A short review on synthesis of dihydrophenanthrene, phenanthrene and its analogues by palladium-catalyzed reaction

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Abstract

Use of transition metal compounds or complexes as catalysts or reagents in organic synthesis is an exciting field in research and numerous novel reactions which are impossible to achieve by conventional synthetic methods have already been discovered. Palladium catalysed C-C bond forming reaction is very important for the synthesis of carbocyclic compounds. In this mini review we have reviewed some efficient methods for the construction of a dihydrophenanthrene, phenanthrene and its analogues by palladium-catalyzed reaction.

Keywords: Phenanthrene, palladium-catalyzed reaction, 9, 10 dihydrophenanthrenes electrocyclic reaction

Palladium catalyzed C-C bond forming reaction is important for the synthesis of heterocyclic and carbocyclic compounds. Polycyclic aromatic hydrocarbons (PAHs), more simply known as polynuclear aromatic hydrocarbons (PAHs), constitute an extraordinary large and diverse class of organic molecules. Within the chemical class of polycyclic aromatic compounds phenanthrene is an important core structure. The phenanthrene moiety can not only be found in several natural products, of which many exhibit interesting biological activity, but more recently phenanthrenes have also been shown as interesting ligands for novel catalyst systems. The discovery of the carcinogenic properties of polycyclic aromatic hydrocarbons stimulated wide-ranging investigations of their structure activity relationships. Previously it was thought that PAHs are direct acting carcinogens, but this was proved to be wrong in latter stage. It is now recognized that PAHs require metabolic activation in order to express tumorigenic reactivity. It is believed that principal primary metabolites are arene oxides which are formed by enzymatic addition of an atom of oxygen to an aromatic -C=C- bond. These relatively unstable intermediates may then i) undergo hydration catalysed by epoxide hydrolase to from dihydrodiols, ii) rearrange spontaneously to phenols, iii) undergo addition of glutathione catalysed by glutathione-s-transferase, iv) from covalent binding with DNA, RNA, and proteins (Figure 1).

Evidences indicate that principal biologically active metabolites are dihydrodiol epoxide derivatives. These metabolically formed diol epoxides exert their carcinogenic and other genotoxic effects through covalent binding to DNA.

Figure 1

Therefore, the development of new short synthetic methods for this important class of organic compounds has regained importance. Several synthetic efforts for the preparation of PAH have been reported by different groups, of which most common procedure involves the classical oxidative photocyclization of stilbene derivatives. Among other methods intramolecular Diels-Alder reaction, flash vacuum pyrolysis, olefin metathesis, Friedel-Crafts type cyclization, dimerisation or trimerisation of acetylenes and arynes, transition metal catalyzed cyclosomisation etc. are used as the key step for construction of a benzene ring for the synthesis of PAH. We also contributed in this field by synthesizing tri-substituted benzene derivatives via base catalyzed condensation and aromatization of various bromoaldehydes with active methylene compound.
Palladium catalyzed activation of aromatic C-H bond has been used extensively in many organic synthesis since this reaction gives a solution for the construction of carbo- and heterocycles from the corresponding halides and triflates.\textsuperscript{20,21,22,23,24,25,26} Larock \textit{et al} have developed a novel Palladium-catalyzed migration/C-H activation methodology for the synthesis of complex fused polycycles.\textsuperscript{27,28} The major sources of PAHs are crude oil, coal, oil shale. Methyl phenanthrene, belong to an important group alkyl-aromatic hydrocarbons which are present in natural environments. Methyl phenanthrene arises through the combustion of wood, coal; etc. There is a great variety of methods which are available for the synthesis of phenanthrene and its derivatives. Perhaps the most extensive method is the classical Haworth synthesis.

Maes \textit{et al.} synthesized phenanthrene\textsuperscript{29} and substituted phenanthrene molecules by using only a weak, non-nucleophilic base for the ring closure of 2-methylbiphenyl-2-carbaldehydes under microwave heating (Scheme 2).

Benzyne is actually very reactive as a carbopalladation partner of \( \pi \)-allyl palladium chloride. Yamamoto \textit{et al.} reported that the palladium-catalyzed\textsuperscript{32} reaction of allyl chlorides with benzyne precursor 15 produces phenanthrene derivatives 16, along with the minor regioisomers 17, in good yields. The reaction of allyl chloride (1.0 equiv) and benzyne precursor 15 (2.0 equiv) in the presence of \([\text{Pd}_{2}(\text{dba})_3] \cdot \text{CHCl}_3\) (2.5 mol\%), dppf (5 mol\%), and CsF (4.0 equiv) in \( \text{CH}_3\text{CN}/\text{THF} \) (1/1) at 60 °C gave 16 in 69% yield (Scheme 5).

Blum \textit{et al.} have employed for the first time a sol gel physically entrapped version of the \( \text{PdCl}_2(\text{PPh}_3)_2 \) catalyst for...
the Heck coupling process. This heterogeneous catalyst is a perfectly leach proof, highly porous material and completely air stable for many months. When a solution of freshly distilled styrene, iodobenzene, and tripropylamine in 15 mL of toluene was refluxed for 12 h in the presence of a sol-gel encapsulated catalyst containing of PdCl$_2$(PPh$_3$)$_2$, the resulting solution containing trans- and cis-stilbene were found. Finally this stilbene under photocyclization yielded phenanthrene molecules (Scheme 6).

Meijere et al. synthesized phenanthrene molecules by palladium catalyzed intramolecular arylation reaction. The o-bromo-cis-stilbenes 22a, b when subjected to react with Pd(0) in sealed tube at 110 °C only phenanthrene (23a), and 3-methylphenanthrene (23b) in 70 and 71% yield, respectively, arising from an intramolecular aryl bromide to arene coupling (Scheme 7).

Barrett et al. examined the model coupling of 2-vinylphenylboronic acid 24 with 2-bromostyrene 25 under the Suzuki coupling conditions. This gave biphenyl 26 in moderate yield (40%). Subsequent RCM using the second generation Grubbs catalyst gave phenanthrene 27, in moderate yield (Scheme 8).

There are several method have been reported for the synthesis of 9,10 dihydrophenanthrene. Phenanthrene under catalytic hydrogenation yielded 9,10 dihydrophenanthrene 29 along with 1,2,3,4,5,6,7,8-octahydrophenanthrene 30, and tetradecahydrophenanthrene 31 (Scheme 9).

Burger and Mosettig took advantage of the greater activity of copper-chromium oxide toward olefinic double bonds as compared with benzenoid nuclei and selectively hydrogenated phenanthrene at 220 °C, obtaining 9, 10-dihydrophenanthrene in yields of about 80%.

Koichiro Oshima et al. synthesized biaryl compound by titanium tetrachloride from aryl magnesium compound. They have developed coupling method starting from aryl halides. They reported the halogen magnesium exchange reaction of aryl bromides and aryl iodides with lithium trialkylmagnesate (R$_3$MgLi). This exchange reaction can generate an arylmagnesium ate-complex which would be a promising precursor for the oxidative coupling reaction. Indeed, the addition of TiCl$_4$ to the resulting arylmagnesium species provided biaryls in good yields. By using this methodology they also prepared 9, 10 dihydrophenanthrene (Scheme 10).

The photochemical conversion of 2-vinylbiphenyl (34) to 9, 10-dihydrophenanthrene (37) was reported by Horgan et al. They proposed a two step mechanism: photocyclization to yield the unstable 8a,9-dihydrophenanthrene intermediate 36, which then underwent a thermal [1,n] sigmatropic hydrogen shift [n = 5, 9, or 13] to yield the observed product in both the absence and the presence of oxygen (Scheme 11).
Ge’lard Cahiez et al. have reported to synthesis of 9, 10-dihydrophenanthrene by intramolecular coupling reactions from di-Grignard reagents such as \( \text{39} \) (Scheme 12). The diiodo compound \( \text{38} \) reacted with \( i-\text{PrMgBr} \) at room temperature for 30 min to give \( \text{39} \). Then, the treatment of the di-Grignard \( \text{39} \) with 1, 2-dibromoethane in the presence of 3% \( \text{FeCl}_3 \) provided the dihydrophenanthrene \( \text{40} \) in 76% overall yield. \(^{39}\)

Leter John J. Eisch et al. have made C-C Bond formation via C-H bond activation by Prior Zirconation reaction. By using this methodology (Scheme 13) they have synthesized 9, 10-dihydrophenanthrene from 2, 2 dimethyl biphenyl in moderate yield. \(^{40}\)

Yasuharu Yoshimi synthesized dihydrophenanthrene by photochemical Birch reduction where sodium hydroxide used as electron source and Jackson also obtained dihydrophenanthrene by Birch reductions at room temperature with alkali metals in silica gel (Scheme 14). \(^{41}\)

Palladium catalyzed reaction also useful reaction for the synthesis of various type carbocyclic molecules. Fagnou synthesized 9, 10-dihydrophenanthrene by a C-H bond activation process, but the reaction condition was more vigorious (Scheme-15). \(^{42}\)

When we treated substrates \( \text{47} \) with \( \text{Pd(OAc)}_2 \) (10 mol %), \( \text{Cs}_2\text{CO}_3 \) (2 equiv), \( \text{PPh}_3 \)(0.5 equiv), \( \text{TBAC} \)(1 equiv), in DMF solvent, heated it at 85 °C-90 °C for 1.5h-2h, the unexpected products \( \text{48} \) resulted in 70% yield. A fused aromatic ring resulted from cleavage of the pyran ring present in the substrate followed by ring closer and aromatization. By using this methodology we have synthesized Fluoranthene in the following way.

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{41} \]
\[ \text{1. Bu}_2^1 \text{Zr(OEt)}_2 \text{, Heat} \quad \text{2. H}_2\text{O} \quad \text{42} \]
The reaction mechanism (Scheme 18) presumably involves a 6π electrocyclic ring closer reaction followed by formaldehyde elimination. The catalytic cycle involves initial oxidation of the Pd(0) to generate alkenyl palladium (II) intermediate (A) via oxidative addition of the Pd (0) to the substrate, which then co-ordinates with oxygen to generate the intermediate (B).

This undergoes proton abstraction followed by rearrangement to afford a nine membered cyclic Pd-O complex (C). This complex undergoes 6π electrocyclic ring closer reaction forming complex (D), followed by formaldehyde elimination to afford 9, 10 dihydro phenantrhene.

Recently, Lan et al. proposed an alternative mechanism that occurs through an intramolecular Heck reaction. Using theoretical calculations they investigated both, mechanisms and find that the intramolecular Heck mechanism (Scheme 19) is lower in energy than the electrocyclic pathway (Scheme 18).

Initially we have synthesized 9, 10 dihydrophenantrhrenes by palladium catalyzed electrocyclic reaction starting from vinyl bromoaldehydes. Then we have employed our methodology to the aromatic bromoaldehydes system, we got successful result to synthesize phenantrhene and alkyl phenantrhene in good yield. Importance of this methodology is that we can introduce alkyl group in any one or two position of newly formed benzene ring(c) of phenantrhene (Scheme 20).

First aromatic bromoaldehydes 53a, 53b were treated with allyl bromide, sodium iodide in presence of indium metal to obtained corresponding alcohols 54a and 54b. These alcohols were allylated in presence of sodium hydride in THF medium at 0 °C to obtained diallylated compound 55a and 55b which were subjected to 2nd generation Grubbs catalyst to Obtained desired cyclic precursor 56a and 56b respectively. Then these cyclic precursor were finally treated with Pd(OAc)$_2$, Cs$_2$CO$_3$, PPh$_3$, TBAC, DMF 95-100°C to afforded phenantrhrenes 57a and 2-methoxy phenantrhene 57b in good yield which is shown in Scheme 21.
To introduce alkyl group in phenanthrene ring aromatic bromoaldehydes 53a, 53b, and 53c were treated with allyl bromide, sodium iodide in presence of indium metal to obtained corresponding alcohols 54a, 54b, and 54c. These alcohols were methyallated in presence of sodium hydride in THF medium at 0°C to obtained diallylated compound 55a, 55b, and 55c which were subjected to 2nd generation Grubbs catalyst to obtained desired cyclic precursor 56a, 56b, and 56c respectively. Then these cyclic precursor were finally treated with Pd(OAc)₂, PPh₃, Cs₂CO₃ in DMF solvent at 85-90°C to afforded alkyl phenanthrenes 57a, 57b, and 57c respectively (Scheme 21).

To alternate the position of methyl group, same aromatic bromoaldehydes 53a, 53b, and 53c were first treated with methallyl bromide, sodium iodide in presence of indium metal to obtained compounds 54d, 54e, and 54f. These alcohols were then allylated in presence of sodium hydride in THF medium at 0°C to obtained diallylated compounds 55d, 55e, and 55f which were subjected to 2nd generation Grubbs catalyst to obtained desired cyclic precursor 56d, 56e, and 56f respectively. Then these cyclic precursor were finally treated with Pd(OAc)₂, PPh₃, Cs₂CO₃ in DMF solvent at 85-90°C to afforded alkyl phenanthrenes 57f, 57g, and 57h respectively (Scheme 22).
We can introduce two alkyl groups in phenanthrene ring. Few methods are known for the introduction of two alkyl group. First Aromatic bromoaldehydes $53a$, $53c$ were treated with methallyl bromide, sodium iodide in presence of indium metal to obtained corresponding alcohols $54d$ and $54e$. These alcohols were methyallated in presence of sodium hydride in THF medium at 0 °C to obtained diallylated compound $55i$ and $55j$ which were subjected to 2nd generation Grubbs catalyst to obtained desired cyclic precursor $56i$ and $56j$ respectively. Then these cyclic precursor were finally treated with Pd(OAc)$_2$, PPh$_3$, Cs$_2$CO$_3$ in DMF solvent at 85-90 °C to afforded dialkyl phenanthrenes $57i$ and $57j$ in good yield (Scheme 24).

Scheme-23

A palladium-catalyzed benzannulation with o-bromobenzyl alcohols enabled the facile construction of phenanthrene skeletons via the sequential multiple carbon–carbon bond formations. A variety of multi-substituted phenanthrenes were synthesized by the reaction of (Z)-β-halostyrenes with o-bromobenzyl alcohols as well as by the three-component coupling of alkynes, aryl bromides, and ortho-bromobenzyl alcohols. The electron-deficient phosphine ligand played an important role to control the sequential oxidative addition of two different organic halides employed, which realized the selective formation of the desired phenanthenes in good yields. $^{44}$

Scheme-25

Ling Zhou envisioned that Pd-catalyzed γ-C(sp2)−H arylation of phenylacetaldehydes with aryl iodide by using an amino acid as a transient directing group would produce compound $66$ undergo sequential intramolecular cationic cyclization, dehydration, and 1,2-migration in the presence of an acid to generate phenanthrenes $67$ (Scheme 26). The major challenges of this strategy arise from questions regarding whether the acid generated during the course of the reaction is sufficiently reactive to activate the following cascade reaction and selective 1,2-migration to give a single isomer of phenanthrenes. $^{45}$

Scheme-26

Conclusion:

We have discussed different method for synthesis of phenanthrene, mono and dialkylated phenanthrene derivatives by using palladium catalyzed reaction. These methods are also useful for the synthesis of higher homologous of polynuclear aromatic hydrocarbons provided the efficient route to synthesis of suitable starting material.

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