Synthesis of Phenanthridine by Palladium Catalyzed Suzuki Coupling and Condensation Reaction

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Introduction

Transition metal catalyzed cross-coupling reactions such as Suzuki-Miyaura[1], Heck[2-10], Stille[11], Hiyama,[12] Negishi[13], and Sonogashira reactions are likely to be the most power tool for the formation of C-C bonds for the past four decades. All these reactions have shown their widespread applicability ranging from academic area to research. Some of the reactions have also been applied in pharmaceuticals, agrochemicals, and fine material industries. The Suzuki-Miayura cross coupling was remained the most attractive alternative for C-C bonds formation since its discovery in 1979. The wide range of applicability of this reaction is largely attributed to mild reaction conditions, broad range of functional group tolerance, easy access to organo-boron reagents, and their stability under air and moisture. Furthermore, boron compounds show low toxicity and easy to separate boron from the reaction mixtures.

Phenanthridine (**3.1**) is a nitrogen heterocycle that is the basis of DNA-binding fluorescent dyes through intercalation. Ethidium bromide and propidium iodide are the examples of such intercalating dyes. Phenanthridine is an isomeric compound of acridine (**3.2**) (Fig. 3.1).

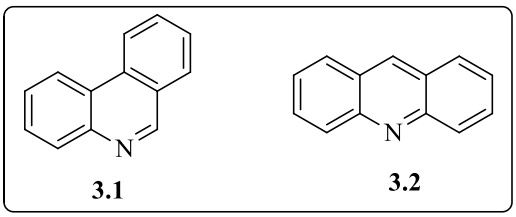


Fig. 3.1: Phenanthridine and acridine

Phenanthridine was first discovered by Ame Pictet and H. J. Ankersmit in 1891 by pyrolysis of the condensed product of benzaldehyde and aniline. Earlier, phenanathridine and related

compounds were prepared using mainly Pictect-Hurbert and modified Morgan-Walls type of condensation reactions.

3.1.1 Bioactivity and natural occurrences

Phenanthridines and Benzo[*c*]phenanthridines are prevalent in a large number of natural and unnatural bioactive molecules exhibiting important pharmacological activities and applications, such as antibacterial, antiprotozoal, and anticancer agents. A well known member of this class of compound is ethidium (**3.3**), a common DNA intercalator and stain. Representative alkaloids of this kind with promising pharmacological potential are nitidine (**3.4**), chelerythrine (**3.5**), sanguinarine (**3.6**) (Fig. 3.2).

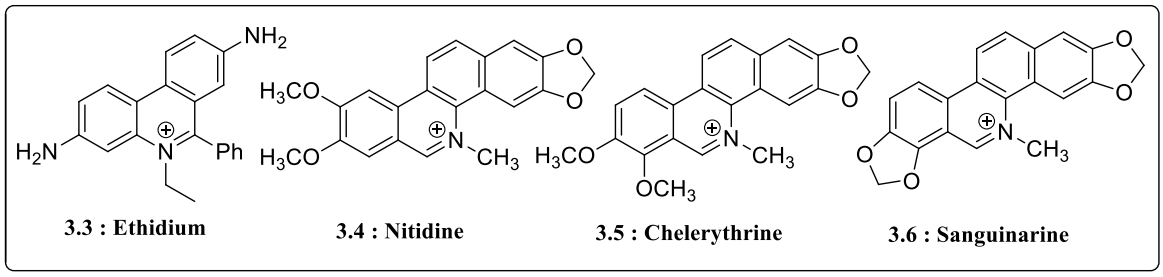
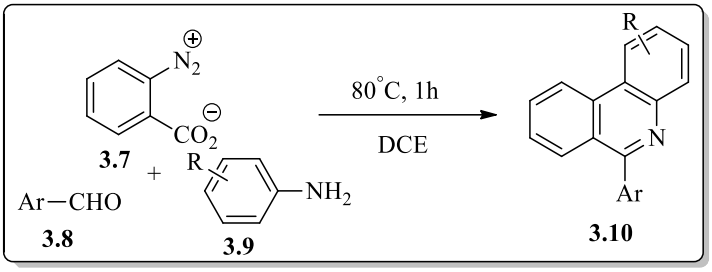


Fig. 3.2: Some phenanathridiene and benzo[*c*]phenanthridine alkaloids.

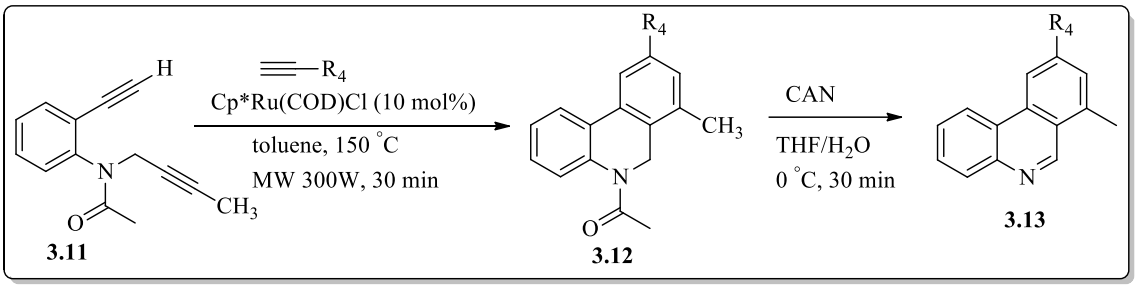
Because of great importance of these compounds in biology and medicine, shorter and high yielding synthetic methodologies are of great interest in synthetic organic chemistry as isolation from natural sources described is less than 1%.

In literature, various reports are there to construct these heterocycles. Among them, the Bischler-Napieralski cyclisation has been extensively used to synthesise phenanthridine derivatives. *Wang et al.* reported a cascade approach to 6-arylphenanthridine **3.10** from aromatic aldehyde **3.8**, aniline **3.9** and benzenediazonium-2-carboxylate **3.7** (Scheme 3.1). The *in situ* generated benzyne from benzenediazonium-2-carboxylate **3.7** underwent a [4+2] cycloaddition reaction with the imine formed from aromatic amine and aldehyde to give dihydrophenanthridine. Finally, dehydrogenation in the reaction medium gave the 6-arylated phenanthridine **3.10** in quantitative yields.



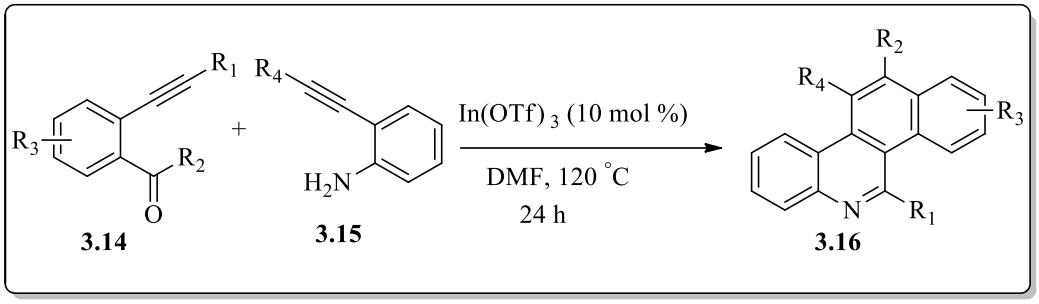
Scheme 3.1: Cascade approach to phenanthridine

Deiters *et al.* described a cyclotrimerization approach to build the phenanthridine moiety. Different transition metal complexes have been evaluated to catalyze the cyclotrimarization and the Ru-catalyst results the best. The Ru-catalyzed microwave assisted [2+2+2] cyclotrimerisation of diyne **3.11** afforded to dihydrophenanthridine **3.12.** Then CAN mediated deprotective aromatization ultimately gave the substituted phenanthridine **3.13** (Scheme 3.2).



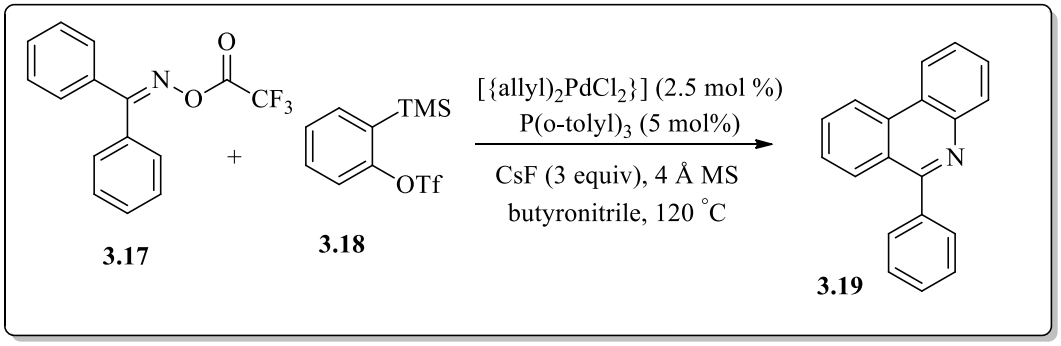
Scheme 3.2: Cyclotrimerisation towards phenanthridine

In other way Yanada *et al.* constructed analogous benzo[*c*]phenanthridine *via* Lewis acid catalyzed tandem cyclization. The Lewis acid $In(OTf)_3$ cyclizes *ortho*-alkynylbenzaldehydes **3.14** and *ortho*-alkynylanilines **3.15** to form the benzo[*c*]phenanthridine **3.16** in very good yields (Scheme 3.3). A series of other Lewis catalysts have been screened to effect the cyclization and $In(OTf)_3$ was proved to be the best. The reaction goes *via* 6-*endo-dig* nucleophilic addition of carbonyl oxygen on the $In(OTf)_3$ co-ordinated electrophilic *o*-alkynyl moiety to give the pyrilium cation intermediate. The intermediate pyrilium cation undergoes a Diels-Alder type cyclization with the *o*-alkynylaniline and followed by condensation to give the final product **3.16**.



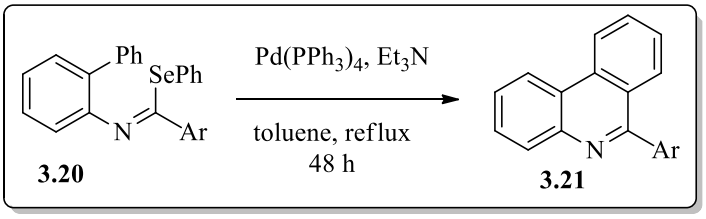
Scheme 3.3: Lewis acid catalysed Tandem cyclization

Annulation of acyloximes with aryne or alkyne has been adopted by Zhu and co-workers (Scheme 3.4). Among a series of palladium catalysts allyl-palladium complex (APC) along with a bulky phosphine ligand were the most promising catalytic system. The oxidative palladium insertion into the N-O bond of acyloxime **3.17** and *cis*-aminopalladation to the benzyne formed from the compound **3.18**, followed by intramolecular C-H activation afforded the 6-phenylphenanthridine **3.19**.



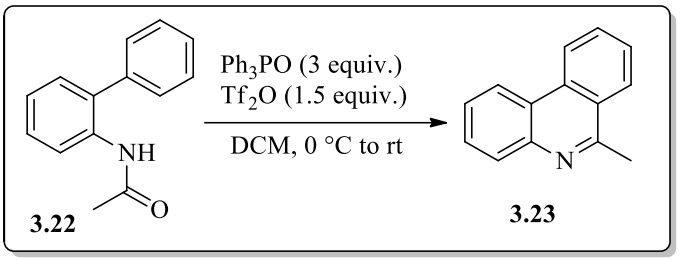
Scheme 3.4: APC –catalyzed synthesis of phenanthridine

Palladium catalyzed synthesis of phenanthridine has been accomplished by Pritchard and co-workers from imidoyl selenides. This was the first report of palladium insertion into the C-Se bond. The palladium insertion into the imidoyl selenides **3.20** followed by intramolecular cyclization and subsequent aromatization *via* the elimination of HSePh lead to the formation of substituted phenanthridines **3.21** (Scheme 3.5).



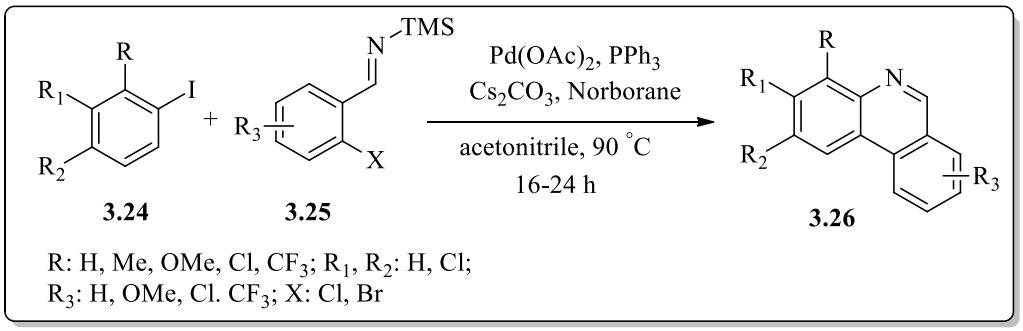
Scheme 3.5: Pd-catalysed synthesis of phenanathridine

A cascade reaction of *N*-acetylated biaryl **3.22** for the construction of phenanthridine ring has been described by Yao *et al.* The amide of biphenyl-2-amine undergoes a cascade annulations reaction initiated by Hendrickson reagents and subsequent Friedel-Crafts reaction to afford the 6-methyl phenanthridine **3.23** under mild reaction conditions (Scheme 3.6).



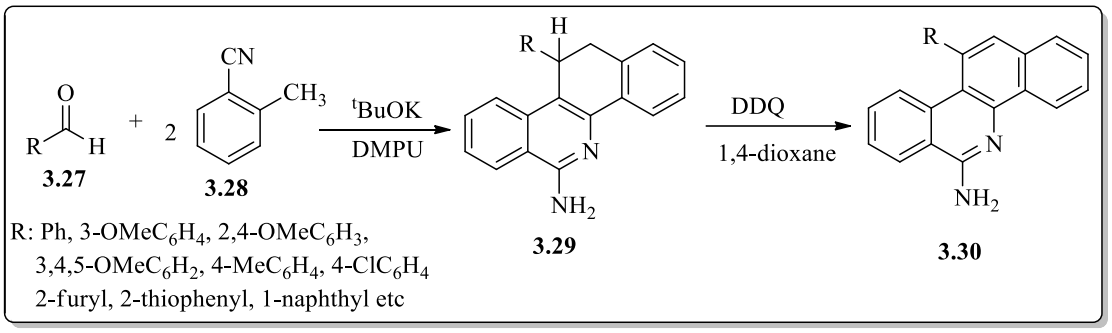
Scheme 3.6: Cascade synthesis of phenanthridine

Alternatively, Lautens group have synthesized phenanthridine by domino arylation, *N*-arylation protocol under Pd-catalysis. The $Pd(OAc)_2$ catalyzed *domino N*-arylation of the silylimine **3.25** with aryl iodide **3.24** and followed by intramolecular C-H-activation produced the substituted phenanthridine **3.26** (Scheme 3.7).



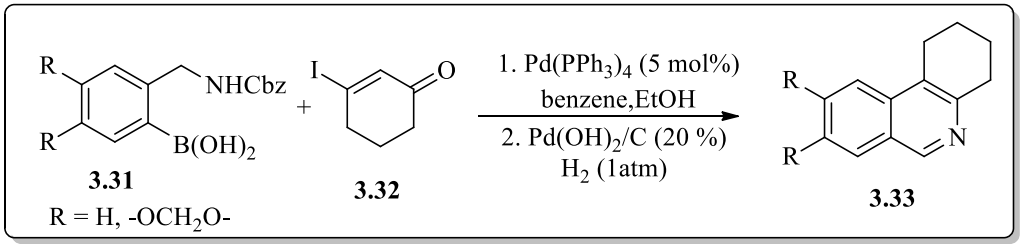
Scheme 3.7: Convenient synthesis of phenanthridine

A very simple method of non-nucleophilic base ^{t}BuOK mediate condensation between 2-methylbenzonitrile **3.28** and an arylaldehyde **3.27** has been demonstrated by Clement *et al.* Subsequently, resulting 6-amino-11,12-dihydrobenzo[*c*]phenanthridine **3.29** was converted to 11-substituted 6-aminobenzo[*c*]phenanthridine **3.30** *via* DDQ oxidation (Scheme 3.8).



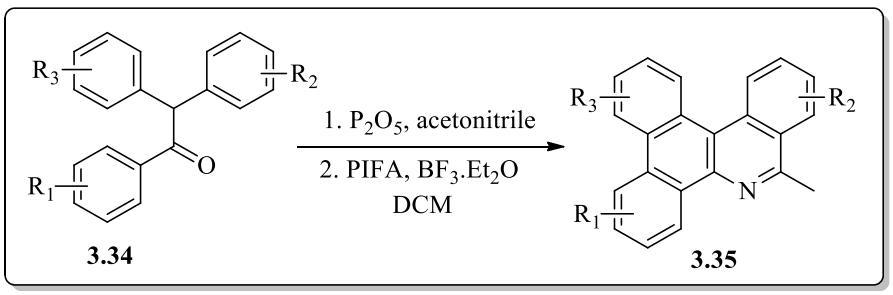
Scheme 3.8: Synthesis of 6-aminobenczo[*c*]phenanthridine

An efficient method for the formation of [*c*]annulated isoquinoline has been developed by Pandey *et al. via* Pd-mediated sequential reactions. The Suzuki cross coupling between *α*-iodoenone **3.32** and protected aminoboronic acid **3.31**, and subsequent condensation results the [*c*]annulated isoquinoline derivatives **3.33** (Scheme 3.9).



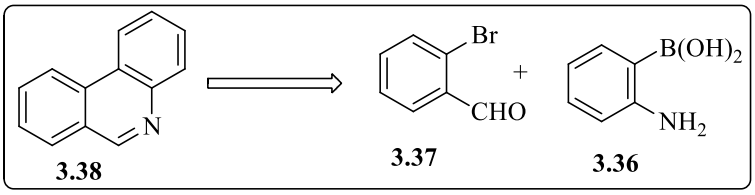
Scheme 3.9: Sequential reaction towards the formation of [*c*]annulated isoquinoline

Dominguez *et al.* applied a two-step synthetic protocol towards the efficient synthesis of novel dibenzo[*a,c*]phenanathridine. Highly substituted novel dibenzo[*a,c*]phenanthridines **3.35** have been prepared from aryl ketone **3.34** *via* sequential reactions of Ritter-type heterocyclization and the classical two-step reductive amination/Bischler-Napieralski cyclization (Scheme 3.10).



Scheme 3.10: Synthesis of dibenzo[*a,c*]phenanthridine

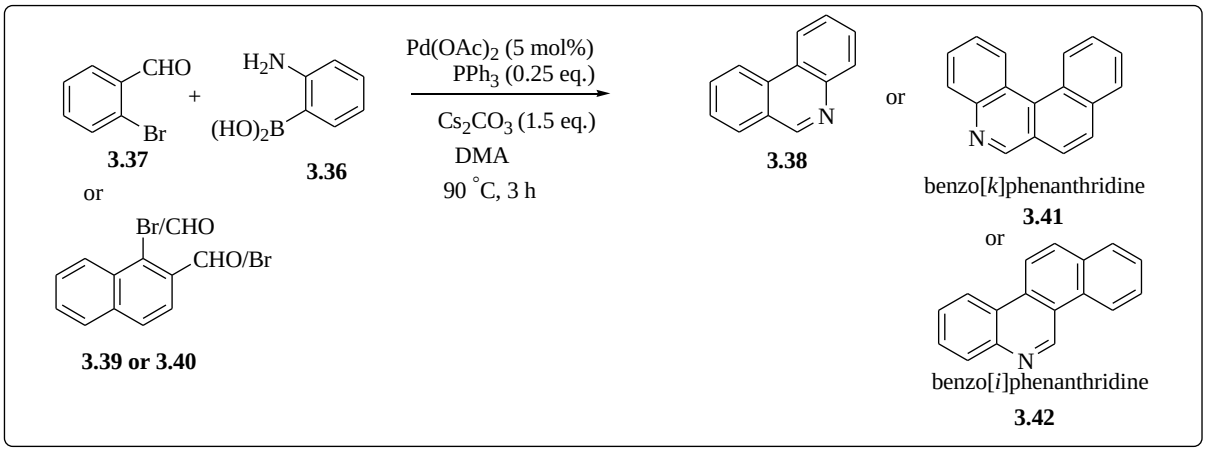
In our continuous effort in finding the shorter and economic synthetic methods *via* palladium catalysis, we have achieved a synthesis of phenanthridines and its analogs in this chapter. Our aim was to find out one step method for the synthesis of phenanthridine. We envisioned that Suzuki coupling between **3.36** and **3.37** would be very effective for the construction of phenanathridine **3.38** in one-pot (Scheme 3.11).



Scheme 3.11: Retrosynthesis of phenanthridine

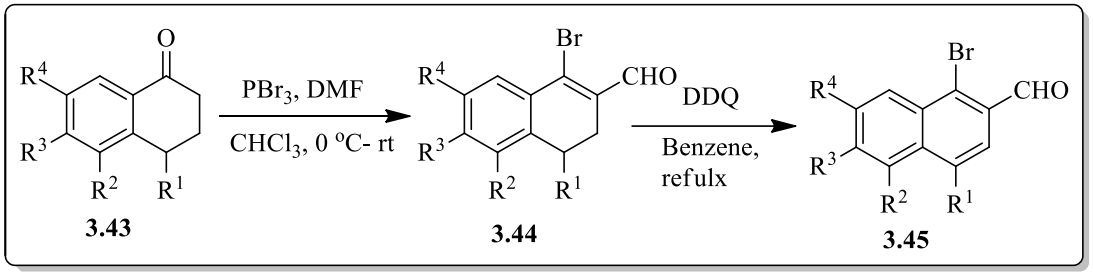
Results and Discussions

We report a one-pot strategy to achieve phenanthridine **3.38** and analogous derivatives **3.41** or **3.42** *via* Suzuki coupling of suitably substituted aromatic *ortho*-bromoaldehyde **3.39** or **3.40** and *ortho*-aminobenzenboronic acid **3.36** in quantitative to good yields (Scheme 3.12).



Scheme 3.12: Synthesis of phenanthridine and its analogues

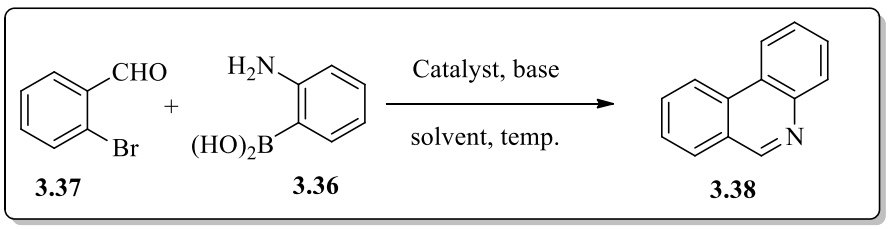
For the synthesis of phenanthridine analogs the starting aromatic *o*-bromoaldehydes **3.45** were synthesized by Vilsmeier-Haack reaction upon corresponding ketones **3.43** and followed by DDQ aromatization of *o*-bromoaldehyde **3.44** (Scheme 3.13).



Scheme 3.13: Synthesis of the aromatic *o*-bromoaldehyde

We have attempted the coupling step with 2-bromobenzaldehyde **3.37** and 2-aminobenzeneboronic acid **3.36**. A variety of the palladium catalysts were tried in combination with ligand and different organic or inorganic bases as the catalytic system. The palladium (0) catalysts $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ gave phenanathridines 41 to 60 %. Among the palladium(II) catalysts the $Pd(OAc)_2$was the best catalyst with 95 % formation of phenanthridine **3.38**. The inorganic base Cs_2CO_3 was proved to be superior to its other inorganic and organic analogues. When the reaction was carried out at 80 °C the reaction gave only 50 % of phenanathridine in the presence of $Pd(PPh_3)_2Cl_2$, Et_3N, and in DMF solvent. Increasing the reaction temperature to 90 °C afforded 82% of phenanthridine in the presence of $Pd(OAc)_2$, PPh_3 and K_2CO_3 catalytic system in DMF in 5 h. Changing the base to Cs_2CO_3 and solvent to DMA shorten the reaction time from 5 to 3 h with 95 % of yields. Further increase of reaction temperature and changing the solvent to DMSO has no effect on the reaction. So, the set of optimal reaction conditions were finalized to be $Pd(OAc)_2$ (5 mol %), PPh_3 (0.25 equiv.), Cs_2CO_3 (1.5 equiv.), in DMA (3 mL), at 90 °C, for 3 h (Table 3.1, entry 10).

Table 3.1: Catalyst Screening [a]



Entry	Catalyst	Ligand	Base	Solvent	T (h)	Temp (°C)	Yields (%)[b]
1	$Pd(PPh_3)_2Cl_2$	-	Et_3N	DMF	5	80	50
2	$PdCl_2$	PPh_3	Et_3N	DMF	5	80	80
3	$Pd_2(dba)_3$	-	Et_3N	DMF	5	80	41

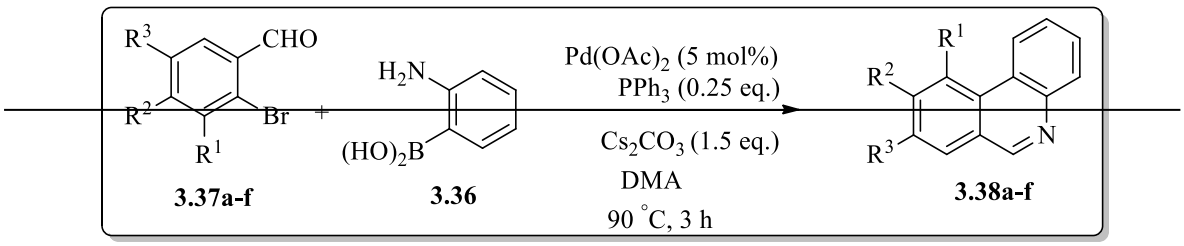
4	$Pd(CH_3CN)_2Cl_2$	PPh_3	Et_3N	DMF	5	80	63
5	$Pd(PPh_3)_4$	-	Et_3N	DMF	5	80	60
6	$Pd(OAc)_2$	PPh_3	Et_3N	DMF	5	80	72
7	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	5	90	82
8	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	5	90	74
9	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	3	90	90
10	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMA	3	90	95
11	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMSO	3	90	51
12	$Pd(OAc)_2$	PPh_3	NaOAc	DMA	3	90	45
13	$Pd(OAc)_2$	-	Cs_2CO_3	DMA	3	90	40

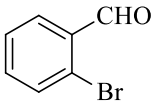
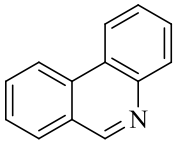
a) 1 mmol of **3.37**, 1.2 mmol of **3.36**, Pd $(OAc)_2$ (5 mol%), PPh_3 (0.25 equiv.), Cs_2CO_3 (1.5 equiv.), DMA (3mL), 90 °C, 3-5 h.

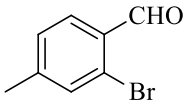
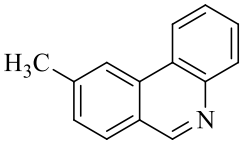
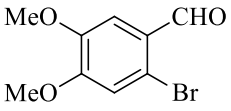
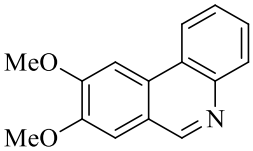
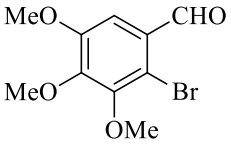
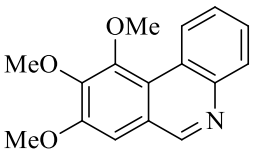
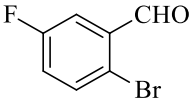
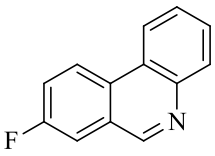
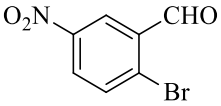
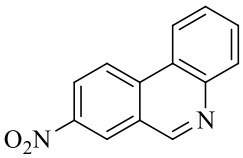
b) Isolated yields.

Once we got the standard conditions for the cyclization procedure, we have generalized our methodology synthesizing various types of phenanthridine and analogous derivatives in excellent to good yields. The results are shown in the Table 3.2. Different substituted phenanthridines **3.38a-f** were synthesized from the corresponding 2-bromobenzaldehydes **3.37a-f** in good yields. The results in the Table 3.2 shows that this methodology is well tolerated both the electron-donation and electron with-drawing functionalities such as, nitro, methyl, methoxy group in the coupling partner **3.7**.

Table 3.2: Synthesis of phenanthridine derivatives[c]



Entry	Substrate	Products	Yields (%)[d]
1	 **3.37a**	 **3.38a**	95

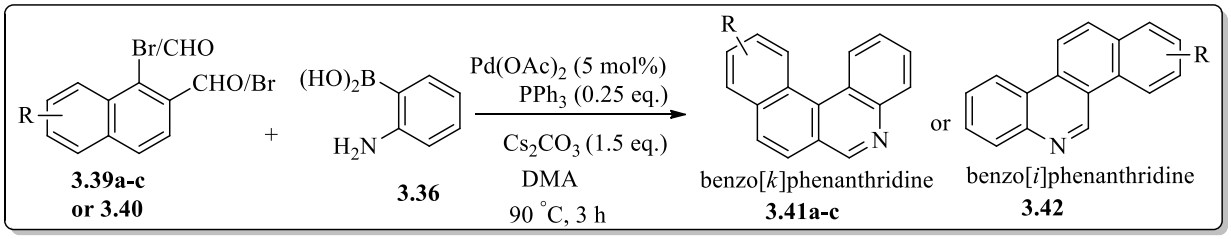
2	 **3.37b**	 **3.38b**	83
3	 **3.37c**	 **3.38c**	93
4	 **3.37d**	 **3.38d**	78
	 **3.37e**	 **3.38e**	
5	 **3.37f**	 **3.38f**	73
6			75

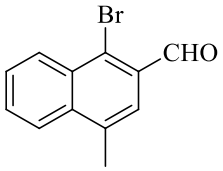
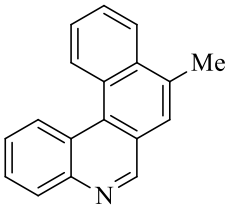
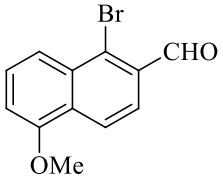
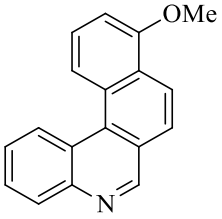
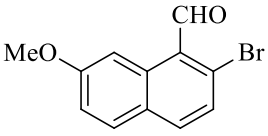
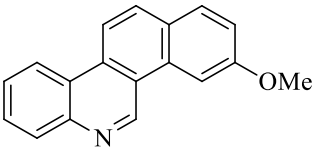
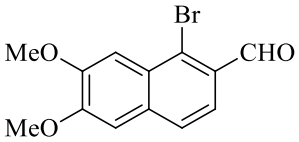
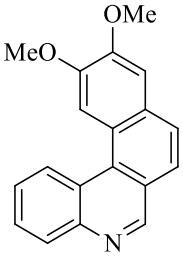
c) Reaction Conditions and Reagents: 1 mmol of substrate **3.37a-f**, 1.2 mmol of aminobenzeneboronic acid **3.36**, Pd $(OAc)_2$ (5 mol%), PPh_3 (0.25 equiv.), Cs_2CO_3 (1.5 equiv.), DMA (3mL), 90 ˚C, 3-5 h.

d) Isolated yields after purification

We have further extended the scope of our procedure to synthesize different higher analogues of phenanthridines. With the aforesaid optimal set of reaction conditions we have synthesized benzo[*k*]phenanthridines **3.41a-c** and benzo[*i*]phenanthridine **3.42** from the corresponding bromonaphthaldehyde in good yields (Table 3.3). Here also different functionalities have been well tolerated.

Table 3.3: Synthesis of phenanthrine analogs[e]



Entry	Substrate	Product	Yields (%)
1	 **3.39a**	 **3.41a**	75
2	 **3.39b**	 **3.41b**	91
3	 **3.40**	 **3.42**	52
4	 **3.39b**	 **3.41c**	89

a) Reaction Conditions and Reagents: 1 mmol of substrate **3.39a-c or 3.40**, 1.2 mmol of aminobenzeneboronic acid **3.36**, Pd $(OAc)_2$ (5 mol%), PPh_3 (0.25 equiv.), Cs_2CO_3 (1.5 equiv.), DMA (3mL), 90 °C, 3-5 h.

b) Isolated yields.

The cyclization reaction was believed to follow the sequential steps of Suzuki coupling followed by condensation. The Suzuki coupling occurs first between the coupling partners to produce the intermediate **I** which then undergoes intramolecular cyclization to afford the phenanthridine **II**. In contrast, if the condensation is to be occurred first it would result the more stable *trans*-imine **III** from which intramolecular coupling is quite impossible as the two functional groups are far apart (Fig 3.3). Evidence in support of our proposal comes from that fact no imine was isolated during the reaction course.

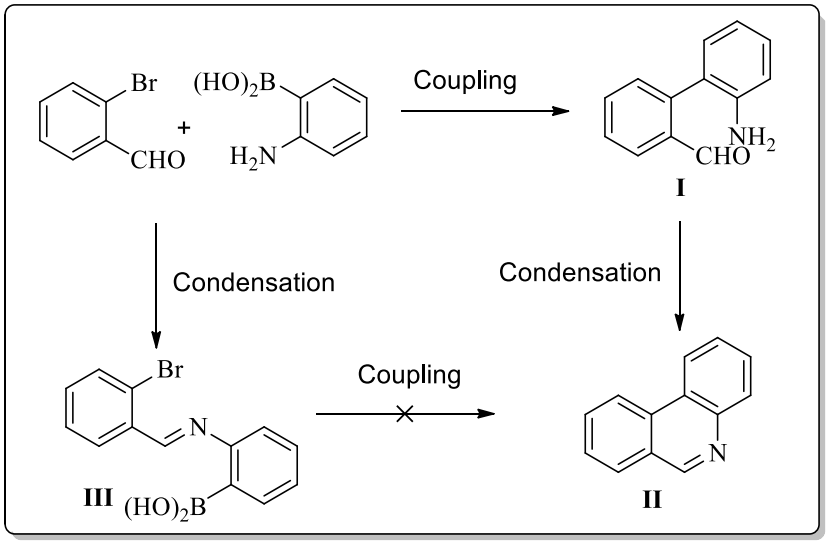


Fig 3.3: Plausible course of the reaction

3.6 Experiments and Results Section

3.6.1 General procedure for the preparation of aromatic naphthaldehyhe (3.45):

A mixture of 1 mmol of *ortho*-bromovinylaldehyde and 3 mmol of DDQ were taken in dry benzene in a 25 mL two necked round bottomed flask and refluxed for overnight. Completion of the reaction was confirmed TCL. After completion of the reaction the mixture was cool to room temperature and benzene was evaporated under reduced pressure. The crude product was purified the usual column chromatography using silica gel and mixture of petroleum ether and ethyl acetate as eluents.

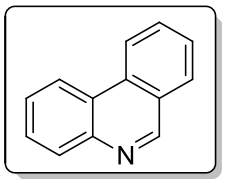
3.6.2 General procedure of Suzuki coupling for synthesis of phenanthridine (3.38):

Ortho-bromobenzaldehyde (50 mg, 0.273 mmol.), *ortho*-aminobenzeneboronic acid (53.5 mg, 1.2 equiv.), Pd $(OAc)_2$ (5 mol%), PPh_3 (0.25 equiv.), Cs_2CO_3 (133.5 mg, 1.5 equiv.) were taken in a two-necked round bottom flask in argon atmosphere. 3 mL of dry DMA was

added to the reaction mixture and degassed with nitrogen and heated at 90 ^{o}C temperature for 3 h. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to rt and diluted with water. It was then extracted with ethyl acetate (50 mL × 3). Combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and crude product was purified by column chromatography using Silica gel and petroleum ether: ethyl acetate (5:1) as eluent.

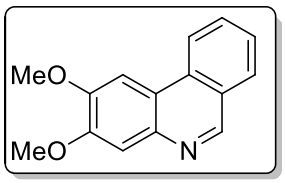
Spectral data of the representative Compounds:

Phenanthridine (3.38a):



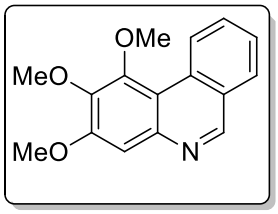
Yellow solid, mp: 102-104 ^{0}C (lit.[1] 104-106 ^{o}C); Yields : 90 %; ^{1}H NMR ($CDCl_3$, 200 MHz): 9.18 (1H, s), 8.41 (2H, d, J = 8.0 Hz), 8.17 (1H, dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.87 (1H, t, J = 7.0 Hz), 7.52-7.75 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): 153.4, 144.1, 132.4, 131.0, 129.9, 128.7 (2C), 127.4, 127.1, 126.2, 124.0, 122.2, 121.7; Anal.Calcd for $C_{13}H_9N$: C: 87.12; H: 5.06; N: 7.82 %; Found: C: 87.00; H: 4.95; N: 7.72 %.

2,3-dimethoxyphenanthridine (3.38c):



Brown solid; mp: 127-129 ^{o}C Yield: 85 %; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.17 (1H, s), 8.45 (1H, d , J = 7.6 Hz), 8.16 (1H, d, J = 8.0 Hz), 7.89 (1H, s), 7.63-7.71 (2H, m), 7.37 (1H, s), 4.15 (3H, s), 4.10 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.2, 152.0, 150.2, 139.5, 130.3, 130.0 128.5, 128.0, 126.8, 121.9, 114.3, 108.1, 102.1, 56.4, 56.3; Anal.Calcd for $C_{15}H_{13}NO_2$: C: 75.30; H: 5.48; N: 5.85 %; Found : C: 75.25; H: 5.36; N: 5.72 %.

1,2,3-trimethoxyphenanthridine (3.38d):



Brown Sticky masss; Yield: 78 %; ^{1}H NMR ($CDCl_3$, 200 MHz): 9.34 (1H, dd, J_1 = 2.4 Hz, J_2 = 7.0 Hz), 9.14 (1H, s), 8.18 (1H, t, J = 7.0 Hz), 7.27-7.71 (2H, m), 7.27 (1H, s), 4.10 (9H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): 153.6, 152.6, 151.6, 146.6, 144.2, 130.0, 127.9, 127.4, 126.4, 124.3, 123.8, 121.8, 105.4, 61.5, 60.6, 56.3; Anal.Calcd for $C_{16}H_{15}NO_3$: C: 79.09; H: 5.23; N: 6.50 %; Found : C: 79.0; H: 5.15; N: 6.43 %; HRMS calcd for $C_{16}H_{16}NO_3^+$ [M+ H^+]: 270.1125; Found : 270.1125.

Conclusion

In conclusion a simple and efficient method for the synthesis of different substituted phenanthridine and it higher analogues benzo[*k*] and benzo[*i*] derivatives have been developed. Our synthetic strategy is a general one with tolerability to a variety of substituent and gave highly substituted phenanthridines in quite good yields from very cheap starting materials under mild reaction conditions. We anticipate that our methodology could be applicable to synthesize phenanthridine natural products of important medicinal value[5, 8, 10, 14-40].

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