JOC The Journal of Organic Chemistry

Article

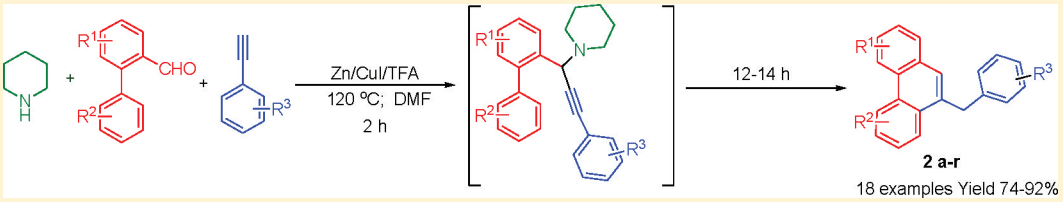
pubs.acs.org/joc

One-Pot Zn/CuI/TFA-Catalyzed Domino Three-Component−Carbocyclization Reaction Involving Biphenyl-2-carbaldehydes/Alkynes/Piperidine: Allenes-Mediated Construction of Phenanthrenes

Mohammad Saifuddin, Piyush K. Agarwal, and Bijoy Kundu*

Medicinal & Process Chemistry Division, Central Drug Research Institute, CSIR, Lucknow 226 001, India

Supporting Information



ABSTRACT: A one-pot protocol involving Zn/CuI/TFA-catalyzed domino three-component and subsequent carbocyclization reactions is described. The reaction proceeds via formation of propargyl amines from biphenyl-2-carbaldehydes/terminal alkynes/piperidine followed by the elimination of piperidine and ring closure to furnish phenanthrene derivatives in good yields. The strategy involves C(*sp*)-H activation−CH functionalization with imine-alkyne activation−1,5 hydride shift−β-elimination of piperidine−allene formation−6π cycloaddition−isomerization domino sequence. Evidence for the involvement of allenes as an intermediate during carbocyclization is discussed.

INTRODUCTION

Phenanthrene skeletons are ubiquitous substructures in many natural[1] and synthetic products with applications to medicinal chemistry and material sciences (polycyclic aromatic electronic materials).[2] Among a variety of methods described in the literature for the phenanthrene class of compounds, reports dealing with the [4 + 2] cycloaddition/benzannulation reaction with functionalized tethered biaryls and alkynes have drawn significant attention.[3] In general, these multistep strategies involve transition-metal-catalyzed [4 + 2] annulation of halobiaryls/2-phenylbenzoic acid/2-biaryl Grignard reagent with alkynes. In yet another multistep strategy involving alkynes, 9-substituted phenanthrenes were obtained by subjecting 2-alkynylated biphenyl derivatives to an intramolecular hydroarylation in the presence of Au[4]/DBU[5] as catalysts. However, to the best of our knowledge there are no reports dealing with multicomponent reaction (MCR)-based protocols with alkynes as one of the components leading to the synthesis of phenanthrenes. Motivated by these observations, we envisaged that propargyl amines generated from biphenyl-2-carbaldehyde/alkynes/amines in MCR format could be further subjected to an intramolecular carbocyclization following activation of the internal alkyne to afford phenanthrenes. In recent years, great efforts have been made to develop strategies involving sequenced MCRs/post-MCR modifications either in one pot or in tandem with the view to generate chemprobes with increased architectural complexity and diversity.[6] In this article, we report a one-pot protocol for 9/10-substituted phenanthrenes through the intermediacy of allenes following a three-component−carbocyclization domino reaction by employing biphenyl-2-carbaldehydes, terminal alkynes, and piperidine as reactants. The studies are part of our ongoing studies for the synthesis of annulated polyheterocycles in one pot.[7]

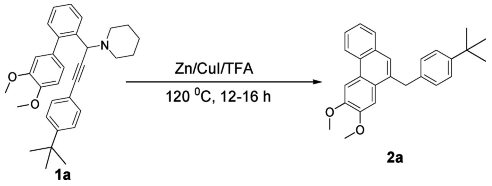
RESULTS AND DISCUSSION

We commenced our studies by examining the ability of the propargyl amine 3′-4′-dimethoxy-1-(1-biphenyl-2-yl-3-(4-(*tert*-butyl)-phenyl-prop-2-ynyl)-piperidine **1a** to undergo intramolecular cyclization. Intermediate **1a** was obtained by treating biphenyl-2-carbaldehyde with 4-*tert*-butyl-phenylacetylene and piperidine in the presence of Zn dust in acetonitrile under reflux as described elsewhere in the literature.[8] To enforce carbocyclization in the resulting propargyl amine **1a**, we envisioned that activating the alkyne moiety using iodine-derived electrophilic reagents,[9] Bronsted/Lewis acids,[10] or transition metals[11] as a catalyst may initiate a ring closure via C−C bond formation.

For our studies, we selected transition metals as a catalyst of choice and were especially attracted toward zinc and copper salts as they have been traditionally used to activate the alkynes.[12] We screened a variety of copper and zinc salts as catalysts for facilitating cyclization, and the results of our optimization studies have been summarized in Table 1 (entries 1−19). Attempts to cyclize **1a** in either in the absence of any metal catalyst (entry 1) or in the presence CuI or Zn dust/ZnI_2

Received: September 24, 2011
Published: November 4, 2011

Table 1. Optimization of Reaction Condition for the Conversion of Propargyl Amine 1a to Phenanthrene 2a via Carbocyclization[a]



entry	solvent	catalyst(s)	acid	yield (%) 2a
1	DMF			NR
2	DMF	CuI		NR
3	DMF	Zn		NR
4	toluene	ZnI_2		NR
5	DMF	Zn/CuI		NR
6	DMF	Zn/CuI	TFA	94[c]
7	DMF		TFA	NR
8	DMF	Zn	TFA	NR
9	DMF	CuI	TFA	NR
10	DMF	Zn/CuI	triflic acid	NR
11	DMF	Zn/CuI	trichloroacetic acid	NR
12	DMF	Zn/CuI	MsOH	37[c]
13	DMSO	Zn/CuI	TFA	55[c]
14	ACN	Zn/CuI	TFA	52[c]
15	DMF	Zn/CuI/μW[b]	TFA	NR
16	water	Zn/CuI/μW[b]	TFA	NR
17	ACN	Zn/CuI/μW[b]	TFA	NR
18	DMF	Zn/Cu(OAC)$_2$	TFA	NR
19	DMF	Zn/CuBr	TFA	15[d]

[a]All reactions were carried out on a 1 mmol scale, 15 mol % of each metal catalyst, 0.1 equiv of acid, 1.5 mL of solvent, 12 h, 100 or 120 °C. [b]Microwave for 45 min. [c]Isolated yield. [d]Yield based on HPLC.

alone failed to furnish any product (entries 2–4). Similarly, carrying out reaction in the presence of a mixture of Zn and CuI yet again failed to facilitate cyclization (entry 5); however, adding a catalytic amount of TFA to the mixture of Zn/CuI furnished a tricyclic annulated 10-benzyl phenanthrene derivative **2a** after 12 h in 94% isolated yield (entry 6). Use of TFA alone as a catalyst or in combination with Zn or CuI was ineffective in promoting cyclization (entries 7–9). Replacement of TFA with other acids such as triflic acid, trichloroacetic acid, and methanesulfonic acid (MSA) in the presence of Zn/CuI mixture was detrimental as the former two acids did not favor cyclization (entries 10 and 11) at all, whereas the MSA furnished **2a** in diminished yield (entry 12). Switching solvent from DMF to DMSO and acetonitrile furnished products in reduced yield (entries 13 and 14). Carrying out reactions under microwave conditions was found to be ineffective (entries 15–17). Similarly, when replacing CuI with other copper salts, Cu(OAc)$_2$ (entry 18) was inconclusive, and CuBr furnished **2a** in 15% yield (entry 19). Thus, the optimal conditions leading to the cyclization of **1a** required the combined presence of Zn dust (15 mol %)/CuI (15 mol %)/TFA (0.1 equiv) in DMF. A careful survey of the literature revealed Zn/CuI/TFA as a new catalytst system hitherto not reported except for a Zn/CuI-mediated coupling of akyl halides and vinyl sulfones via involvement of a possible new Zn–Cu species.[13]

Mechanistically, formation of phenanthrenes **2** from propargyl amines **1** may involve initial coordination of Zn/Cu to the carbon–carbon triple bond to give complex **A**. This may be then accompanied by the β-elimination of piperidine via 1,5 hydride shift[14] to form an allene intermediate **3**, which may subsequently undergo a 6π cycloaddition to form an annulated tricyclic intermediate **B**. The latter may then undergo isomerization to afford a phenanthrene derivative based on **2** (Figure 1). Experimental evidence for the plausible mechanism was established by synthesizing the allene intermediate **3** by treating **1a** with $AgNO_3$ using literature procedure.[15] The resulting allene intermediate 3,4-dimethoxy-2′-[3-(4-*tert*-butyl-phenyl)propa-1,2-dienyl]-1,1′-biphenyl **3a** after its purification by column chromatography was isolated in 65% yield. The allene **3a** so obtained was then subjected to intramolecular cyclization by exposing it to Zn/CuI/TFA catalyst system to afford phenanthrene **2a** within 1 h in quantitative yield (Scheme 1). Indeed, the allene intermediate **3a** was found to have poor shelf life stability, which led us to work with a freshly isolated sample for its characterization and cyclization.

Once the reaction conditions for the conversion of propargylamine **1a** to phenanthrene **2a** were optimized, we

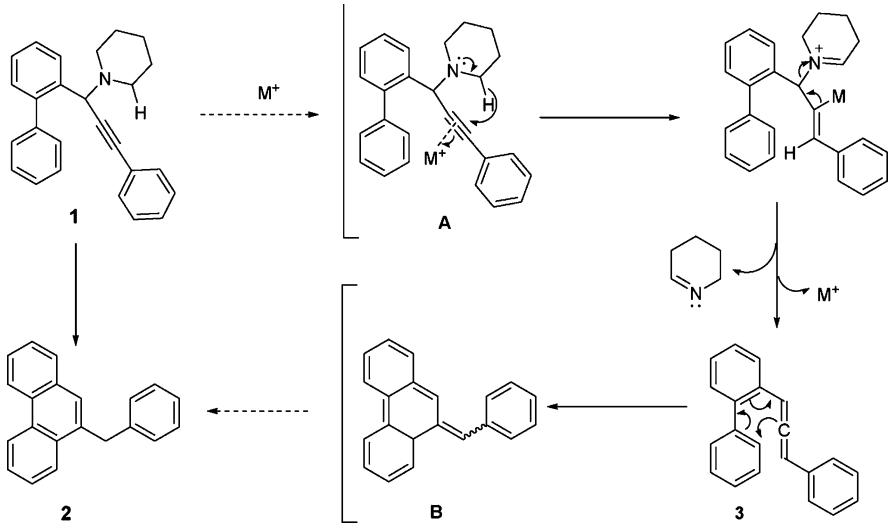
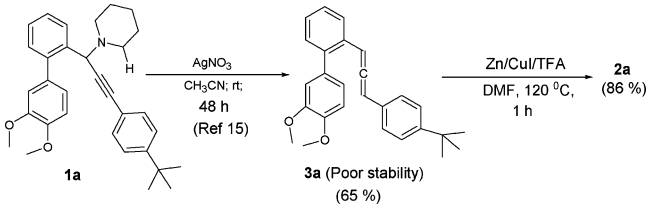


Figure 1. Plausible mechanism for the formation of phenanthrenes **2** from propargyl amines **1** (M represents Zn/Cu).

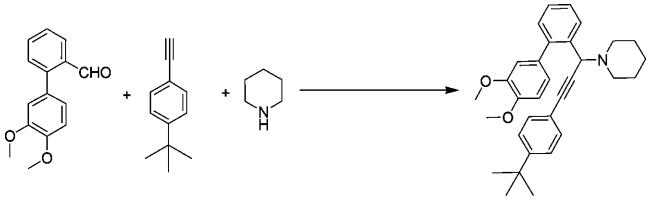
dx.doi.org/10.1021/jo201942r | J. Org. Chem. 2011, 76, 10122–10128

Scheme 1. Experimental Evidence for the Formation of 2a via Allene Intermediate 3a



then embarked with the development of a three-component strategy for the synthesis of propargylamine **1a**. In the literature, metal-catalyzed formation of propargyl amines is known to proceed via C(*sp*)-H activation of the alkyne followed by functionalization with imines.[16] Following this strategy, one of the literature procedures[8] involving Zn-catalyzed three-component reaction furnished **1a** in 52% isolated yield (entry 1, Table 2), which prompted us to improve its yield by treating

Table 2. Optimization of Reaction Conditions for the Synthesis of Propargyl Amine 1a in a Three-Component Format[a]



entry	reagents and conditions	yield (%) **1a**
1	Zn dust, DMF, 120 °C, 12 h	52[a]
2	Zn/CuI/TFA, DMF, 120 °C, 2 h	95
3	Zn dust, DMF, 120 °C, 2 h	traces
4	Zn dust, CH_3CN, Reflux, 2 h	traces
5	CuI, DMF, 110 °C, 2 h	>10
6	TFA, DMF, 110 °C, 2 h	NR
7	Zn/CuI, DMF, 120 °C, 2 h	traces
8	CuI/TFA, DMF, 120 °C, 2 h	traces
9	Zn/TFA, DMF, 120 °C, 2 h	traces

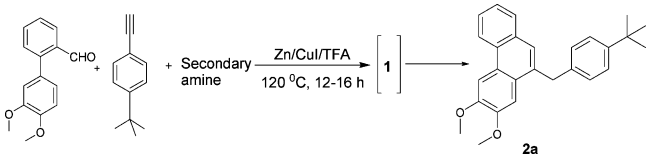
[a]All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.5:1.2, 15 mol % of each metal catalyst, 0.1 equiv of acid, 1.5 mL of DMF. [a]Reference 7.

3′,4′-dimethoxy[1,1′-biphenyl]-2-carbaldehyde with 4-*tert*-butyl-phenylacetylene and piperidine in a MCR format by employing the same Zn/CuI/TFA catalyst system identified above for the carbocyclization. Using the same catalyst system for both steps may facilitate development of a one-pot strategy for phenanthrenes following a domino three-component−carbocyclization reaction. Pleasingly, the three-component reaction using Zn/CuI/TFA catalyst system afforded propargyl amine **1a** within 2 h in 95% isolated yield (entry 2, Table 2).

Notably, we did not observe any subsequent formation of **2a** from **1a** in the presence of the Zn/CuI/TFA catalyst system in the first 2 h of the reaction. It is thus evident that, using the Zn/CuI/TFA catalyst system, although formation of the **1a** seemed to occur smoothly (2 h), longer duration (12 h) was required for its post-MCR conversion to **2a**. Attempts to carry out the reaction in the presence of Zn, CuI, and TFA alone or as a metal−acid combination furnished propargylamine **1a** in traces (<10%) as evident by HPLC (entries 3−9, Table 2). Thus, the one-pot three-component reaction involving formation of the propargyl amine and subsequent carbocyclization proceeds via a C(*sp*)-H activation−CH functionalization with imine-alkyne activation−1,5 hydride shift−*β*-elimination of piperidine−allene formation−6*π* cycloaddition−isomerization domino sequence.

After optimizing the reaction conditions for the synthesis of propargylamine **1a** in quantitative yield, we proceeded with the scope and limitation of the Zn/CuI/TFA catalyst system for the one-pot synthesis of phenanthrenes (**2**) following a three-component−carbocyclization domino reaction. Initially, we treated 3′,4′-dimethoxy[1,1′-biphenyl]-2-carbaldehyde with 4-*tert*-butyl-phenylacetylene in the presence of a variety of secondary amines, and the results are summarized in Table 3.

Table 3. Effect of Amines on the Synthesis of Phenanthrenes (2) Using Domino Three-Component and Subsequent Carbocyclization Reactions



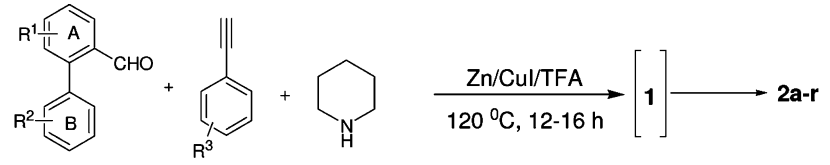
entry	secondary amines	yield (%) **2a**
1	piperidine	92
2	diethylamine	68
3	diisopropylamine	56
4	morpholine	58
5	pyrrolidine	63

As is evident, piperidine furnished **2a** in 92% isolated yields, whereas DIPA, DEA, morpholine, and pyrrolidine furnished **2a** in reduced isolated yields of 56−68%.

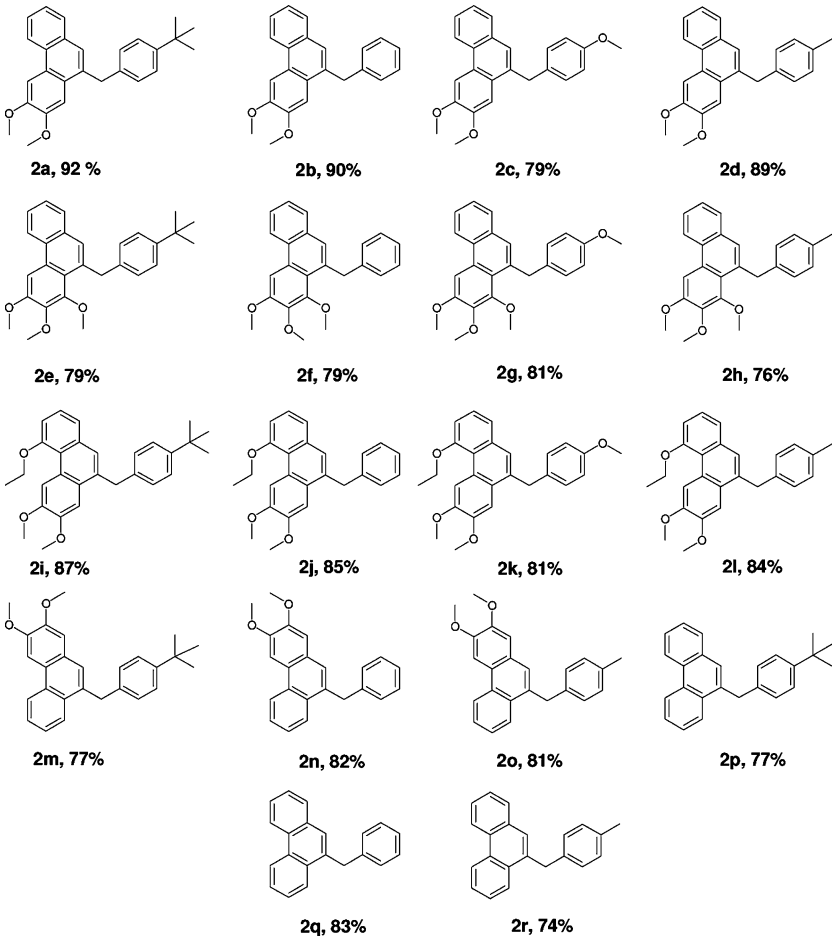
In subsequent studies, we treated a series of biphenyl-2-carbaldehydes with terminal alkynes and piperidine in the presence of the Zn/CuI/TFA catalyst system to generate corresponding propargyl amines in three-component format followed by in situ elimination of piperidine and intramolecular cyclization to furnish 9/10-substituted phenanthrenes **2a**−**r** (Table 4). The crude products were purified by column chromatography. Substitution in the B ring of biphenyl-2-carbaldehyde in the form of 3′,4′-dimethoxy and 3′,4′,5′-trimethoxy as R^2 had no effect on the outcome of the reaction when treated with phenylacetylene/piperdine, furnishing corresponding phenanthrene derivatives **2b** and **2f** in the isolated yield of 90% and 79%, respectively. Similarly, substitution in the A ring of the biphenyl-2-carbaldehyde in the form 6-ethoxy and 3,4-dimethoxy groups as R^1 had no effect on the yield when treated with aromatic terminal alkynes/piperdine except that the reaction was found to be sluggish and required addition of fresh Zn/CuI/TFA catalyst system after 10 h to drive the reaction to completion (**2i**−**2l**; 81−87% and **2m**−**2o**; 77−82%). Among aromatic terminal alkynes, the electronic effect in the phenyl ring represented by R^3 had negligible effect on the reactions, offering products with minimal variation in yields. An attempt to employ aliphatic alkynes failed to furnish phenanthrene from the corresponding propargylamine intermediate formed in situ.

dx.doi.org/10.1021/jo201942r | J. Org. Chem. 2011, 76, 10122−10128

Table 4. Synthesis of Phenanthrenes (2) Using Domino Three-Component and Subsequent Carbocyclization Reactions[a]



R^1= H, 6-OC_2H_5, 3, 4-dimethoxy
R^2= H, 3',4'-dimethoxy, 3',4',5' trimethoxy;
R^3= H, 4-CH_3, 4-OCH_3; 4-$C(CH_3)_3$



[a]All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.5:1.2, 15 mol % of each metal catalyst, 0.1 equiv of acid, 1.5 mL of solvent.

CONCLUSION

In summary, we have developed a one-pot atom-economical construction of polycyclic 9/10-substituted-phenanthrenes via Zn/CuI/TFA-catalyzed domino three-component and subsequent carbocyclization reactions. The protocol may find application in the diversity oriented synthesis of chemprobes with structural complexity.

EXPERIMENTAL SECTION

I. General Information and Methods. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 200 and 300 MHz spectrometers for ^{1}H NMR and 50 and 75 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/DMSO-d_6 for ^{1}H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). High resolution mass spectra were recorded with a mass spectrometer. Column chromatography was performed using silica gel (100−200 mesh) as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). The purity and characterization of these compounds were further established using HR/EI Mass spectroscopy. Melting points were measured on a capillary melting point apparatus and are uncorrected.

II. General Procedure for the Synthesis of Biphenyl-2-carbaldehyde via Suzuki Coupling. A solution of phenylboronic acid (1.4 g, 11.89 mmol) and 2-bromobenzaldehyde (2.0 g, 10.81 mmol) in DMF (10 mL) was degassed with nitrogen for 15 min followed by addition of Na_2CO_3 (5.8 g, 2 M in water) under continuous flow of nitrogen. $Pd(PPh_3)_4$ (1.25 g, 1.08 mmol) was added to the reaction mixture under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 3 h. The solution was diluted with H_2O (5 mL), and then the product was extracted three times with EtOAc (10 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified

dx.doi.org/10.1021/jo201942r | J. Org. Chem. 2011, 76, 10122−10128

on a silica gel column using hexane/ethyl acetate (95:5, v/v) as eluent to afford biphenyl-2-carbaldehyde in 81% yield.

3′,4′-Dimethoxy[1,1′-biphenyl]-2-carbaldehyde. Yield = 85%, white solid, mp 90−93 °C, R_f = 0.16 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3012, 2937, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.65−7.60 (m, 1H), 7.47 (t, J = 7.9 Hz, 2H), 6.98−6.90 (m, 3H), 3.95 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 149.3, 148.9, 145.8, 133.9, 133.5, 130.7, 130.4, 127.6, 127.5, 122.9, 113.2, 111.1, 56.0 ppm; HRMS (ESI) calcd for $C_{15}H_{15}O_3$ [M + H] 243.1021 found 243.1019.

3′,4′,5′-Trimethoxy[1,1′-biphenyl]-2-carbaldehyde. Yield = 77%, white solid, mp 102−106 °C, R_f = 0.34 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3370, 2930, 2847, 1695, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.01 (dd, J_1 = 0.93 Hz, J_2 = 7.65 Hz, 1H), 7.66−7.60 (m, 1H), 7.52−7.45 (m, 2H), 6.57 (s, 2H), 3.92 (s, 3H), 3.88 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 153.1, 146.0, 138.0, 133.9, 133.5, 133.4, 130.5, 127.8, 127.5, 107.5, 61.0, 56.3 ppm; HRMS (ESI) calcd for $C_{16}H_{17}O_4$ [M + H] 273.1127 found 273.1117.

6-Ethoxy-3′,4′-dimethoxy[1,1′-biphenyl]-2-carbaldehyde. Yield = 65%, white solid, mp 116−118 °C, R_f = 0.20 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3360, 2939, 2823, 1675,1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.63−7.57 (m, 1H), 7.43−7.37 (m, 1H), 7.21−7.15 (m, 1H), 6.95−6.92 (m, 2H), 6.82 (dd, J_1 = 1.2 Hz, J_2 = 8.2 Hz, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 1.30 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 156.5, 148.8, 148.3, 135.8, 134.9, 128.5, 125.6, 124.3, 119.2, 117.3, 114.4, 110.5, 64.6, 56.0, 14.8 ppm; HRMS (ESI) calcd for $C_{17}H_{19}O_4$ [M + H] 287.1283 found 287.1283.

[1,1′-Biphenyl]-2-carbaldehyde.[17a] Yield = 81%, yellow liquid, R_f = 0.15 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3063, 2851, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.06 (dd, J_1 = 0.63 Hz, J_2 = 7.74 Hz, 1H), 7.69−7.63 (m, 1H), 7.54−7.46 (m, 5H), 7.42−7.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 146.0, 137.8, 133.8, 133.6, 130.9, 130.2, 128.5, 128.2, 127.8, 127.7 ppm; HRMS (ESI) calcd for $C_{13}H_{11}O$ [M + H] 183.0809 found 183.0820.

4,5-Dimethoxy[1,1′-biphenyl]-2-carbaldehyde.[17b] Yield = 73%, white solid, mp 124−126 °C, R_f = 0.21 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3022, 2925, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.82 (s, 1H), 7.54 (s, 1H), 7.49−7.41 (m, 3H), 7.39−7.36 (m, 2H), 6.86 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.1, 153.5, 148.8, 141.5, 137.6, 130.2, 128.4, 128.0, 127.0, 121.7, 108.7, 56.2, 56.1 ppm; HRMS (ESI) calcd for $C_{15}H_{15}O_3$ [M + H] 243.1021 found 243. 1019.

III. Procedure for the Synthesis of 3-Ethoxy-2-trifluoromethanesulfonylmethyl-benzaldehyde. To a stirred solution of 3-ethoxy-2-hydroxy-benzaldehyde (5.0 g, 30.12 mmol) and triethylamine (4.70 mL, 33.13 mmol) in DCM (20 mL) at 0 °C was added triflic anhydride (5.56 mL, 33.13 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. After completion of reaction, $NaHCO_3$ solution was added, and the product was extracted three times with DCM (10 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was subjected to Suzuki coupling using the above-described procedure.

3-Ethoxy-2-trifluoromethanesulfonylmethyl-benzaldehyde. Yield = 81%, white liquid, R_f = 0.61 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3460, 2152, 1700, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.52−7.49 (m, 1H), 7.46−7.41 (m, 1H), 7.30−7.26 (m, 1H), 4.18 (q, J = 6.9 Hz, 2H), 1.50 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.8, 151.0, 139.0, 129.5, 129.0, 121.0, 119.3, 65.4, 14.0 ppm; HRMS (ESI) calcd for $C_{10}H_{10}F_3O_5S$ [M + H] 299.0201 found 299.0203.

IV. Procedure for the Synthesis of 3,4-Dimethoxy-2′-[3-(4-*tert*-butyl-phenyl)propa-1,2-dienyl]-1,1′-biphenyl 3a. To a solution of **1a** (1.0 mmol) in CH_3CN was added $AgNO_3$ (0.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h in the absence of light. After the completion of the reaction, the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate as eluent to afford allene (**3a**).

*3,4-Dimethoxy-2′-[3-(4-tert-butyl-phenyl)propa-1,2-dienyl]-1,1′-biphenyl (**3a**).* Yield = 65%, yellow oil, R_f = 0.61 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3206, 2950, 1723, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57−7.54 (m, 1H), 7.35−7.24 (m, 7H), 6.98−6.92 (m, 3H), 6.66 (d, J = 6.5 Hz, 1H), 6.52 (d, J = 6.4 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 150.5, 148.7, 148.5, 140.4, 133.7, 131.5, 130.9, 130.4, 127.7, 127.5, 127.2, 126.7, 125.8, 122.2, 113.3, 111.1, 97.8, 96.7, 56.0, 34.7, 31.4 ppm; HRMS (ESI) calcd for $C_{27}H_{29}O_2$ [M + H] 385.2167 found 385.2170.

V. Procedure for the Synthesis of Phenanthrene (2a) from Allene (3a). To a solution of allene **3a** (1.0 mmol) in DMF were added Zn (15 mol %), CuI (15 mol %), and TFA (0.1 mmol) at room temperature. The reaction mixture was heated at 120 °C for 1 h. After completion of reaction, $NaHCO_3$ soltion was added, and the product was extracted three times with EtOAc (5 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate as eluent to afford phenanthrene **2a**.

*2,3-dimethoxy-10-(4-(tert-butyl)benzyl)phenanthrene (**2a**).* Yield = 92%, white solid, mp 132−135 °C, R_f = 0.32 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 2958, 1622, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.44 Hz, 1H), 8.02 (s, 1H), 7.82 (d, J = 6.93 Hz, 1H), 7.60−7.48 (m, 3H), 7.33−7.17 (m, 5H), 4.40 (s, 2H), 4.08 (s, 3H), 3.84 (s, 3H), 1.28 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 149.1, 148.9, 137.5, 134.4, 131.4, 129.5, 128.5, 128.4, 126.6, 126.4, 125.9, 125.7, 125.5, 122.1, 106.0, 103.8, 56.0, 55.8, 39.9, 34.5, 31.5 ppm; HRMS (ESI) calcd for $C_{27}H_{29}O_2$ [M + H] 385.2167 found 385.2152.

VI. General Procedure for the Synthesis of Phenanthrenes. To a solution of biphenyl-2-carbaldehyde (1.0 mmol), piperidine (1.5 mmol), and phenyl acetylene (1.2 mmol) in DMF were added Zn (15 mol %), CuI (15 mol %), and TFA (0.1 mmol) at room temperature. The reaction mixture was heated at 120 °C for 12−14 h. After completion of reaction, $NaHCO_3$ solution was added, and the product was extracted three times with EtOAc (5 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate as eluent to afford phenanthrenes.

*10-Benzyl-2,3-dimethoxyphenanthrene (**2b**).* Yield = 90%, white solid, mp 174−177 °C, R_f = 0.60 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3026, 2911, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.83−7.80 (m, 1H), 7.61−7.49 (m, 3H), 7.31−7.17 (m, 6H), 4.44 (s, 2H), 4.09 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.9, 140.5, 134.2, 131.4, 129.5, 128.8, 128.5, 126.5, 126.5, 126.3, 125.9, 125.8, 125.7, 122.1, 105.9, 103.8, 56.0, 55.8, 40.5 ppm; HRMS (ESI) calcd for $C_{23}H_{21}O_2$ [M + H] 329.1541 found 329.1533.

*2,3-Dimethoxy-10-(4-methoxybenzyl)phenanthrene (**2c**).* Yield = 79%, white solid, mp 122−125 °C, R_f = 0.17 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3006, 2959, 1611, 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.81−7.79 (m, 1H), 7.60−7.48 (m, 3H), 7.32 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.37 (s, 2H), 4.08 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 149.1, 148.9, 134.5, 132.4, 131.4, 129.7, 129.5, 128.5, 126.5, 126.2, 125.9, 125.7, 125.6, 122.1, 114.0, 105.7, 103.8, 56.0, 55.8, 55.3, 39.5 ppm; HRMS (ESI) calcd for $C_{24}H_{23}O_3$ [M + H] 359.1647 found 359.1641.

*2,3-Dimethoxy-10-(4-methylbenzyl)phenanthrene (**2d**).* Yield = 89%, white solid, mp 148−152 °C, R_f = 0.38 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3011, 2916, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.61−7.49 (m, 3H), 7.35 (s, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.40 (s, 2H), 4.09 (s, 3H), 3.87 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.9, 137.4, 135.8, 134.5, 131.4, 129.5, 129.3, 128.7, 128.5, 126.5, 126.3, 125.9, 125.7, 125.7, 122.1, 105.8, 103.8, 56.0, 55.8, 40.0, 21.1 ppm; HRMS (ESI) calcd for $C_{24}H_{23}O_2$ [M + H] 343.1698 found 343.1688.

*1,2,3-Trimethoxy-10-(4-(tert-butyl)benzyl)phenanthrene (**2e**).* Yield = 79%, yellow oil, R_f = 0.44 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3439,

3172, 2958, 1656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.9 Hz, 1H), 7.92 (s, 1H), 7.72 (d, J = 6.4 Hz, 1H), 7.58−7.48 (m, 2H), 7.33 (s, 1H), 7.28−7.25 (m, 2H), 7.15−7.09 (m, 2H), 4.66 (s, 2H), 4.08 (s, 3H), 3.92 (s, 3H), 3.67(s, 3H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.7, 148.4, 142.4, 139.3, 134.4, 131.8, 129.0, 128.7, 128.4, 128.2, 126.5, 126.0, 125.1, 122.5, 121.6, 100.0, 61.3, 60.9, 56.0, 42.0, 34.4, 31.6 ppm; HRMS (ESI) calcd for $C_{28}H_{31}O_3$ [M + H] 415.2273 found 415.2261.

10-Benzyl-1,2,3-trimethoxyphenanthrene (**2f**). Yield = 79%, yellow oil, R_f = 0.44 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3329, 2930, 2947, 1657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.73−7.70 (m, 1H), 7.56−7.50 (m, 2H), 7.33 (s, 1H), 7.27−7.23 (m, 2H), 7.22−7.15 (m, 3H), 4.69 (s, 2H), 4.08 (s, 3H), 3.91 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.7, 142.4, 134.0, 131.7, 129.1, 128.8, 128.7, 128.6, 128.3, 128.2, 126.5, 126.1, 125.6, 122.6, 121.6, 100.0, 61.3, 60.9, 56.0, 42.6 ppm; HRMS (ESI) calcd for $C_{24}H_{23}O_3$ [M + H] 359.1647 found 359.1648.

1,2,3-Trimethoxy-10-(4-methoxybenzyl)phenanthrene (**2g**). Yield = 81%, yellow oil, R_f = 0.28 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3417, 3152, 2938, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.8 Hz, 1H), 7.91 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.57−7.47 (m, 2H), 7.30 (s, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 7.9 Hz, 2H), 4.62 (s, 2H), 4.07 (s, 3H), 3.92 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 152.6, 151.7, 142.5, 134.6, 134.4, 131.7, 130.4, 129.7, 129.0, 128.7, 128.3, 128.2, 126.5, 126.0, 122.5, 121.6, 113.7, 100.0, 61.4, 60.9, 56.0, 55.3, 41.6 ppm; HRMS (ESI) calcd for $C_{25}H_{25}O_4$ [M + H] 389.1753 found 389.1749.

1,2,3-Trimethoxy-10-(4-methylbenzyl)phenanthrene (**2h**). Yield = 76%, yellow oil, R_f = 0.43 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3420, 2958, 1650, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.7 Hz, 1H), 7.92 (s, 1H), 7.72 (d, J = 6.2 Hz, 1H), 7.58−7.48 (m, 2H), 7.32 (s, 1H), 7.06 (m, 4H), 4.65 (s, 2H), 4.09 (s, 3H), 3.92 (s, 3H), 3.68 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.7, 142.4, 139.2, 135.0, 134.4, 131.7, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 126.4, 126.0, 122.5, 121.6, 100.0, 61.3, 60.9, 56.0, 42.0, 21.1 ppm; HRMS (ESI) calcd for $C_{25}H_{25}O_3$ [M + H] 373.1803 found 373.1798.

2,3-Dimethoxy-5-ethoxy-10-(4-(tert-butyl)benzyl)phenanthrene (**2i**). Yield = 87%, white solid, mp 139−141 °C, R_f = 0.26 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3439, 2363, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.51 (s, 1H), 7.44−7.42 (m, 2H), 7.35 (s, 1H), 7.28 (s, 1H), 7.17 (d, J = 8.2 Hz, 3H), 7.05 (dd, J_1 = 2.7 Hz, J_2 = 6.5 Hz, 1H), 4.40 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.05 (s, 3H), 3.84 (s, 3H), 1.69 (t, J = 6.9 Hz, 3H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 149.0, 147.8, 137.5, 134.8, 133.9, 128.4, 127.3, 126.9, 126.0, 125.6, 125.4, 121.4, 120.1, 114.2, 110.3, 108.1, 105.5, 64.4, 55.8, 55.6, 40.0, 34.5, 31.5, 15.5 ppm; HRMS (ESI) calcd for $C_{29}H_{33}O_3$ [M + H] 429.2429 found 429.2428.

10-Benzyl-2,3-dimethoxy-5-ethoxyphenanthrene (**2j**). Yield = 85%, white solid, mp 133−136 °C, R_f = 0.25 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3444, 2841, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.49 (s, 1H), 7.44−7.42 (m, 2H), 7.32 (s, 1H), 7.25−7.17 (m, 5H), 7.07−7.04 (m, 1H), 4.43 (s, 2H), 4.31 (q, J = 6.9 Hz, 2H), 4.05 (s, 3H), 3.83 (s, 3H), 1.68 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 147.8, 140.5, 139.4, 134.5, 133.9, 128.8, 128.6, 127.2, 127.0, 126.3. 126.0, 125.7, 121.4, 120.1, 114.2, 110.3, 108.2, 105.3, 64.4, 55.8, 55.6, 40.5, 15.5 ppm; HRMS (ESI) calcd for $C_{25}H_{25}O_3$ [M + H] 373.1803 found 373.1803.

2,3-Dimethoxy-5-ethoxy-10-(4-methoxybenzyl)phenanthrene (**2k**). Yield = 81%, white solid, mp 136−138 °C, R_f = 0.92 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3016, 2963, 1623, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.47 (s, 1H), 7.43−7.39 (m, 2H), 7.34 (s, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.05 (dd, J_1 = 3.6 Hz, J_2 = 5.5 Hz, 1H), 6.80 (d, J = 8.6 Hz, 2H), 4.37 (s, 2H), 4.31 (q, J = 7.0 Hz, 2H), 4.06 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H), 1.69 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 157.3, 147.8, 134.9, 133.9, 132.5, 129.7, 127.2, 126.8, 125.9, 125.6, 121.4, 120.0, 114.0, 110.3, 108.1, 105.2, 64.3, 55.8, 55.6, 55.3, 39.6, 15.5 ppm; HRMS (ESI) calcd for $C_{26}H_{27}O_4$ [M + H] 403.1909 found 403.1900.

2,3-Dimethoxy-5-ethoxy-10-(4-methylbenzyl)phenanthrene (**2l**). Yield = 84%, white solid, mp 128−132 °C, R_f = 0.25 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3172, 2958, 1656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.48 (s, 1H), 7.43−7.39 (m, 2H), 7.34 (s, 1H), 7.13 (d, J = 7.8 Hz, 2H), 7.06−7.04 (m, 3H), 4.38 (s, 2H), 4.37 (q, J = 6.8 Hz, 2H), 4.05 (s, 3H), 3.85 (s, 3H), 2.29 (s, 3H), 1.68 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 147.8, 137.4, 135.7, 134.8, 133.9, 129.3, 128.7, 127.3, 126.9, 125.9, 125.6, 121.4, 120.1, 110.3, 108.1, 105.3, 64.4, 55.8, 55.6, 40.0, 21.1, 15.5 ppm; HRMS (ESI) calcd for $C_{26}H_{27}O_3$ [M + H] 387.1960 found 387.1947.

2,3-Dimethoxy-9-(4-(tert-butyl)benzyl)phenanthrene (**2m**). Yield = 77%, white solid, mp 130−135 °C, R_f = 0.61 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3012, 2958, 1622, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.99 (s, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.30−7.24 (m, 2H), 7.18 (d, J = 5.8 Hz, 3H), 4.43 (s, 2H), 4.10 (s, 3H), 4.01 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 149.2, 149.0, 137.5, 133.4, 130.8, 130.4, 128.5, 127.0, 127.0, 125.9, 125.7, 125.5, 125.3, 124.5, 122.7, 108.3, 103.4, 56.1, 56.0, 39.0, 34.5, 31.5 ppm; HRMS (ESI) calcd for $C_{27}H_{29}O_2$ [M + H] 385.2167 found 385.2150.

9-Benzyl-2,3-dimethoxyphenanthrene (**2n**). Yield = 82%, white solid, mp 144−146 °C, R_f = 0.38 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3033, 2925, 1430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 7.99 (s, 1H), 7.59 (t, J = 7.0 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.43 (s, 1H), 7.28−7.20 (m, 5H), 7.16 (s, 1H), 4.46 (s, 2H), 4.10 (s, 3H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 149.2, 140.6, 133.2, 130.6, 130.4, 128.9, 128.5, 127.0, 127.0, 126.2, 125.9, 125.7, 125.1, 124.4, 122.7, 108.2, 103.4, 56.1, 55.9, 39.5 ppm; HRMS (ESI) calcd for $C_{23}H_{21}O_2$ [M + H] 329.1541 found 329.1538.

2,3-Dimethoxy-9-(4-methylbenzyl)phenanthrene (**2o**). Yield = 81%, white solid, mp 108−110 °C, R_f = 0.36 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3021, 2923, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.56 (d, J = 7.9 Hz, 1H), 8.03−7.99 (m, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.43 (s, 1H), 7.16−7.07 (m, 5H), 4.42 (s, 2H), 4.11 (s, 3H), 4.01 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 149.2, 137.5, 135.6, 133.5, 130.7, 130.4, 129.3, 128.8, 127.0, 126.9, 125.9, 125.7, 125.2, 124.4, 122.7, 108.2, 103.4, 56.1, 56.0, 39.1, 21.1 ppm; HRMS (ESI) calcd for $C_{24}H_{23}O_2$ [M + H] 343.1698 found 343.1690.

9-[4-(tert-Butyl)benzyl]phenanthrene (**2p**). Yield = 77%, white solid, mp 132−135 °C, R_f = 0.90 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 2927, 2860, 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J = 8.4 Hz, 1H), 8.69 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.68−7.59 (m, 5H), 7.32 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.49 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 137.3, 135.1, 132.0, 131.6, 130.9, 130.1, 128.5, 128.4, 127.9, 126.7, 126.3, 126.3, 125.5, 125.2, 123.2, 122.6, 39.2, 34.5, 31.5 ppm; HRMS (ESI) calcd for $C_{25}H_{25}$ [M + H] 325.1956 found 325.1926.

9-Benzylphenanthrene (**2q**). Yield = 83%, white solid, mp 142−145 °C, R_f = 0.92 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3027, 2913, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J = 8.1 Hz, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.87−7.84 (m, 1H), 7.69−7.56 (m, 5H), 7.37−7.23 (m, 5H), 4.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 140.3, 134.8, 131.9, 131.5, 130.9, 130.0, 128.9, 128.6, 128.3, 128.0, 126.7, 126.7, 126.3, 126.2, 125.1, 123.2, 122.6, 39.7 ppm; HRMS (ESI) calcd for $C_{21}H_{17}$ [M + H] 269.1330 found 269.1333.

9-(4-Methylbenzyl)phenanthrene (**2r**). Yield = 74%, white solid, mp 120−123 °C, R_f = 0.87 (1:19 EtOAc/hexane); IR (KBr) ν_{max} 3022, 2923, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 8.1 Hz, 1H), 8.65 (d, J = 7.9 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.63−7.53 (m, 5H), 7.13 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 7.7 Hz, 2H), 4.44 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 135.7, 135.2, 131.9, 131.6, 130.9, 130.1, 129.3, 128.8, 128.4, 127.9, 126.7, 126.7, 126.3, 126.3, 125.2, 123.2, 122.6, 39.3, 21.1 ppm; DART-HRMS (ESI) calcd for $C_{22}H_{19}$ [M^+] 282.1408 found 282.1406.

3′,4′-Dimethoxy-1-(biphenyl-2-yl)-3-(cyclohex-1-en-1-yl) piperidine. Yield = 93%, yellow oil, R_f = 0.16 (1:19 EtOAc/hexane); IR

(Neat) ν_{max} 3404, 2932, 2368, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (m, 1H), 7.33−7.29 (m, 2H), 7.23 (s, 1H), 7.09−7.05 (m, 2H), 6.89 (d, J = 8.1 Hz, 1H), 6.08 (s, 1H), 4.53 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.51−2.49 (m, 2H), 2.31−2.27 (m, 2H), 2.14−2.07 (m, 4H), 1.61−1.57 (m, 7H), 1.48−1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 148.2, 142.4, 137.1, 134.2, 134.0, 130.4, 129.7, 127.3, 126.6, 122.1, 120.8, 113.5, 110.6, 89.3, 84.2, 59.2, 56.0, 56.0, 50.3, 29.7, 26.4, 25.6, 24.6, 22.4, 21.6 ppm; HRMS (ESI) calcd for $C_{28}H_{34}NO_2$ [M + H] 416.2589 found 416.2571.

*3′,4′-Dimethoxy-1-(1-biphenyl-2-yl-3-(4-(tert-butyl)-phenyl-prop-2-ynyl)-piperidine (**1a**).* Yield = 95%, yellow oil, R_f = 0.16 (1:19 EtOAc/hexane); IR (Neat) ν_{max} 3464, 2938, 2367, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.40−7.35 (m, 2H), 7.33−7.31 (m, 4H), 7.30−7.29 (m, 1H), 7.10 (d, J = 9.4 Hz, 2H), 6.91 (d, J = 8.2, Hz, 1H), 4.64 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 2.64−2.58 (m, 2H), 2.40−2.39 (m, 2H), 1.59 (s, 4H), 1.50 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.3, 148.3, 142.5, 136.8, 134.1, 130.5, 129.8, 127.4, 126.7, 125.3, 122.2, 120.5, 113.6, 110.7, 87.6, 86.5, 59.4, 56.1, 50.4, 34.8, 31.3, 26.4, 24.6 ppm; HRMS (ESI) calcd for $C_{32}H_{38}O_2N$ [M + H] 468.2902 found 468.2879.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all final compounds and 2D spectra of **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bijoy_kundu@yahoo.com,; b_kundu@cdri.res.in.

■ ACKNOWLEDGMENTS

M.S. and P.K.A. are thankful to CSIR, New Delhi, India for fellowships. The authors would like to thank SAIF, CDRI, India for providing analytical data. CDRI communication No. 8151

■ REFERENCES

(1) For a recent review, see: Kovács, A.; Vasas, A.; Hohmann, J. *Phytochemistry* **2008**, *69*, 1084.

(2) (a) Watson, M. D.; Fechtenkotter, A.; Mullen, K. *Chem. Rev.* **2001**, *101*, 1267. (b) Grimsdale, C. G.; Mullen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592. (c) Mitsuhashi, R.; Suzuki, Y.; Yamanari, Y.; Mitamura, H.; Kambe, T.; Ikeda, N.; Okamoto, H; Fujiwara, A.; Yamaji, M.; Kawasaki, N.; Maniwa, Y.; Kubozono, Y. *Nature* **2010**, *464*, 76. (d) Yang, X.; Shi, Q.; Liu, Y.-N.; Zhao, G.; Bastow, K. F.; Lin, J.-C.; Yang, S.-C.; Yang, P.-C.; Lee, K.-H. *J. Med. Chem.* **2009**, *52*, 5262.

(3) (a) Kanno, K.; Yuanhong, L.; Iesato, A.; Nakajima, K.; Takahashi, T. *Org. Lett.* **2005**, *7*, 5453. (b) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (c) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895. (d) Larock, R. C.; Dory, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (e) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (f) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (g) Mandal, A. B.; Lee, G.-H.; Liu, Y.-H.; Peng, S.-M.; Leung, M. K. *J. Org. Chem.* **2000**, *65*, 332. (h) Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 6557. (i) Ye, F.; Shi, Y.; Zhou, L.; Xiao, Q.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5020.

(4) Xie, C.; Zhang, Y.; Yang, Y. *Chem. Commun.* **2008**, 4810.

(5) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 5295.

(6) For recent reviews, see: (a) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48. (c) Campbell, M. J. F.; Toste, D. *Chem. Sci.* **2011**, *2*, 1369 and references therein.

(7) (a) Sharma, S. K.; Mandadapu, A. K.; B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 6798. (b) Mandadapu, A. K.; Sharma, S. K.; Gupta, S.; Krishna, D. G. V.; Kundu, B. *Org. Lett.* **2011**, *13*, 3162. (c) Sharma, S. K.; Gupta, S.; Saifuddin, M.; Mandadapu, A. K.; Agarwal, P. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2011**, *5*, 65. (d) Sharma, S. K.; Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2010**, *51*, 6022. (e) Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. *Synlett* **2007**, 1591. (f) Saha, B.; Kumar, R.; Maulik, P. R.; Kundu, B. *Tetrahedron Lett.* **2006**, *47*, 2765.

(8) Kantaman, M. L.; Balasubrahmanyam, V.; Kumar, K. B. S; Venkanna, G. T. *Tetrahedron Lett.* **2007**, *48*, 7332.

(9) (a) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814. (b) Togo, H.; Iida, S. *Synlett* **2006**, 2159. (c) Da Silva, F. M.; Junior, J. J.; De Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393. (d) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652. (e) Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 897.

(10) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T. *Chem. Commun (Cambridge)* **2009**, *14*, 5075.

(11) (a) Ji, K. G.; Zhu, H. T.; Yang, F.; Shaukat, A.; Xia, X. F.; Yang, Y. F.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2010**, *75*, 5670. (b) Patil, N. T.; Raut, V. S. *J. Org. Chem.* **2010**, *75*, 6961. (c) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (d) Chernyak, N.; Tilly, D.; Li, Z.; Gevorgyan., V. *Chem. Commun.* **2010**, *46*, 150. (e) Shi, Z.; Zhang, B.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4036. (f) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 4619.

(12) (a) Jiang, B.; Si., Y. *Tetrahedron Lett.* **2006**, *44*, 6767. (b) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2010**, *6*, 1107. (c) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (d) Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C.; H. Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 478. (e) Mejuch, T.; Botoshansky, M.; Marek, I. *Org. Lett.* **2011**, *13*, 3604. (f) Shen, W. W., Y.; Meng, X.; Zhao, M.; Chen, Y.; Chen, B. *Org. Lett.* **2011**, *13*, 4514.

(13) Zhao, M. M.; Qu, C.; Lynch, J. E. *J. Org. Chem.* **2005**, *70*, 6944.

(14) (a) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786−1787. (b) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (c) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (d) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (e) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129.

(15) Lo, V. K. Y.; Zhou, C.; Wong, M.; Che, C. *Chem. Commun.* **2010**, *46*, 213.

(16) (a) Wei, C.; Li, C. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (b) Ramu, E.; Varala, R.; Sreelathaa, N.; Adapaa, S. R. *Tetrahedron Lett.* **2007**, *48*, 7184. (c) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001. (d) Huma, H. Z. S.; Halder, R.; Karla, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485. (e) Kabalka, W. L.; Wang, R.; Pagni, M. *Synlett* **2001**, 676. (f) Park, S. B.; Alper, H. *Chem. Commun.* **2005**, 1315−1317. (g) Wei, C.; Li, Z.; Li, C. *Org. Lett.* **2003**, *5*, 4473. (h) Shi, L.; Tu, Y.; Wang, M.; Zhang, F.; Fan, C. *Org. Lett.* **2004**, *6*, 1001.

(17) (a) Wu, L.; Ling, J.; Wu, Z. *Adv. Synth. Catal.* **2011**, *353*, 1452−1456. (b) Parnes, J. S.; Carter, D. S.; Kurz, L. J.; Flippin, L. A. *J. Org. Chem.* **1994**, *59*, 3497−3499.