NaOH | DMF | 100 | 53 |

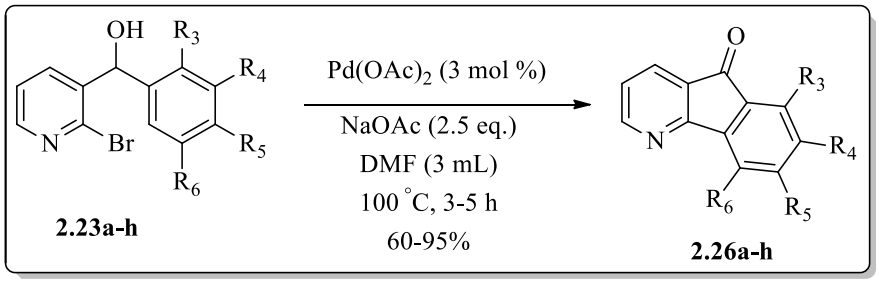
b) 1 mmol of substrate **2.23a-h**, $Pd(OAc)_2$ (3 mol%), NaOAc (2.5 equiv.), DMF (3 mL), 100 $^0$C, 3 h.

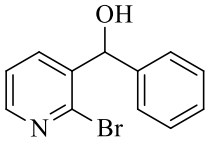
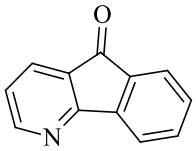
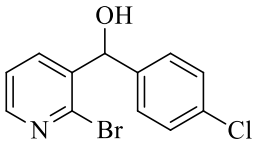
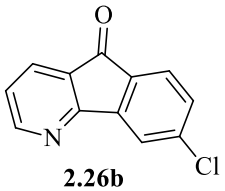
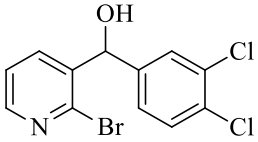
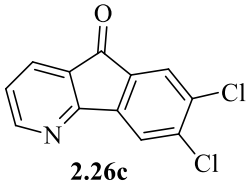
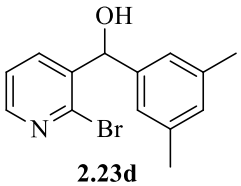
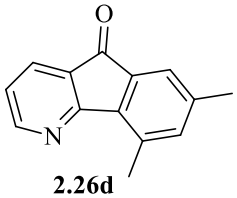
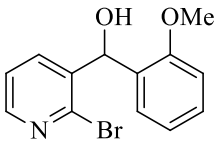
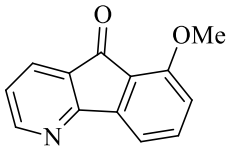
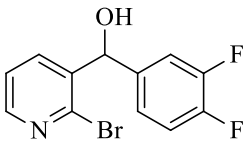
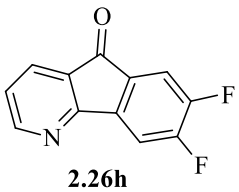
c) Isolated yields after purification.

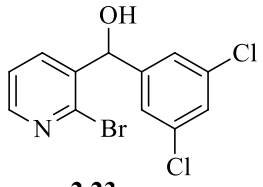
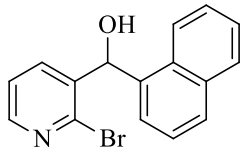
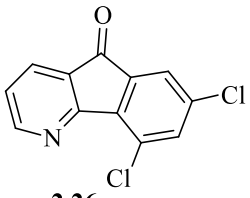
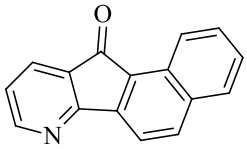
Then with the set optimal reaction conditions in hand, we have further studied the general scope and applicability of our reaction protocol. Different substituted azafluorenones (**2.26a-h)** with varying substituents ranging from electron withdrawing to electron donating groups were efficiently synthesized. The results are described in the Table 2.3. It was clear from the Table 2.3 that substituents chloro and fluoro retarded the oxidative cyclisation to afford the azafluorenone in 61 to 75 %. In contrast, the electron donating groups, like methyl and methoxy, enhances the oxidative addition with comparatively higher yields of products. Interestingly the naphthalene moiety has been well tolerated by this synthetic method. Our

findings demonstrate that this synthetic strategy is very general and efficient one with both the electron donating and electron withdrawing substituents.

**Table 2.3:** Synthesis of azafluorenone derivatives[d]




| Entry | Alcohols | Products | Yields (%) |
|---|---|---|---|
| 1 |  **2.23a** |  **2.26a** | 95 |
| 2 |  **2.23b** |  **2.26b** | 75 |
| 3 |  **2.23c** |  **2.26c** | 68 |
| 4 |  **2.23d** |  **2.26d** | 93 |
| 5 |  **2.23e** |  **2.26e** | 78 |
| 6 |  **2.23f** |  **2.26h** | 61 |

| | | | |
|---|---|---|---|
| 7<br><br>8 |  <br>**2.23g**<br>  <br>**2.23g** |  <br>**2.26g**<br>  <br>**2.26g** | 74<br><br>53 |

c) 1 mmol of substrate **2.23a-h**, $Pd(OAc)_2$ (3 mol%), NaOAc (2.5 equiv.), DMF (3 mL), 100 °C, 3 h.

d) Isolated yields after purification.

While searching the most probable rationale of the reaction, one very interesting observation was that the reaction did not required any added ligand in the catalytic system. Only the catalyst $Pd(OAc)_2$ could complete the whole catalytic cycle to formed the product **VI** from the starting material **I**. That is something in the reaction mixture reduced Pd (II) to Pd (0) which was the actual catalyst. We assumed that substrate itself with the nitrogen lone pair in the pyridine moiety can play the ligand's role and reduces Pd (II) to Pd (0) (Fig 2.3) to complete the reaction cycle.

**Plausible Reaction Mechanism**

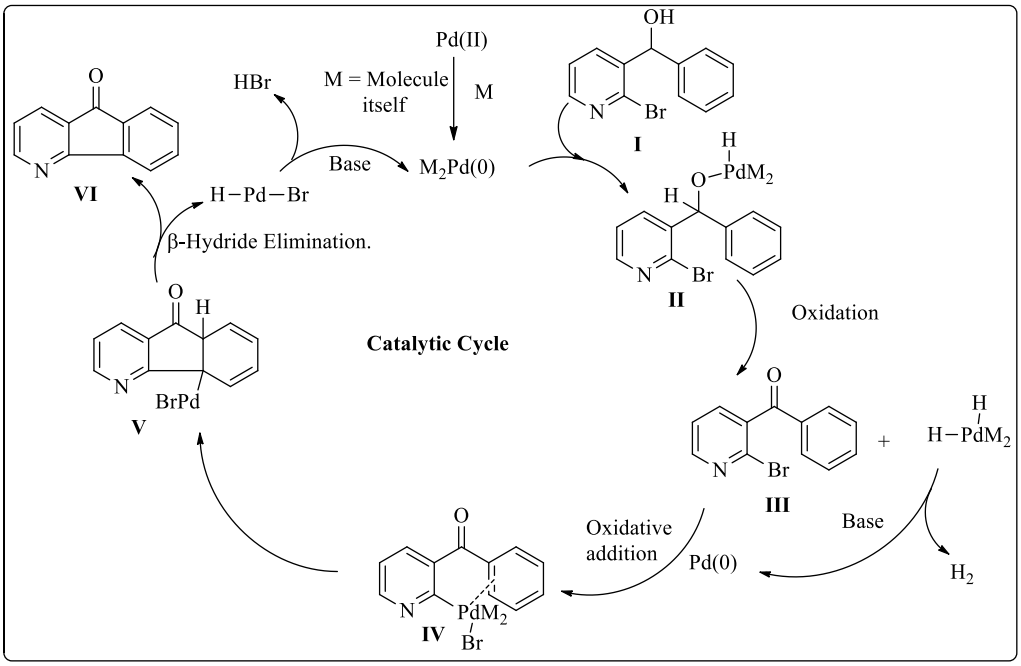


**Fig 2.3:** Catalytic Cycle of intramolecular Heck cyclisation[15]

## Conclusion

In conclusion, we have developed a two-step strategy for the construction of azafluorenone alkaloids. Our developed method is simple and general one with good range of substrate scope and functional group tolerance. In addition this method needs inexpensive reagents and catalysts and afforded excellent yields of azafluorenone under mild reaction conditions. We believe that our method have the potential to be utilized in total synthesis of azafluorenone based bioactive natural products.

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