Recent Advances in C–H Functionalization of Pyrenes

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Abstract: In recent years, transition metal-catalyzed C–H activation and site-selective functionalization have been considered to be valuable synthetic tactics to functionalize organic compounds containing multiple C–H bonds. Pyrene is one of the privileged and notorious polycyclic aromatic hydrocarbons. Pyrene and its derivatives have found applications in various branches of chemical sciences, including organic chemistry, chemical biology, supramolecular sciences, and material sciences. Given the importance of pyrene derivatives, several classical methods, including the C–H functionalization method, have been developed for synthesizing modified pyrene scaffolds. This review attempts to cover the recent developments in the area pertaining to the modification of the pyrene motif through the C–H activation process and the functionalization of C–H bonds present in the pyrene motif, leading to functionalized pyrenes.

Keywords: C–H activation; C–H functionalization; directing group; polycyclic aromatic hydrocarbon; pyrene; synthetic methods

1. Introduction

Pyrene and its derivatives have gained significant interest in various branches of chemical sciences, including organic chemistry, chemical biology, supramolecular sciences, and material sciences [1–25]. The exceptional photophysical properties of pyrene derivatives, coupled with their capability to facilitate efficient energy transfer, have led to significant investigation and innovation. Photophysical properties, including exceptional fluorescence characteristics, effective excimer emission, and impressive charge carrier mobility, attribute the position of pyrene as an important element for constructing a diverse array of small molecules and materials. Pyrene is a pivotal building block in the fabrication of applied materials, including organic light-emitting diodes (OLEDs), organic semiconductors used in organic field-effect transistors (OFETs), supramolecular sensors, solar cells, etc. (e.g., compounds 1a–g, Figure 1). Further, the versatility of pyrene-based organic materials has led to their exploitation in various categories of photoelectric devices [1–10]. Furthermore, the pyrene motif has been admired for its binding capabilities, and it can be involved in π-stacking and C–H–π interactions. This property has been widely utilized in the noncovalent modification of various extended planar π-systems, such as carbon nanotubes and graphene sheets [11–18]. Additionally, pyrene derivatives have found applications in the field of chemical biology, e.g., in constructing systems to bind to nucleic acids [4] and in creating artificial receptors for aromatic and carbohydrate molecules [19–25].

The specific substituents incorporated and their corresponding positions within the pyrene molecule 2a have been found to influence the optoelectronic and photophysical characteristics of pyrene derivatives [1–25]. The 1-, 3-, 6-, and 8-positions of the pyrene molecule identified are referred to as ‘active’ or ‘common sites’ (Figure 2) [9,10]. These sites possess a higher electron density and readily undergo electrophilic aromatic substitution (SEAr) reactions. The synthesis of functionalized pyrene derivatives by introducing substitutions at these sites has been commonly explored. On the other hand, the 2- and 7-positions of pyrene are designated as ‘nodal plane positions’ and are considered ‘uncommon’ or ‘less
accessible sites for functionalization’. Thus, functionalizing the 2- and 7-positions of pyrene is considered challenging. The other positions, 4-, 5-, 9-, and 10-, are called K-regions due to the carcinogenic effect of pyrene upon its oxidation [1–10].

The substantial orbital co-efficient present at positions 1-, 3-, 6-, and 8- enables the occurrence of electrophilic reactions at these carbon atoms [1–10]. Representative primitive works related to the substitution of pyrene at different sites are described in Scheme 1 [10]. Vollmann et al. demonstrated the preliminary synthesis of pyrene derivatives bearing mono-, bis-, tri-, or tetra-substituted groups [26]. Introducing substituents at the 2- and 7-positions in a single step was considered difficult, and multi-step pathways were established to synthesize 2- and 7-disubstituted pyrenes [9,10]. In 2005, Marder et al. [27] reported the iridium-catalyzed direct C–H borylation of pyrene at the 2- and 7-positions, affording the corresponding products 3e and 3f. An intermediate complex [Ir(bpy)(Bpin)3] formed in the process seemed to play a key role in selectively engaging the C–H bonds present at the 2- and 7-positions (Scheme 1). Notably, the C(2)- and C(7)-borylated pyrene derivatives have been utilized for synthesizing various pyrene derivatives possessing alcohol, ether, triflate, and bromide functionalities and also new pyrene products formed through classical methods [10,28–33] and cross-coupling reactions [34]. The treatment of
pyrene with bromine has led to bromination at the 1-, 3-, 6-, and 8-positions, affording the corresponding products 3a–d [35]. The reaction with bromine [9,10] does not lead to the functionalization of the four positions, such as 4-, 5-, 9-, and 10- in the K-region of pyrene [35]. Similarly, the introduction of bulky tert-butyl groups at positions 2 and 7 does not effectively alter the bromination outcome by preventing access to the active positions 1, 3, 6, and 8 [9,10,36–39]. Pyrenes containing the bromide substituent at different positions were used in cross-coupling reactions to obtain functionalized pyrenes [9,10]. Friedel–Crafts alkylation with tert-butyl chloride in the presence of AlCl₃ gave 2,7-di-tert-butyl pyrene [40]. Notably, the installation of the tert-butyl group served as the bulky substituent to introduce other groups at the different sites in the pyrene core [10]. Oxidation reactions at the 4-, 5-, 9-, and 10-positions of the K-region of pyrene have been carried out, which led to the assembling of 3g,h (Scheme 1), and their oxidation chemistry was also explored to obtain various functionalized pyrenes [10,41–43].

Given the notorious applications of pyrene and its derivatives, developing valuable pyrene-based materials with tuned molecular structures and photoelectric properties would be possible by introducing different functional group attachments into the suitable positions of the pyrene core. While the substitution of pyrenes in all positions would be valuable, apart from the functionalization of the active positions, a few methods enabling selective and effective functionalization of some of the inaccessible sites of pyrene suffer from limitations.

In recent years, C–H functionalization has emerged as one of the most fruitful strategies to introduce a functional group at the C–H bonds of the small molecules, and is considered an alternative method to the cross-coupling reactions [44–64]. Particularly, the transition metal-catalyzed C–H bond activation and functionalization of various classes of organic molecules has been well documented. C–H activation and functionalization can be accomplished in two ways: (i) via direct C–H activation/functionalization; and (ii) via directing group-assisted C–H activation/functionalization. C–H activation and functionalization depend on the reactivity of substrates, metal catalysts, and other conditions. The

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(i): Br₂
(ii): [Ir(OMe)COD]₂ (5 mol%), dtbpy (10 mol%), Bpin₂, cyclohexane, 80 °C, 16 h.
(iii): RuCl₂, NaI, DCM-CH₂CN-H₂O (1:1:1:25), rt or 40 °C.

Scheme 1. Representative primitive works related to the substitution of pyrenes at different sites [27,35,41–43].
direct C–H activation/functionalization of a molecule does not provide the desired product with efficiency, as there will be regio- or site-selectivity issues. Notably, the directing group-assisted C–H activation concept has helped to overcome the regioselectivity issues when similar types of C–H bonds are present in a molecule. The directing group initially coordinates to a transitional metal and brings the coordinating metal center to a C–H bond present in proximity in a molecule, enabling site selection [54–64]. There have been various efforts to use the functional groups present in organic molecules as directing groups. Notably, the transition metal-catalyzed bidentate directing group-assisted C–H functionalization of small organic molecules, viz., carboxamides possessing or assembled using a bidentate directing group, has been considered a reliable method [54–64]. Accordingly, the Pd(II)-catalyzed bidentate directing group-aided functionalization including C–H arylation, alkylation, halogenation, amidation, and oxygenation, are well-documented methods in organic synthesis. Different directing groups, such as 8-aminoquinoline, 2-(methylthio)aniline, 4-amino-2,1,3-benzothiadiazole, 2-picolinic acid, etc., have been introduced to accomplish the C–H functionalization of molecules at desired positions [44–64]. A wide range of organic compounds, including aromatic, heteroaromatic, heterocyclic, aliphatic, and alicyclic compounds, along with amino acids, have been subjected to site-selective C–H functionalization [54–64].

Nevertheless, the pyrene motif was also subjected to C–H activation and functionalization to obtain substituted pyrenes [10]. This review was focused on delineating the recent developments in the area pertaining to the modification of the pyrene skeleton involving the transition metal-catalyzed functionalization of C–H bonds of the pyrene skeleton, affording functionalized pyrenes. This review covered the current status of various C–H functionalization reactions, including arylation, alkylation, olefination, etherification, chalcogenation, allylation, and carbonylation of the pyrene core at different sites (Scheme 2).

![Diagram of C–H activation and functionalization](image)

**Scheme 2.** C–H activation and functionalization of organic molecules.
2. Direct C–H Activation and Functionalization of Pyrene, Affording Functionalized Pyrenes

In this section, we have presented the recent developments pertaining to the direct C–H activation and functionalization of pyrene motifs without using any directing group. In 1993, Perutz et al. reported [65] one of the primitive C–H activation attempts of the pyrene core and the synthesis of an arene–rhodium complex through C–H activation of pyrene, naphthalene, perylene, and triphenylene via C–H bond cleavage. The rhodium catalyst (4a) successfully formed an \( \eta^1 \)-complex with pyrene, while naphthalene, perylene, and triphenylene gave an equilibrium mixture of their corresponding \( \eta^2 \)-complex and C–H activation products. Pyrene was added into a solution of 4a in hexane and heating the reaction mixture at 60 °C for 21 h gave the pyrene-based \( \eta^2 \)-complex 4b with a 90% yield (Scheme 3).

![Scheme 3. Attempt at C–H activation in pyrene and synthesis of the pyrene-based \( \eta^2 \)-complex [65].](image)

2.1. Direct Functionalization of the C2 and C7 Positions of Pyrenes

Marder et al. described an Ir-catalyzed [27]-selective borylation of polycyclic aromatic hydrocarbons, including pyrene and the structure of pyrene-2,7-bis(boronate) esters. Borylation reactions occurred at the C(2) and C(7)-positions and resulted in the formation of the pyrene-2,7-bis(boronate) ester. The catalyst derived in situ between [Ir(OMe)COD]$_2$ and 4,4′-di-tert-butyl-2,2′-bipyridine (dtbpy) demonstrated notable effectiveness and specificity in facilitating the C–H borylation reaction of pyrene [27,66]. The observed site selectivity was attributed to the highly congested structure of the five-coordinate fac-tris(boryl)species, designated as [Ir(bpy)(Bpin)$_3$]. This complex has been believed to be a crucial intermediate, which is responsible for the pivotal C–H activation step that determines the reaction rate. The reaction of pyrene (1 equiv), B$_2$pin$_2$ (1.1 equiv), [Ir(OMe)COD]$_2$ (5 mol%), and dtbpy (10 mol%) in cyclohexane at 80 °C for 16 h produced the C(2)-borylated product 3e and the C(2), C(7)-bis-borylated product 3f of 68% and 6% yields, respectively. The exclusive synthesis of the C(2), C(7)-bis-borylated product (97%) was also achieved using excess boron reagent (2.2 equiv of B$_2$pin$_2$) (Scheme 4).

![Scheme 4. Functionalization of the C2 and C7 positions of pyrenes. Synthesis of borylated pyrenes via C–H borylation [27,66].](image)

Driess designed [67] a cobalt catalyst termed 5, which has been used for the C–H borylation reaction of pyrene core 2a, affording the C(2), C(7)-bis-borylated pyrene 3f. Catalyst
A tentative mechanistic pathway for the Co-catalyzed C–H borylation of pyrene was proposed, involving cobalt(I) hydride generated in situ upon the addition of NaBHEt to the Co catalyst. Then, B2Pin2 undergoes oxidative addition to cobalt(I) hydride, forming an intermediate, which, after reductive elimination of HBPin, produces an active cobalt(I) boryl intermediate. Then, a C–H oxidative addition reaction of pyrene to the cobalt(I) boryl intermediate, followed by reductive elimination, results in the expected C–H-borylated product 3f. When cyclohexene is available, it interacts with cobalt(I) hydride via a coordination insertion pathway, and this intermediate with HB results in cobalt(I) hydride and cobalt(I) boryl intermediates, respectively. It was suggested that the elevated levels of HBPin in the catalytic cycle help to generate cobalt(I) boryl intermediates in the absence of cyclohexene.

Scheme 5. Functionalization of the C2 and C7 positions of pyrenes. Synthesis of borylated pyrenes via C–H borylation [67].

Murai’s group presented [68] an iridium-catalyzed intermolecular dehydrogenative silylation reaction of polycyclic aromatic compounds, including pyrene 2a, without using directing groups (Scheme 6). The C2-substituted 6a1 pyrene as well as the C2- and C7-disubstituted 6a2 pyrene were obtained. Pyrene, HSiEt3 (0.5 equiv), [Ir(OMe)(COD)]2 (2.5 mol%), tmphen (5 mol%), and 3,3-dimethyl-1-butene (2 equiv) were mixed in 1,4-dioxane and heated for 9 h at 100 °C to afford the C2-silylated product 6a1 (54%) and C2, C7-silylated product 6a2 (3%). In another reaction, pyrene was treated with 3 equiv of HSiEt3 in the presence of [Ir(OMe)(COD)]2 (5 mol%), tmphen (10 mol%), and 3,3-dimethyl-1-butene (3 equiv) in 1,4-dioxane at 100 °C for 9 h. This reaction gave the C2-silylated product 6a1 (63%) and C2, C7-silylated product 6a2 (20%). The authors stated a plausible mechanism for the intermolecular dehydrogenative silylation reaction. An Ir–H species is generated through the oxidative addition reaction of Ir–OMe to Et3SiH, followed by a reductive elimination reaction, releasing Et3Si–OMe. Then, the initially generated Ir–H species reacts with Et3SiH, undergoes insertion into 3,3-dimethyl-1-butene to afford 7c (via 7b), and subsequently undergoes reductive elimination to afford Ir-SiEt3 species. Ir–SiEt3 then undergoes oxidative addition to the C(sp2)–H bond of pyrene 2a, affording intermediate 7d, which then undergoes reductive elimination to yield the C2-substituted pyrene 6a1. The C2 silylation of 2a followed by C7 borylation afforded 6b. Subsequently, C2- and C7-disubstituted pyrene 6b was used as a coupling partner in the cross-coupling reaction, and it was subjected to the sequential cross-coupling reactions to afford the pyrene motif 9a.

2.2. Direct Functionalization of the C4 Position of Pyrenes

Following the earlier work on direct C–H borylation of C2 and C7 positions of pyrene, Liu and Marder’s group revealed [66] the direct C–H borylation of pyrene core 2a at the C(4) position using [Ir(COD)Cl]2/dtbpy as the catalyst precursor, while the C(2)- and C(7)-positions of pyrene 5b are occupied with a bulky substituent. Accordingly, the C–H-borylated pyrene 10b was obtained, and then it was subjected to the cross-coupling reaction to afford 11a (Scheme 7). Along this line, the C(2), C(7)-bis-borylated pyrene 3f

5 (8 mol%), NaBHEt3 (16 mol%), and 2 equiv of B2Pin2 in the presence of cyclohexene (2 equiv) resulted in the bis-borylated product of pyrene 3f with a 78% yield (Scheme 5).
was obtained from pyrene 2a. Then, 3f was subjected to C(4)–H borylation to afford the tris C—H-borylated product 10c. Subsequently, 10c was subjected to the cross-coupling reaction to afford 11b (Scheme 7).

Scheme 6. Functionalization of the C2 and C7 positions of pyrenes. Iridium-catalyzed intermolecular dehydrogenative silylation of pyrenes and plausible mechanism for the silylation of pyrenes [68].
Itami reported [69,70] the direct C–H activation and arylation of pyrenes 2a and 10a with arylboroxins 12a as arylating agents using Pd(OAc)$_2$ as the catalyst and o-chloral as an oxidant, affording C–H-arylated pyrene 13. Accordingly, a wide range of pyrenes, namely 13a–i, 13j–l, 14a,b, and 14c, were assembled (Scheme 8). The screening of the reaction conditions via varying oxidants and solvents resulted in the mixture of Pd(OAc)$_2$ (2.5 mol%) and o-chloral (1 equiv) in DCE at 80 °C as the optimized condition for accomplishing the synthesis of the C–H-arylated pyrene 13 via direct C–H arylation of pyrene. Other oxidants, such as DDQ, p-chloranil, p-benzoquinone, CuCl$_2$, and K$_2$S$_2$O$_8$, were ineffective. Other than o-chloranil, 2-benzoquinone was found to display some reactivity, affording the C–H arylation product. The C4 selectivity that was observed could be explained via various pathways. One possible mechanism proposed by Itami et al. [69] was based on the electrophilic palladation of pyrene with aryl palladium species at the C1 position, forming a cationic intermediate species, which then generates intermediates (15c via 15a,b) through the σ-π-σ isomerization process. Subsequent deprotonation of intermediates (15c) followed by reductive elimination generates the C–H-arylated product 13 via 15d (Scheme 9). Alternatively, the formation of a palladium complex at the C4–C5 double bond and the electrophilic palladation reaction would generate a cationic intermediate (15c). Furthermore, the Heck-type insertion of aryl palladium species may take place to form an intermediate (15f via 15c), which then gives the C–H-arylated product 13 either via β-hydrogen elimination or via protodepalladation (through 15g). Furthermore, Itami et al. demonstrated [70] the formation of 4-mesitylpyrene when pyrene was treated with Pd(OAc)$_2$ (10 mol%), o-chloranil (1 equiv), and AgOTf (20 mol%) in mesitylene (36 equiv) at 50 °C for 14 h. Along this line, C4-arylated pyrene was synthesized by Glorious et al. using Pd/C (Scheme 8) [71] Two different coupling partners were employed to accomplish
the C–H arylation reaction of pyrene 2a to obtain their corresponding C4-arylated pyrenes 13b,c,g. Pyrene 2a was treated with either [Ar₂I]BF₄ (1 equiv) or [ArI(TRIP)]BF₄ in the presence of Pd/C (5 mol%) in DME at 100 °C to give the desired C–H-arylated pyrenes. In this case, the reaction seemed to be involving a similar plausible mechanism proposed by Itami et al., affording the C–H-arylated pyrenes (Schemes 8 and 9) [69].


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**Scheme 8.** Functionalization of the C4 and C10 positions of pyrenes. Synthesis of C–H-arylated pyrenes via direct C–H arylation of pyrenes [69–71].

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a Ratio of major regioisomer to any other regioisomers.
b Conditions: 80 °C, Pd/C (2.5 mol%).
c Conditions: 100 °C, Pd/C (2.5 mol%). TRIP = 2,4,6-trisopropylphenyl.
Oi et al. demonstrated [72] a palladium-catalyzed C–H bond arylation reaction of arenes, including pyrene with aryltrimethylsilanes, in the presence of CuCl₂ as an oxidant (Scheme 10). Pyrene, phenyltrimethylsilane (2 equiv), PdCl₂ (5 mol%), and CuCl₂ (4 equiv) in 1,2-DCE were heated for 16 h at 80 °C to afford 13a (34%) and 16a (14%). Electrophilic transmetalation of PdCl₂ with ArSiMe₃ takes place at the ipso-Si position, generating an aryl palladium intermediate in the presence of CuCl₂. Subsequently, aromatic electrophilic substitution occurs between pyrene 2a and the aryl palladium intermediate, leading to the formation of a diaryl palladium intermediate (16b). The exact structure of the aryl palladium intermediate has not been definitively determined, but the involvement of CuCl₂ in this step is considered crucial for the reaction to proceed. Reductive elimination takes place from the diaryl palladium species 16b, affording the cross-coupled product 13. Then, CuCl₂ oxidizes the palladium species to regenerate PdCl₂.

2.3. Direct Functionalization of the C1 and C6 Positions of Pyrenes

Agarwal et al. established [73] a ferrocene-catalyzed C–H arylation reaction of arenes including pyrene, and a reaction mechanism study using cyclic voltammetry. Ferrocene-catalyzed C–H arylation of pyrene was accomplished using an aryl diazonium salt as an arylating agent (Scheme 11). The formation of arylated pyrene 13a was observed by treating pyrene 2a and phenyl diazonium tetrafluoroborate 17a in the presence of ferrocene (10 mol%) at rt in acetone medium. The formation of a radical intermediate in the initial step of the reaction was evident by the EPR experiment, which was further supported by the DFT calculation. A plausible reaction mechanism was stated. Ferrocene triggers the formation of a phenyl radical (17d) from 17a via the single-electron transfer mechanism and 17c. The formation of phenyl radicals was investigated via cyclic voltammetry. Then, the phenyl radical reacts with pyrene 2a, followed by electron transfer to a ferrocenium ion (via 17e), and abstraction of a proton from 17f generates C–H-arylated pyrene 13a.

Scheme 9. A plausible mechanism proposed by Itami et al. for the synthesis of C–H-arylated pyrenes via direct C–H arylation of pyrenes at the C4 position [69–71].
A plausible mechanism was stated by the authors of [75] for the C–H phosphonylation reaction of electron-rich arenes. Yoshida et al. divulged [74] an example of metal- and chemical-oxidant-free electrochemical C–H/C–H coupling of indole 17b and pyrene 2a compounds using radical cation pools (Scheme 11). Anodic oxidation was carried out using an H-type divided cell equipped with a carbon felt anode and a platinum plate cathode. The electrochemical C–H/C–H coupling of indole and pyrene compounds was performed using the following typical procedure to afford 17j. An indole compound solution (0.66 mmol) in a 0.1 M solution of Bu4NPF6 in DCM (10 mL) was placed in the anodic chamber. Then, trifluoromethanesulfonic acid (150 mL) and a 0.1 M solution of Bu4NPF6 in DCM (10 mL) were placed in the cathodic chamber. Constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring of the reaction mixture for 60 min. Pyrene substrate (0.05 mmol) and 1,2-dimethoxyethane (0.1 mL) were added to the anodic chamber at −40 °C. The resulting mixture was stirred at −40 °C for 3 h, followed by at −15 °C, and the reaction mixture was stirred for 1.5 h. Then, Et3N (0.2 mL) was added, and the resulting mixture was warmed to room temperature and subjected to workup and purification to afford the product 17j.

König’s group revealed [75] the C–H phosphorylation reaction of electron-rich arenes and heteroarenes using visible light photoredox catalysis. Pyrene 2a was reacted with Ru(bpz)3 (2 mol%), (NH4)2S2O8, and P(OEt)3 in CH3CN at 25 °C for 20 h under visible light irradiation (455 nm). The reaction yielded two products, namely C1-substituted pyrene (18a) and C1- and C6-disubstituted pyrene (18b), both with a 48% yield (Scheme 12). A plausible mechanism was stated by the authors of [75] for the C–H phosphorylation reaction of electron-rich arenes, such as pyrene 2a using visible light photoredox catalysis. Upon photoexcitation, the photocatalyst [Ru(II)O4]2−[PF6]2− produces an excited state [*Ru(II)O4]2−[PF6]2+, which accepts an electron from pyrene 2a, converting it into its corresponding pyrenyl cation. Ammonium persulfate (NH4)2S2O8 accepts an electron from the reduced Ru(II) species, completing the catalytic cycle and affording a sulfate dianion and a sulfate radical anion. The pyrenyl radical cation reacts with nucleophilic P(OEt)3, generating the species 18c. Hydrogen atom abstraction via SO4− anions leads to the generation of a transient pyrenyl phosphonium intermediate species. Then, with the help of the sulfate dianion, the desired C–H phosphorylation product is generated. Takai et al. disclosed [76] the nitration of pyrene under mild conditions using Fe(NO3)3·9H2O, which...
generates a nitrogen dioxide free radical species, giving product 19a with a 89% yield. This C–H nitration process does not need any acidic promoters, pyridine-based-directing groups, ionic liquids, or supported metal nitrates (Scheme 12). Itami’s group reported [77] a gold-catalyzed C–H imidation reaction of polycyclic aromatic hydrocarbons and the introduction of an amino group at the C(2) position of the pyrene core 2a/2a (Scheme 12). In the presence of AuCl (10 mol%) and biquinoline 19b (12 mol%), the pyrene core reacted with NFSI in DCE at 70 °C for 12 h. The formation of a Au–ligand complex is believed to react with NFSI to generate an imidyl radical, which would then undergo radical addition to the pyrene core. Single-electron transfer from the resulting radical intermediate affords a cationic intermediate, which is then aromatized to generate the corresponding imidated pyrene 19c.

Scheme 11. Functionalization of the C1 position of pyrenes. Ferrocene catalyzed C–H arylation of pyrenes using an aryldiazonium salt as an arylating agent and electrochemical C–H/C–H coupling of indole and pyrene compounds using radical cation pools [73,74].
2.4. Direct Functionalization of the C9 and C10 Positions of Pyrenes

Nowicka and Willock disclosed [78] their experimental and computational approaches comprising the mechanistic insights of the selective ruthenium ion-catalyzed oxidation of pyrenes. A mechanistic investigation into the ruthenium ion-catalyzed oxidation of various aromatic hydrocarbons led to an understanding of the chemistry of aromatic C=C bond cleavage. The DFT calculations showed that the regioselectivity in the reaction can be understood in terms of the preservation of aromaticity in the initial formation of a metallacycle at the C(9), C(10) and C(4), C(5) double bonds of pyrene 2a (Scheme 13). Two competing pathways comprising the C=C bond cleavage leading to a dialdehyde 20h and C–H activation followed by H-migration to the RuOx complex to give diones 20f were identified. Based on the experimental data, it was concluded that the preferred pathway in oxidation was strongly dictated by the choice of reaction solvent. Pola et al. [79] synthesized [Zn(TPTTP)]Cl2 20a and [Ru(TPTTP)]Cl2 20a’ complexes and explored their properties and utility. Both [Zn(TPTTP)]Cl2 and [Ru(TPTTP)]Cl2 complexes were tested for their C–H oxidation of pyrene 2a. Treatment of the Zn(II) or Ru(II) complexes with pyrene 2a resulted in the formation of dione 20b via the photo-oxidation pathway (Scheme 13).

![Chemical structures and reactions](image)

Sequence of oxidation based on 1H NMR of monophasic, HPLC-MS analysis of biphasic reaction and DFT calculations (Nowicka and Willock et al.)


2.5. C–H Functionalization and Involving the Pyrene Backbone

Mastarlerz and co-workers demonstrated [80] a new synthetic route to synthesize tetraindenopyrene 21f using the C–H functionalization route. The synthesis of tetraindenopyrene was accomplished starting with commercially available hexahydropyrene. Hexahydropyrene was selectively four-fold C–H brominated to afford 21b with a 84 % yield via simple filtration. Subsequent Suzuki–Miyaura cross-coupling under Fu’s conditions (Pd4dba3 and HPr3Bu3BF4) and oxidation of the unsaturated propylene tethers using DDQ gave the pyrene derivative 21d with a 70 % yield over two steps. The next step was the tetra C–H chlorination of pyrene 21d, which was performed using a slight excess (4.5 equiv) of N-chlorosuccinimide (NCS) in chloroform to afford 21e with a 94 % yield. Finally, the
synthesis of tetraindenopyrene 21f was accomplished through the C–H activation step (Scheme 14).

Scheme 14. Synthesis of tetraindenopyrene via the C–H functionalization reaction and involving the pyrene backbone [80].


In this section, we have presented the recent developments pertaining to the C–H activation and functionalization of pyrene motifs using directing groups. There have been successful efforts in using the direct C–H activation/functionalization of different positions of the pyrene core (as described in the previous section). The efficiency and region- or site-selectivity issues and expansion of the scope of C–H functionalization of pyrene were tackled using the directing group-assisted C–H activation concept.


Miura et al. revealed [81] two examples of copper-mediated dehydrogenative biaryl coupling of the pyrene core using the picolinamide bidentate directing group-assisted C–H functionalization strategy [81–89]. Substrate N-(pyren-1-yl)picolinamide 22a was treated with the azole derivatives 22aa and 22ab (2 equiv) in the presence of Cu(OAc)$_2$ (3 equiv) and PivOH (1 equiv) in mesitylene at 165 °C for 4 h under a nitrogen atmosphere (Scheme 15). These trials successfully afforded the C10-functionalized pyrene derivatives 22ca and 22cb of 71% and 69% yields, respectively. A plausible mechanism [81] for the C10 site-selective functionalization process involving the bidentate directing group, the chelation-assisted pathway, has been proposed. The C–H cupration of a relatively acidic C–H bond of 22ab, followed by N,N-bidentate coordination with 22a, generates the organocopper intermediate 22d. Subsequently,
substrate 22a undergoes C–H cleavage, accompanied by oxidation with additional Cu(II), to form the Cu(III) metallacycle 22f. Reductive elimination then generates the corresponding C10-functionalized pyrene 22cb. The site-selectivity of this reaction is guided by the formation of the kinetically favored five-membered metallacycle intermediate 22e.

Scheme 15. Functionalization of the C10 position of pyrenes. Copper-mediated dehydrogenative biaryl coupling of 1-aminopyrene with 1, 3-azoles [81].
Our research group [89] reported the application of the bidentate directing group-assisted C–H functionalization tactics to functionalize the pyrene core. The relatively inaccessible K-region C10 position of the pyrene core was subjected to C–H arylation and alkylation. The Pd(II)-catalyzed γ-C–H arylation and alkylation of the C10 position of N-(pyren-1-yl)picolinamide possessing a picolinamide bidentate directing group resulted in various C1- and C10-disubstituted pyrene scaffolds (23a,b) (Scheme 16). We have also shown the removal of the picolinamide directing group following the C–H arylation/alkylation reactions. The structures of representative pyrene derivatives were confirmed via X-ray structure analysis, which confirmed the site-selective γ-C–H functionalization of the inaccessible K-region C10 position of the pyrene core. Given the importance of the pyrene derivatives across different fields of chemical sciences, our work contributed to the augmentation of the library of pyrene derivatives with C1- and C10-disubstituted pyrene amide motifs [89].


Nishihara et al. reported [90] an example of peri-selective chalcogenation of 1-aminopyrene with diaryl disulfide through C–H bond cleavage using a palladium catalyst (Scheme 17). N-(pyren-1-yl)picolinamide 22a, diphenyl disulfide (1.2 equiv), PdCl2(NCPh)2 (10 mol%), CuCl2 (10 mol%), and PivOH (1.2 equiv) in DMSO were heated at 100 °C for 12 h to afford N-(10-(phenylthio)pyren-1-yl)picolinamide with a 62% yield. A plausible mechanism for the C10 site-selective C–H chalcogenation reaction involving the bidentate directing group, the chelation-assisted pathway, has been proposed [90]. Palladium complex 24c is formed with picolinamide; then, cyclopalladation selectively occurs at the C10 position of the pyrene core to afford 24d. Oxidative addition of diphenyl disulfide to 24d generates 24e. Reductive C-S bond formation from 24e gives the product ligand complex 24f. Ligand exchange in 24f affords 24g. The final product 24b dissociates from 24g, while 22a simultaneously captures the released palladium in the catalytic cycles. PivOH may assist in the cleavage of the C–H bond in the concerted metalation-deprotonation (CMD) step to generate 24d.

In 2017, Punniyamurthy et al. demonstrated [91] a copper(II)-mediated chelation-assisted regioselective C–N coupling involving pyrene and indoles through the dehydrogenative cross-coupling method and an example of N-pyrenylation of a 5-methoxy indole affording 24i (Scheme 17). The N-(pyren-1-yl)picolinamide 22a was treated with 5-methoxy-1H-indole (2 equiv) in the presence of Cu(OAc)$_2$ (20 mol%), Ag$_2$CO$_3$ (25 mol%), K$_3$PO$_4$ (2 equiv), and NMO (2 equiv) in DMSO at 140 °C for 14 h, and this reaction gave the C10-functionalized pyrene 24i with a 35% yield. The plausible mechanism for the site-selective C–N coupling reaction involving pyrene and indole affording 24i has been
proposed. Initially, N-cupration of substrate 22a with Cu(OAc)₂ may form 24j, which may undergo substitution with indole 24h to generate the intermediate 24k. Then, the intermediate 24k may generate 24i in the presence of Cu(OAc)₂ via oxidative addition, which can lead to pyrenyl C(γ)–H cupration to make organocopper(III) species 24m. Then, the C–N coupled product 24i may be formed through reductive elimination from 24m.

Punniyamurthy et al. unveiled [92] a copper-mediated regioselective C–H etherification of 1-aminopyrene with arylboronic acids utilizing water as an oxygen source (Scheme 18). The N-(pyren-1-yl)picolinamide substrate 22a, phenylboronic acid (2 equiv), Cu(OAc)₂ (1.5 equiv), Cs₂CO₃ (2.5 equiv), and DMSO mixture was heated at 130 °C for 8 h, which resulted in an etherification product 25a. The etherification reaction occurred at the C10 position of pyrene core 22a. A plausible mechanism for the selective C10 etherification of pyrene was proposed. Initially, the reaction of Cu(OAc)₂ with substrate 22a in the presence of a base forms a Cu(II) species, which is further oxidized by Cu(OAc)₂, leading to the formation of a tetracoordinated Cu(III) complex 25b. Next, an intramolecular cyclometallation process through C–H bond activation forms a copper(III) species 25c. This copper(III) species can then react with a boronate complex and water, forming a copper(III) intermediate 25d. The reductive elimination step then affords the etherification product 25a.

Scheme 18. Functionalization of the C10 position of pyrenes. Copper-mediated regioselective C–H etherification of 1-aminopyrene with arylboronic acid using water as an oxygen source [92].

Chatani's group reported [93] a rhodium(I)-catalyzed C(10) alkylation of 1-aminopyrene with alkenes through a bidentate picolinamide chelation system, affording 26b (Scheme 19). A plausible mechanism for the rhodium(I)-catalyzed C(10) alkylation of 1-aminopyrene with alkenes through a bidentate picolinamide chelation system, affording 26b, has been proposed. Initially, the amide N–H bond of pyrene substrate 22a undergoes oxidative addition to the
Rh center, leading to the formation of a Rh(III) hydride species 26c. Then, intermediate 26c eliminates a carboxylic acid motif, resulting in the generation of species 26h. It is also possible that the species 26c can form intermediate 26i. The hydride species 26c can reversibly bind to the acrylate motif. The acrylate then undergoes insertion into the H–Rh bond in intermediate 26d, generating the species 26e. Then, species 26e releases a carboxylic acid motif, leading to the formation of the carbine species 26f. Subsequently, a C–H insertion into species 26f occurs, generating the cyclometalated species 26g. Finally, in the presence of carboxylic acid, reductive elimination takes place, affording the C10-alkylated pyrene, and the active Rh(I) catalyst is regenerated.

Scheme 19. Functionalization of the C10 position of pyrenes. Rhodium(I)-catalyzed C(10) alkylation of 1-aminopyrene with alkenes through a bidentate picolinamide chelation system [93].

Wu et al. described [94] the cobalt-catalyzed C–H carbonylation of 1-aminopyrene and synthesis of pyrene-derived (NH)-benzo[cf]indol-2(1H)-one through a bidentate picolinamide chelation system (Scheme 20). This reaction employs picolinamide as a traceless directing group and uses benzene-1,3,5-triyl triformate (TFBen, 27a) as the CO source,
affording 27b. A plausible mechanism for the cobalt-catalyzed C–H carbonylation of 1-aminopyrene and synthesis of 27b through a bidentate picolinamide chelation system has been proposed. Initially, the Co(II) catalyst coordinates with 22a and is oxidized by Ag(I) to generate the Co(III) complex 27c, which undergoes a selective C–H activation reaction at the C10 position of 22a, leading to the formation of intermediate 27d. Then, coordination of in situ-generated CO from TFBen gives the acyl Co(III) complex 27e, which undergoes reductive elimination, generating species 27f. The hydrolysis of species 27f gives the expected product 27b and releases Co(I) species. The active Co(II) catalyst is then regenerated through the oxidation of Co(I) by Ag(I) in the catalytic cycle.

Scheme 20. Functionalization of the C10 position of pyrenes. Cobalt-catalyzed C–H carbonylation of 1-aminopyrene and synthesis of the pyrene-derived (NH)-benzo[cd]indol-2(1H)-one derivative 27b through a bidentate picolinamide chelation system [94].

Feng et al. revealed [95] an example of cobalt-catalyzed hydroarylation of 1,3-diynes with N-(pyren-1-yl)picolinamide promoted by TFE, affording C10-alkenylated pyrene 28b
Substrate N-(pyren-1-yl)picolinamide, 1,4-diphenylbuta-1,3-diyne (2 equiv), Co(OAc)$_2$·H$_2$O (30 mol%), and KOAc (2 equiv) in TFE were heated at 100 °C for 12 h, which successfully gave (E)-N-(10-(1,4-diphenylbut-1-en-3-yn-1-yl)pyren-1-yl)picolinamide (28b) with a 76% yield. A plausible mechanism for the cobalt-catalyzed hydroarylation of 1,3-diynes with N-(pyren-1-yl)picolinamide promoted by TFE, affording C10-alkenylated pyrene 28b, has been proposed via intermediates 28c and 28d. The protonolysis of intermediate 28d results in the formation of 28b, and the protonolysis step is facilitated by trifluoroethanol.

Punniyamurthy showed [96] an example of copper-mediated oxidative C–H/N–H annulation of 1-aminopyrene with diethyl malonate, affording 29b through a bidentate picolinamide chelation system (Scheme 22). Substrate N-(pyren-1-yl)picolinamide 22a was treated with diethyl malonate (2 equiv) in the presence of Cu(OAc)$_2$ (1 equiv) and NaOPiv·H$_2$O (2 equiv) in dimethyl sulfoxide at 120 °C for 4 h in air. This reaction gave the diethyl 3-picolinoylcyclopenta[c]pyrene-4,4(3H)-dicarboxylate product 29b with a 51% yield. A plausible mechanism for the copper-mediated oxidative C–H/N–H annulation of 1-aminopyrene with diethyl malonate, affording 29b through a bidentate picolinamide chelation system, has been proposed. First, diethyl malonate 29a reacts with Cu(OAc)$_2$ in the presence of a base to give intermediate 29c which reacts with N-(pyren-1-yl)picolinamide 22a and forms species 29d. Then, 29d may oxidize to generate species 29e in the presence of Cu(OAc)$_2$ and can further undergo ortho-C(sp$^2$)–H cupration to deliver the organocopper(III) complex 29f. Species 29f then affords 29g via reductive elimination. Product 29b is then formed via intramolecular N–H/C(sp$^2$)–H dehydrogenative cross-coupling in the presence of Cu(OAc)$_2$ and bases.
Miura et al. showed [97] an iridium-catalyzed acylmethylation reaction and a rhodium-catalyzed amidation reaction at the C10 position of a pyrene moiety via the thio group-assisted C–H activation strategy. The reaction of 30a with sulfoxonium ylide 30b in the presence of [Cp*IrCl2]2 (2.5 mol%) and AcOH (2 equiv) in HFIP at 100 °C afforded the C10-alkylated pyrene moiety 30c with a 73% yield. Similarly, the reaction of 30a with the dioxazolone moiety 30d in the presence of [Cp*Rh(MeCN)3][SbF6] (5 mol%) in HFIP at 100 °C gave the C(10) amidation product 30e with a 23% yield (Scheme 23).

Scheme 22. Functionalization of the C10 position of pyrenes. Copper-mediated oxidative C–H/N-H annulation of 1-aminopyrene with diethyl malonate, affording 29b [96].
Hierso and Roger reported [98] the Rh(I)-catalyzed, diphenylphosphino group-assisted C(10)–H arylation of 1-pyrenylphosphine. A wide range of ortho-, meta-, and para-substituted aryl bromides and heteroaryl bromides were reacted with 1-pyrenylphosphine in the presence of the [Rh(COD)2]BF4 catalyst to afford the corresponding C(10)-arylated 1-pyrenylphosphine derivatives (Scheme 24). Notably, 1-pyrenylphosphine was also reacted with bulky ortho-functionalized bromoarenes 1- or 2-bromonaphthalene, 9-bromophenanthrene, 9-bromoanthracene, 3-bromofluoranthene, and 1-bromopyrene to afford the corresponding 1-pyrenylphosphine derivatives. The observed selective arylation at the C(10) position of the pyrene core was confirmed with X-ray structures of representative C(10)-arylated 1-pyrenylphosphine derivatives. The C(10)–H arylation reaction of 1-pyrenylphosphine was also accomplished using a Rh(III) catalyst (e.g., [RhCl2(Cp*)]2).

This encouraged the authors to synthesize the Rh(III) complexes 31aa, 31ab, and 31ac, which are expected to be the key intermediate complexes in the catalytic process affording the C(10)-arylated 1-pyrenylphosphine (Scheme 25). Complex 31aa was synthesized from 1-pyrenylphosphine and [RhCl2(Cp*)]2. Next, complex 31ab was synthesized from 1-pyrenylphosphine, [RhCl2(Cp*)]2 and KOAc. The structure of complexes 31aa and 31ab was confirmed via X-ray structure analysis. Then, the Rh(III) cationic complex 31ac was obtained by treating the complex 31ab with 1-pyrenylphosphine in the presence of KPF6. Then, complexes 31aa, 31ab, and 31ac were employed as catalysts in the C(10)–H arylation of 1-pyrenylphosphine with 4-bromoanisole. The Rh(III) complex 31aa and the cationic metallacycle 31ac gave the C(10)-arylated 1-pyrenylphosphine 31ai of 77–88% yields, and the metallacycle 31ab gave the C(10)-arylated 1-pyrenylphosphine 31ai of a low yield (29%). It was found that the metallacycle 31ab may travel out of the catalytic cycle for a while by forming complex 31ad through halogen exchange. A plausible mechanism for the Rh-catalyzed C(10)–H arylation of 1-pyrenylphosphine was stated (Scheme 25) [98]. An ortho-metalation reaction occurs in complex 31aa to afford 31ab through a concerted metalation-deprotonation reaction assisted by the base, which then generates the cationic complex 31ac. Then, the oxidative addition of aryl bromide on the complex 31ac gives the complex 31ae through a reductive elimination/C–C bond formation process. Subsequently, the coupling product 31b is released, generating the cationic complex 31af that is ready for further cyclometallation process in the catalytic cycle. Overall, Hierso and Roger’s report described a facile condition for the peri-functionalization of the topical π-extended 1-pyrenylphosphine derivative using a cationic Rh(III) C–H arylation strategy. The arylation reaction took place at the K-region of the pyrene core, which is generally inaccessible by conventional organic synthesis.

3.2. Directing Group-Assisted C–H Functionalization of the C2 and C7 Positions of Pyrenes

Nakamura et al. described [99] an example of iron-catalyzed C2 allylation of pyrene-1-carboxamide with allyl phenyl ether 32a, affording 32b through a bidentate 8-aminoquinoline system (Scheme 26). Substrate N-(quinolin-8-yl)pyrene-1-carboxamide 32b, allyl phenyl ether (2 equiv), Fe(acac)3 (20 mol%), dppen (10 mol%), ZnCl2·TMEDA (2 equiv), and t-BuCH2MgBr (3.4 equiv) in THF were heated at 70 °C for 135 h to afford the 2-allyl-N-(quinolin-8-yl)pyrene-1-carboxamide 32b. Nakamura et al. noticed [99] an unexpected generation of intermediate 32d that formed after the cleavage of the C–H bond of the substrate under investigation, which interacts with an allyl ether to afford 32e via path A. This is in contrast to the conventional cross-coupling reaction involving an allyl group (path B) or the extensively studied oxidative C–C bond formation process (path C), both of which have been extensively explored (Scheme 26).
released, generating the cationic complex $31af$ that is ready for further cyclometallation process in the catalytic cycle. Overall, Hierso and Roger’s report described a facile condition for the peri-functionalization of the topical $\pi$-extended 1-pyrenylphosphine derivative using a cationic Rh(III) C–H arylation strategy. The arylation reaction took place at the K-region of the pyrene core, which is generally inaccessible by conventional organic synthesis.

Scheme 24. Functionalization of the C10 position of pyrenes. Phosphorus-directed rhodium-catalyzed C–H arylation of 1-pyrenylphosphines is selective at the K-region [98].

$\text{PhCF}_3$ (0.16 M) reflux, 18 h

selected examples

$R^1 = \text{Me, NPh}_2, \text{Ac, CF}_3, \text{Cl, CHO, NO}_2$

$^1H$ NMR yield: up to 96% (isolated yield up to 90%)

yield: 92% (87)

yield: 90% (85)

yield: 65% (85)

yield: 88% (80)

yield: 47% (41)

yield: 7% (-)
Scheme 25. Functionalization of the C10 position of pyrenes. Phosphorus-directed rhodium-catalyzed C–H arylation of 1-pyrenylphosphines selective at the K-region [98].
Our research group [89] also reported the application of the 8-aminoquinoline bidentate directing group-assisted C–H functionalization tactics to functionalize pyrene-1-carboxamide. The relatively inaccessible C2 position of the pyrene core 22b was subjected to C–H arylation and alkylation. The Pd(II)-catalyzed β-C–H arylation and alkylation of the C2 position of pyrene-1-carboxamide 22b possessing the 8-aminoquinoline bidentate directing group yielded various C1- and C2-disubstituted pyrene scaffolds 32g,h (Scheme 26). The structures of representative pyrene derivatives were confirmed via X-ray structure analysis, which confirmed the site-selective C–H functionalization of the inaccessible C2 position of the pyrene core. This work contributed to the augmentation of the library of pyrene derivatives with C1- and C2-disubstituted pyrene amide motifs [89].

In 2020, Larrosa and co-workers [100] successfully synthesized a diverse range of C–H arylated pyrene derivatives (33b) by employing a palladium-catalyzed C–H ortho-arylation method on pyrene-1-carboxylic acid (33a) (Scheme 27). This approach provided a convenient route to access a variety of arylated pyrene compounds with substituents at the C1- and C2-positions. The C1 substituent (carboxylic acid unit) was converted into different functional groups, such as iodide, alkenyl, aryl, or alkyl functionalities. By utilizing this flexibility, the Larrosa group was able to produce arylated pyrene ammonium salts, which exhibited superior performance compared to the original non-arylated compound in the aqueous liquid phase exfoliation (LPE) process of graphite. Using the PEPPSI-Ipr catalyst, the decarboxylative C–H arylation of pyrene-1-carboxylic acid 33a gave C2-arylated pyrenes (33c). Pyrene-1-carboxylic acid (33a) was treated with aryl iodides (3 equiv) in the presence of Pd(OAc)2 (6 mol%), KOAc (2.8 equiv), NMe3Cl (2.16 equiv), and AcOH (1.5 equiv) at 120 °C for 45 h, resulting in the formation of C–H-arylated pyrene derivatives (33b) with up to a 90% yield. The arylation of pyrene-1-carboxylic acids (33b) were subsequently converted into their corresponding iodoarenes 33d by treating pyrene-1-carboxylic acid (33b) with I2 (3 equiv) and K3PO4 (1 equiv) in ortho-dichlorobenzene (0.2 M) at 120 °C for 21 h. On the other hand, 2-arylpyrene (33c) was synthesized by treating pyrene-1-carboxylic acid (33a) with aryl iodide (3 equiv) in the presence of PEPPSI-Ipr (2 mol%), Ag2CO3 (1 equiv) and AcOH (1 M) at 150 °C for 19 h. Iodopyrene (33d) underwent further derivatization through well-stabilized cross-coupling reactions, such as the Suzuki and Sonogashira reactions using aryllithium, primary aryl alkynes, and trimethylsilylacetylene. These reactions resulted in the formation of the corresponding products 33e and 33f. The Pd-catalyzed C–H arylation of pyrene-1-carboxylic acid is believed to occur through a Pd(II)-Pd(IV) mechanism. Initially, cyclometallation takes place, leading to the formation of 33g, following which a Pd(IV) intermediate (33h) is generated upon oxidative addition of ArI with 33g. Subsequently, rapid reductive elimination occurs, resulting in the production of the arylated carboxylic acid 33b and the restoration of the Pd(II) species.

Zhong et al. reported [101] a Ru(II)-catalyzed pyridyl moiety-directed protocol for the synthesis of C2- or C2- and C7-arylated pyrene derivatives via the C–H activation pathway under microwave and conventional heating conditions (Scheme 28). The pyrene core, containing the pyridyl moiety, was treated with aryl bromides with [RuCl2(p-cymene)]2 (5 mol%), MesCOOH (0.6 equiv), and K2CO3 (4 equiv) in toluene under reflux for 36 h to afford the C–H arylated pyrenes 34b/35b (C2- or C2- and C7-arylated pyrene derivatives). A plausible reaction pathway for the Ru(II)-catalyzed pyridyl moiety-directed C–H arylation of pyridine core 34a was proposed (Scheme 29). The coordination of the pyridine moiety with the Ru catalyst, followed by a metalation-deprotonation C–H bond activation process at the C2 position, gave the intermediate 36c. The C–H activation reaction is possibly promoted by carbonyl oxygen of the MesCOO− group, as represented in species 36b. Due to the steric hindrance, the possibility of C–H activation at the C10 position of the pyrene core is neglected. Dissociation of the MesCOO− unit from species 36c, followed by oxidative addition of aryl iodide with 36c, gives the cationic Ru(IV) intermediate 36d. Reductive elimination of species 36d affords the C2-arylated pyrene derivative 34c and the Ru catalyst.
Scheme 27. Functionalization of the C2 position of pyrenes. Pd-catalyzed C–H arylation of pyrene-1-carboxylic acid [100].
Due to the steric hindrance, the possibility of C–H activation at the C10 position of the pyrene core is neglected. Dissociation of the MesCOO⁻ unit from species 36c, followed by oxidative addition of aryl iodide with 36c, gives the cationic Ru(IV) intermediate 36d. Reductive elimination of species 36d affords the C2-arylated pyrene derivative 34c and the Ru catalyst.

This reaction afforded the C(9)-arylated pyrene-1-carboxamide derivative 37c. The desired product was obtained through a plausible six-membered metalacyclic intermediate 37d, followed by aryl migration. You et al. revealed [103] an example of Cu-catalyzed C9 arylation of pyrene-1-carboxamide (37e) with mesityl(phenyl)iodonium triflate (37f) through a bidentate 8-aminoquinoline system, affording 37g (Scheme 30). Substrate N-(tert-butyl)pyrene-1-carboxamide 37e was treated with mesityl(phenyl)iodonium triflate in the presence of Cu(OTf)2 (10 mol%) in 1,2-dichloroethane at 70 °C for 24 h. This reaction afforded the C(9)-arylated pyrene-1-carboxamide derivative 37g of 65%. A plausible mechanism for the Cu-catalyzed C9 arylation of pyrene-1-carboxamide 37e with mesityl(phenyl)iodonium triflate (37f) through a bidentate 8-aminoquinoline system was proposed. Initially, Cu(I) is generated by the reduction or disproportionation of Cu(II) species. Then, phenyliodinium salt oxidizes Cu(I) to a highly electrophilic Cu(III)-phenyl intermediate. The coordination of the carbonyl oxygen of pyrene 37e to the Cu(III)-phenyl intermediate generates Cu(III) species 37h, which undergoes an aryl transfer reaction via the Heck-like four-membered ring transition state to afford intermediate 37i with Cu(III) and an aryl group-added pyrene system. Then, the breakdown of the C(10)-Cu bond generates Cu(I), and simultaneously, the OTf− anion abstracts the proton from the C(9) position, generating the desired C(9)-arylated pyrene derivative 37g. Our group also showed [89] two examples of C(9) arylation of pyrene-1-carboxamide. Substrate 37e was heated with aryl boronic acid (1.25 equiv) in the presence of Pd(OAc)2 (10 mol%) and NFSI (1.25 equiv) in 1,2-DCE (2 mL) at 90 °C for 24 h, which afforded the C(9) arylation of pyrene-1-carboxamide 37j and 37k of 53% and 55% yields, respectively (Scheme 30).

Scheme 29. A plausible reaction pathway for the Ru(II)-catalyzed pyridyl moiety-directed C–H arylation of the pyrene core [101].

3.3. Directing Group-Assisted C–H Functionalization of the C9 Position of Pyrenes

Yang et al. disclosed [102] an example of P=O moiety-directed arylation at the C(9) position of pyrene core 37a using 37b and a Cul catalyst in DCE at 100 °C (Scheme 30). The desired product 37c was obtained through a plausible six-membered metalacyclic intermediate 37d, followed by aryl migration. You et al. revealed [103] an example of Cu-catalyzed C9 arylation of pyrene-1-carboxamide (37e) with mesityl(phenyl)iodonium triflate (37f) through a bidentate 8-aminoquinoline system, affording 37g (Scheme 30). Substrate N-(tert-butyl)pyrene-1-carboxamide 37e was treated with mesityl(phenyl)iodonium triflate in the presence of Cu(OTf)2 (10 mol%) in 1,2-dichloroethane at 70 °C for 24 h. This reaction afforded the C(9)-arylated pyrene-1-carboxamide derivative 37g of 65%. A plausible mechanism for the Cu-catalyzed C9 arylation of pyrene-1-carboxamide 37e with mesityl(phenyl)iodonium triflate (37f) through a bidentate 8-aminoquinoline system was proposed. Initially, Cu(I) is generated by the reduction or disproportionation of Cu(II) species. Then, phenyliodinium salt oxidizes Cu(I) to a highly electrophilic Cu(III)-phenyl intermediate. The coordination of the carbonyl oxygen of pyrene 37e to the Cu(III)-phenyl intermediate generates Cu(III) species 37h, which undergoes an aryl transfer reaction via the Heck-like four-membered ring transition state to afford intermediate 37i with Cu(III) and an aryl group-added pyrene system. Then, the breakdown of the C(10)-Cu bond generates Cu(I), and simultaneously, the OTf− anion abstracts the proton from the C(9) position, generating the desired C(9)-arylated pyrene derivative 37g. Our group also showed [89] two examples of C(9) arylation of pyrene-1-carboxamide. Substrate 37e was heated with aryl boronic acid (1.25 equiv) in the presence of Pd(OAc)2 (10 mol%) and NFSI (1.25 equiv) in 1,2-DCE (2 mL) at 90 °C for 24 h, which afforded the C(9) arylation of pyrene-1-carboxamide 37j and 37k of 53% and 55% yields, respectively (Scheme 30).
Scheme 30. Functionalization of the C9 position of pyrenes. Copper-catalyzed arylation of pyrenes assisted by the P=O group [102] Cu-catalyzed arylation of pyrene-1-carboxamide with mesityl(phenyl)iodonium triflate and Pd-catalyzed arylation of pyrene-1-carboxamide with aryloboronic acid [89,103].
4. Annulation of C–H Bonds of Pyrenes, Affording Pyrenes Appended with Additional Rings

In this section, we have presented the recent developments pertaining to the annulation of C–H bonds of pyrenes, affording pyrenes appended with additional rings. Hisler’s group reported [104] transition metal-catalyzed synthesis of benzophosphole-fused pyrene (38c) and benzosilole-fused pyrene (38e) (Scheme 31). A phosphine moiety was introduced in the pyrene core via the Suzuki coupling reaction involving 38a. Compound 38c was synthesized through the C–H activation step involving Chatani’s reaction condition [105]. Similarly, pyrene derivative 38d was obtained through the Suzuki coupling reaction using bromoiodobenzene as the coupling partner, followed by lithiation and quenching with Me₂SiHCl of 1-(2-iodophenyl)pyrene. Compound 38e was synthesized through the C–H activation step involving Takai’s reaction condition [106].

Huang’s group disclosed a facile synthesis of highly fluorescent polycyclic compounds with a pyrene core appended with additional cyclic rings via aza-Michael addition, followed by double C–H activation in the presence of visible light (Scheme 32) [107]. The reaction of 1,8-pyrenedione with two equivalents of N,N′-dimethylethlenediamine (DED) generates 39c under visible light. A plausible photochemical reaction pathway was stated by the authors [107]. The first step of the process affording 39b is the aza-Michael addition reaction, resulting in 39c. The presence of a cis-enone moiety allows for 1,4-addition and hydrogen transfer. The formation of the exited state 39ea from 39c is envisioned as the reactive intermediate responsible for the C–H bond activation reaction (path A), affording 39b. Two facile [1,6]-hydrogen shifts generate the carbon-centered biradical intermediate 39eb from 39ea, which then undergoes oxidation to give the pyrene core-based polycyclic compound 39b in the presence of air. Alternatively, the transformation of intermediate 39c to 39d and then to 39b is an isomerization process enabled by UV light of 254 nm in the presence of a base (paths B and C).
intermediate 39c to 39d and then to 39b is an isomerization process enabled by UV light of 254 nm in the presence of a base (paths B and C).

Scheme 32. Functionalization of the C9 and C10 positions of pyrenes. Synthesis of pyrene core-based polycyclic compounds [107].

Jin et al. developed [108] a Pd-catalyzed cascade reaction of N,N-dialkyl-substituted o-alkynylaniline appended to a pyrene core to construct a pyrene derivative (41b) via peri-C–H annulation, affording 41b (Scheme 33). Treatment of N,N-dialkyl-substituted o-alkynylaniline appended to pyrene 41a with Pd(OAc)$_2$ (10 mol%), Cu(OPiv)$_2$ (1.5 equiv), CsOPiv (0.5 equiv), and AgBF$_4$ (0.5 equiv) in DMAC at 120 °C for 14 h afforded the annulated pyrene derivative 41b. The plausible mechanism was outlined for this reaction. The activation of the triple bond of 41a using the cationic Pd catalyst results in intramolecular 5-endo heteroannulation and indolium-Pd intermediates (41c). Subsequently, a peri-C–H bond activation of the pyrene core takes place via a pivalate-assisted concerted metatation...
deprotonation pathway through transition state 41e. Subsequently, the dealkylation of 41e via the nucleophilic attack of a pivalate counter anion to one of the hexyl groups in 41e generates palladacycle species 41f. Reductive elimination produces the cyclopenta-fused pyrene derivative 41b. The Pd(II) catalyst can be regenerated via the oxidation of Pd(0) with the help of a Cu(II) oxidant.


Ravat’s group reported [109] stereospecific synthesis of pyrene-fused [7]-helicene compounds 42a and 42c, connected via hexagonal and heptagonal rings (Scheme 34). Compounds 42a and 42c were synthesized via a one-pot Suzuki coupling between 5c
and 43a,b, followed by a C–H activation reaction and a two-step Suzuki–Scholl reaction, respectively. The stereospecific synthesis of pyrene-fused [7]-helicene compounds 42a and 42c was accomplished with complete retention of configuration, and the chiroptical properties were studied.

Scheme 34. Stereospecific synthesis of pyrene-fused [7]-helicenes connected via hexagonal and heptagonal rings [109].

Procter et al. established [110] a metal-free annulation method for the synthesis of pyrene core-based benzothiophenes through a two-fold C–H functionalization reaction of pyrene 2a at the C(1) and C(2) positions (Scheme 35). A one-pot annulation of pyrene proceeded through an interrupted Pummerer reaction/[3,3]-sigmatropic rearrangement/cyclization sequence. It has been proposed that the first stage of this process relied on an intermolecular interrupted Pummerer reaction between pyrene and allyl sulfoxide to afford the sulfonium intermediate 44d by activating allyl sulfoxide with triflic anhydride and subsequent trapping with pyrene. Upon heating the mixture, the desired [3,3]-sigmatropic rearrangement of intermediate 44d, followed by spontaneous acid-promoted cyclization, generates sulfonium salt 44e via 44f. In the next stage, the addition of a nucleophilic base, NEt₃, to the same reaction pot converts sulfonium salt 44f into the desired pyrene core-based 2,3-dihydrobenzothiophene product 44b. The conversion of 2a into 44b was accomplished in one pot. Then, exposing the pyrene core-based 2,3-dihydrobenzothiophene product 44b to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave access to the pyrene core-based benzothiophene product 44c. This process has given access to a material-oriented heteroaromatic system-appended pyrene unit.
Scheme 35. Functionalization of the C1 and C2 positions of pyrenes. Stereospecific synthesis of pyrene-fused [7]-helicenes connected via hexagonal and heptagonal rings [110].

5. Miscellaneous C–H Functionalization Transformations Involving Pyrenes

In this section, we have presented miscellaneous C–H functionalization transformations involving pyrenes, affording modified pyrenes. Jin’s group reported an iridium-catalyzed [111] regioselective ortho C2–H bond activation of the pyrene core with the help of an imine moiety (Scheme 36). The reaction between 45a and [Cp*IrCl2]2 in DCM at 50 °C in the presence of sodium acetate resulted in a half-sandwich iridium complex via the C(2)–H bond activation of the pyrene core 45a, affording 45b. A mixture of [Cp*RhCl2]2 (0.05 mmol), NaOAc (0.3 mmol), 45aa (0.1 mmol), and DMAD (0.1 mmol) was stirred at 80 °C in 1,2-dichloroethane (DCE) for 8 h to give an annulated pyrene derivative (45e) with a 93% yield. A mixture of [Cp*IrCl2]2, NaOAc and 45aa (0.1 mmol) gave 45be, which, upon treatment with DMAD, gave the alkenylated species 45c. Treatment of 45c with NaBH4 gave the alkenylated species 45d with a 95% yield. Along this line, treatment of 45be with a terminal alkyne resulted in an alkenylated species of 45f with a 71% yield.

Ganguli et al. disclosed [112,113] a Ru(II)-catalyzed C–H activation reaction in both ortho and peri positions of the pyrene core, affording organometallic species 46b,c (Scheme 37). The pyrene hydrazone motif 46a was treated with different Ru catalysts and depending on the nature of the Ru(II) catalyst, the pyrene benzothiazole-hydrazone hybrid scaffold influenced both ortho and peri metation via C–H activation of the pyrene core under an analogous reaction condition. The reaction of 46a and RuHCl(CO)(PPh3)3 resulted in peri C–H metlation species, whereas the reaction of 46c with RuH2(CO)(PPh3)3 gave ortho metlation species. The C–H activation of 46a using Wilkinson’s catalyst at the peri position of the pyrene moiety was also reported by the same group. This reaction proceeded via the oxidative coordination pathway, where Rh(I) is oxidized to Rh(III), giving the C–H-activated product 46d, and the benzothiazolylhydrazone moiety of 46a acted as a directing group.
Scheme 36. Functionalization of the C2 position of pyrenes. Alkyne insertion induced regiospecific C–H activation with [Cp*MCl₂]₂ (M = Ir, Rh and Cp* = pentamethylcyclopentadienyl) [111].

<table>
<thead>
<tr>
<th>Examples</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>Ar</td>
<td></td>
</tr>
<tr>
<td>45ba: C₂H₅</td>
<td>92%</td>
</tr>
<tr>
<td>45bb: ρ-MeO-C₆H₄</td>
<td>93%</td>
</tr>
<tr>
<td>45bc: ρ-Cl-C₆H₄</td>
<td>89%</td>
</tr>
<tr>
<td>45bd: m-Me-C₆H₄</td>
<td>92%</td>
</tr>
</tbody>
</table>

6. Conclusions

In summary, in this review, we have shown some of the recent advances in the area pertaining to the modification of the pyrene core via the C–H activation and functionalization route. The 1-, 3-, 6-, and 8-positions of the pyrene motif were identified as ‘active’ or ‘common sites’. The synthesis of functionalized pyrene derivatives by introducing substitutions at these sites is commonly explored. The 2- and 7-positions of pyrene are designated as ‘nodal plane positions’, and are considered ‘uncommon’ or ‘less accessible sites for functionalization.’ Other positions, namely 4-, 5-, 9-, and 10-, are called K-regions due to the carcinogenic effect of pyrene upon its oxidation. There have been significant efforts to functionalize the C–H bonds present in these regions. The site-selective C–H functionalization of the pyrene core was attempted with and without using directing groups. The C–H bonds present in the pyrene core were replaced with functional groups, and the corresponding functionalized and modified pyrenes were synthesized. The C–H functionalization method has enabled the introduction of functional groups with ease in the pyrene core and also allowed for the strengthening of the library of modified pyrene scaffolds. Various reviews describe the classical methods affording modified pyrenes. This review reported the developments in the area pertaining to the modification of the C–H bonds in the pyrene core. Pyrene and its derivatives have received significant attention in chemical sciences due to their superior fluorescence properties, efficient excimer emission, high charge carrier mobility, etc. Given this importance, we will witness newer protocols, including the C–H functionalization reaction for synthesizing functionalized pyrene derivatives.

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