Organic & Biomolecular Chemistry

Accepted Manuscript

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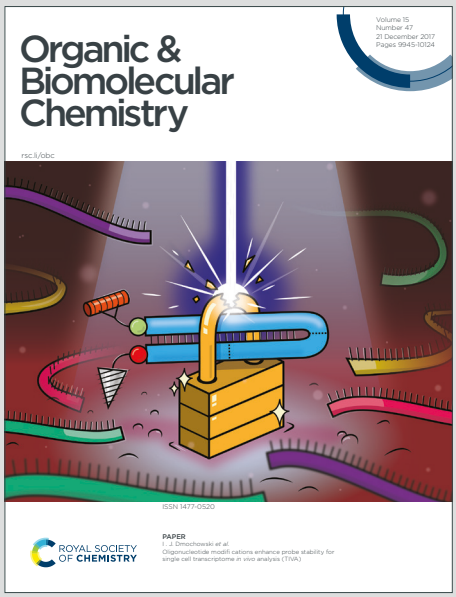

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DOI: 10.1039/D5OB01242B

ARTICLE

Modification of Fluorene and Fluorenone Core *via* C-H Functionalization

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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We report the modification of fluorene and fluorenone cores, and assembling libraries of functionalized fluorenes/fluorenones involving the C(sp^2)-H and C(sp^3)-H functionalization route. Fluorene/fluorenone motifs are versatile components in materials science and some are bio-active compounds. In this work, the C-H bonds of fluorene and fluorenone were subjected to the C-H arylation, alkylation, benzylation, alkoxylation, and annulation reactions to afford modified fluorenes/fluorenones. Alternatively, various functionalized fluorenes/fluorenones were also obtained by subjecting the C-H bonds of aryl or alkyl carboxamides to the C-H arylation process using iodofluorenes or iodofluorenones as the coupling partners. Overall, a comprehensive effort and synthesis of several C(1), C(2), C(3), and C(4) functionalized fluorenes, fluorenones, fluorene-fluorenone couple, fluorene-carbazole couple, π-extended bis fluorenes, and enantioenriched π-extended bis fluorenes are reported. Given the prominence of fluorene/fluorenone motifs, this work contributes to augmenting the library of fluorenes and fluorenones *via* the C(sp^2)-H and C(sp^3)-H functionalization strategy.

Introduction

Fluorene and fluorenone are a biaryl class of cyclic molecules that occupy an important place in the family of functional materials and aromatic compounds.[1-6] Fluorene and fluorenone motifs have been explored for their physicochemical, optical, and electrochemical properties and in developing fluorophores, organic light-emitting devices (OLEDs),[6e] liquid crystals, solar cells, oligomers/polymers, etc (Figure 1).[4,5]

While synthetically derived fluorenes and fluorenones are widespread in materials chemistry, several fluorene- and fluorenone-based natural products are well known (Figure 1).[1] Some fluorene- or fluorenone-based compounds are being used as drug molecules (e.g., lumefantrine (**1d**) and tilorone (**1g**)). Additionally, fluorene- or fluorenone-based molecules have been reported to exhibit promising biological activities and found to be useful in drug discovery/medicinal chemistry research.[7,8] (e.g., Hsp90 inhibition,[7a] tubulin interaction,[7b] antimyocardial ischemia activities[7c,g,h] and *N*-aryl-9-oxo-9*H*-fluorene-1-carboxamide derivative (**1b**) was found to induce apoptosis).[7d] A fluorene motif was shown to reduce the amyloid burden, which initiates neurodegeneration and cognitive deficits in Alzheimer's disease.[7e] Fluorenone **1f** is a probe for studying DNA redox chemistry.[7f] Markedly, 9-fluorenylmethoxycarbonyl (Fmoc) group-based molecules play a pivotal role in amino acid/peptide chemistry.[9]

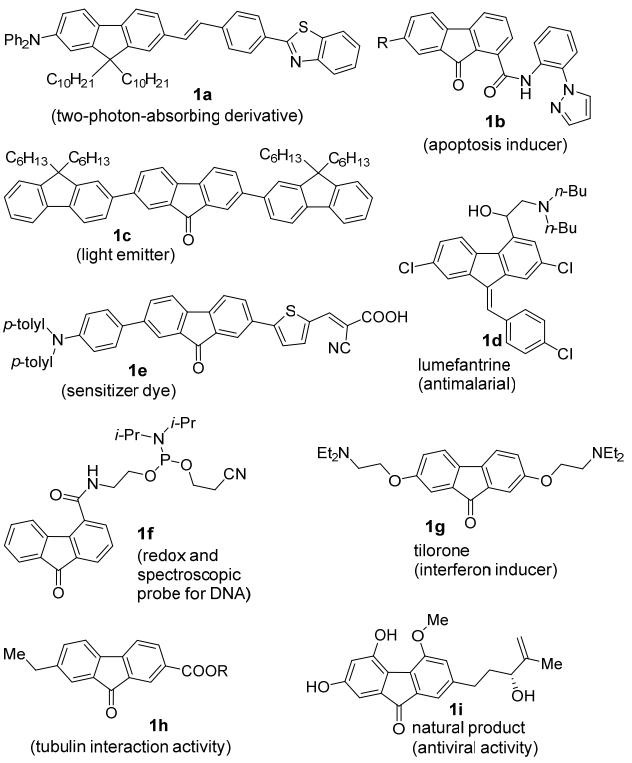

Figure 1. Representative fluorene and fluorenone molecules having applications in materials and medicinal chemistry.

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Electronic Supplementary Information (ESI) available: CCDC 2416200 (for **7c**), and 2416201 (for **11f**). For ESI or other electronic format see DOI: 10.1039/x0xx00000x.

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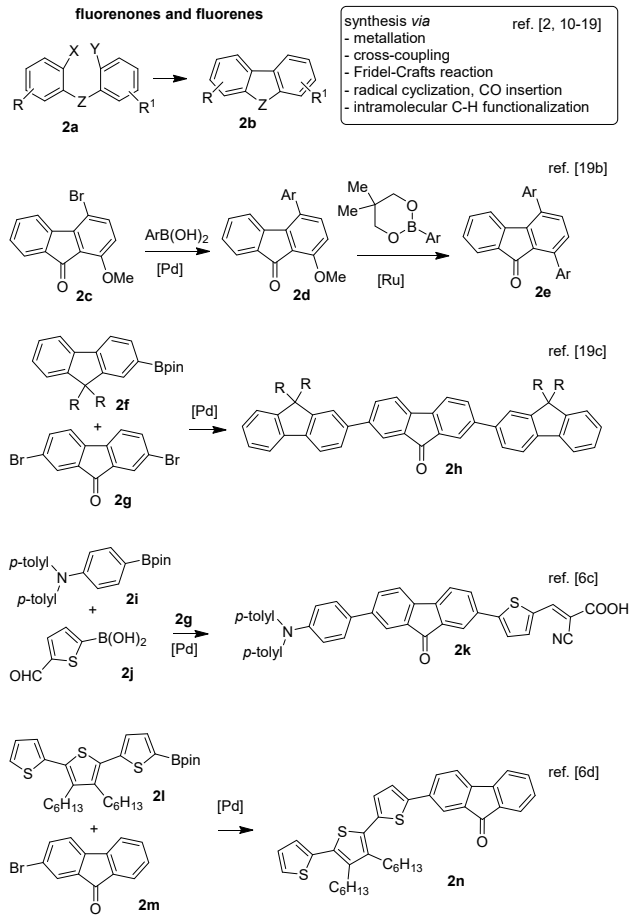
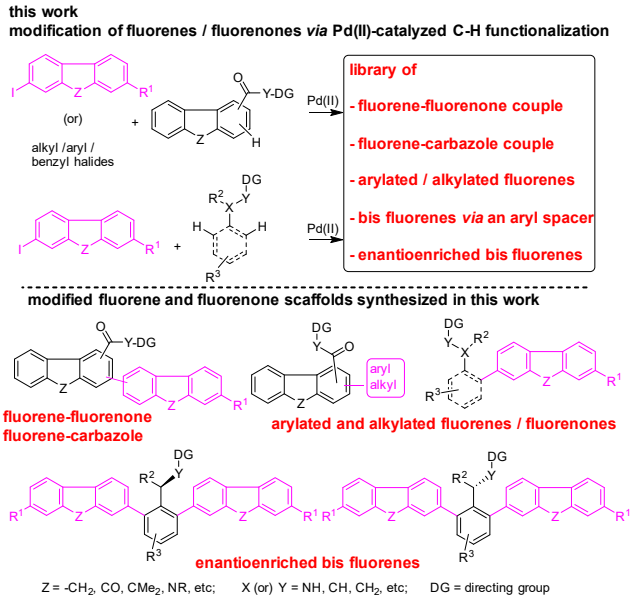


Scheme 1. Representative commonly employed methods for synthesizing functionalized fluorene and fluorenone molecules.

Given their applications and pivotal roles in developing functional materials and medicinally or biologically active agents, various synthetic routes were designed for synthesizing the core structures of fluorenes and fluorenones.[10-19]

Functionalized fluorenone- or fluorene-based monomers are generally synthesized *via* traditional cross-coupling reactions (Scheme 1).[19,20] Some of the reported methods affording fluorenones include: (a) *ortho* metalation,[10] (b) cross-coupling or C-H coupling and Friedel-Crafts reaction,[11] (c) radical cyclization,[12] (d) CO insertion,[13] (e) intra or intermolecular C-H functionalization and decarboxylative coupling reactions,[14] and (f) conversion of fluorene to fluorenones *via* oxidation.[15] The fluorene skeletons have been constructed *via* the Friedel-Crafts,[16] gold-catalyzed C-C bond-forming reactions[17] and intramolecular C-H functionalization, etc.[18]

Some existing methods require assembling pre-functionalized organometallic reagents as starting materials for synthesizing the fluorene or fluorenone skeletons (Scheme 1). Alternatively, the direct functionalization of C-H bonds of fluorene or fluorenone skeleton might lead to a step-economical route for building a library of modified fluorene and fluorenone motifs (Scheme 2).



Scheme 2. Modification of fluorene and fluorenone core *via* C-H functionalization and expansion of their library.

In recent years, the transition-metal-catalyzed site-selective C-H functionalization of small molecules using a directing group has emerged as a practical route for building a library of different classes of functionalized cyclic and aliphatic skeletons.[21-24] Especially, the transition metal-catalyzed directing group-assisted C–C bond-forming reactions leading to biaryls *via* direct C-H coupling constitute a powerful alternative to the traditional cross-coupling tactics. Taking an impetus from the contributions of the Pd(II)-catalyzed directing group-aided sp^2 C-H arylation reactions in the expansion of the library of privileged skeletons;[22-24] we envisaged the direct functionalization of C-H bonds of fluorenes or fluorenones towards building a library of modified fluorene and fluorenone motifs (Scheme 2). This process has enabled assembling a variety of fluorene and fluorenone monomeric motifs, which are expected to have scope in the development of materials and medicinal chemistry.

Results and discussion

To initiate the modification of the fluorenone and fluorene core *via* directing group-aided C-H functionalization, initially, 9-oxo-9*H*-fluorene-4-carboxylic acid was linked with bidentate directing groups[22,23] under standard amide coupling conditions. The preparation of 9-oxo-9*H*-fluorene-4-carboxamides **5a-d** having the corresponding bidentate directing groups (e.g., 8-aminoquinoline (8-AQ), 2-(methylthio)aniline (MTA), and simple amines) was completed (Table 1). Next, we assembled 9-oxo-9*H*-fluorene-1-carboxamides **5e,f** by coupling 9-oxo-9*H*-fluorene-1-carboxylic acid with 8-AQ and MTA directing groups (Table 1). We also assembled fluorene-based carboxamides **5g-i** from their corresponding fluorene

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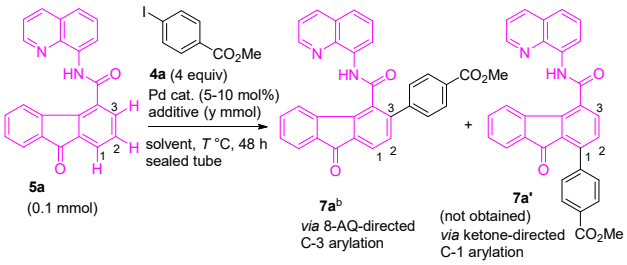
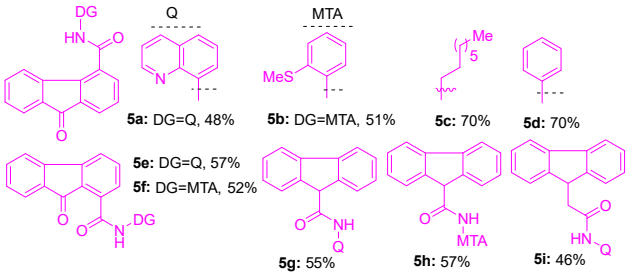
carboxylic acid and 8-AQ or MTA using the standard procedures (Table 1).

Table 1. Pd(II)-catalyzed modification of fluorenone core **5a** *via* C-H arylation.



entry	catalyst (10 mol%)	additive (0.25 mmol)	solvent (mL)	*T* (°C)	**7a:** yield (%)[a,b]
1	$Pd(OAc)_2$	K_2CO_3	*o*-xylene (1)	130	48
2	$Pd(OAc)_2$	Ag_2CO_3	neat	130	30
3	$Pd(OAc)_2$	AgOAc	*o*-xylene (1)	130	50
4	$Pd(OAc)_2$	AgOAc	toluene (1)	110	48
5	$Pd(OAc)_2$	AgOAc	HFIP (1)	100	50
6	$Pd(OAc)_2$	AgOAc $(BnO)_2PO_2H$[c]	toluene (1)	110	48
7	$Pd(OAc)_2$	AgOAc PivOH[c]	toluene (1)	110	45
8	$Pd(TFA)_2$	AgOAc	*o*-xylene (1)	130	33
9	$Pd(MeCN)_2Cl_2$	Cs_2CO_3	*o*-xylene (1)	130	20
10	$Pd(OAc)_2$	AgOAc	*m*-xylene (1)	130	50
11	$Pd(OAc)_2$	AgOAc	*m*-xylene (50 µL)	130	72
12[d]	$Pd(OAc)_2$	AgOAc	*m*-xylene (50 µL)	130	32
13[e]	$Pd(OAc)_2$	AgOAc	*m*-xylene (50 µL)	130	50
14[f]	$Pd(OAc)_2$	AgOAc	*m*-xylene (50 µL)	130	60



[a] Reaction conditions: **5a** (0.1 mmol), **4a** (4 equiv), catalyst, additive, solvent, 100-130 °C, 48 h, sealed tube (filled with N_2 atm). [b] Isolated yield. [c] In addition to AgOAc, $(BnO)_2PO_2H$ or PivOH (0.02 mmol) was used, respectively. [d] ArI (2 equiv) was used. [e] $Pd(OAc)_2$ (5 mol%) was added. [f] Reaction time = 24 h.

At the outset, we attempted the π-extension and sp^2 C-H arylation of 9-oxo-*N*-(quinolin-8-yl)-9*H*-fluorene-4-carboxamide (**5a**) possessing 8-aminoquinoline directing group (DG). We aimed at the site-selective *β*-C(sp^2)–H functionalization of the C3 position of **5a** under standard conditions.[22-24] Table 1 reveals the optimization studies conducted for the C3 arylation of **5a** in the presence of Pd(II) catalysts, silver or alkali metal salt additives, and solvents. Apart from the Pd(II) catalyst, an additive such as a silver salt (AgOAc or Ag_2CO_3) or an alkali metal-based salt/base (e.g., Cs_2CO_3 and K_2CO_3) is essential for accomplishing the required Pd(II)-catalyzed, 8-aminoquinoline DG-aided C–H arylation reactions.[22] The silver or alkali metal salt additive plays the role of a halide ion scavenger, and it helps in the regeneration of the Pd(II) catalyst in the proposed Pd^{II}–Pd^{IV} catalytic cycle.[22,23a]

The C(3)–H arylation of the fluorene-4-carboxamide **5a** was attempted using methyl 4-iodobenzoate (**4a**, 4 equiv) in the presence of the $Pd(OAc)_2$ (10 mol%) and K_2CO_3 (2 equiv) in *o*-xylene at 130 °C for 48 h (entry 1, Table 1). This reaction afforded the C(3)–H arylated fluorenone **7a** in 48% yield. Heating a mixture of **5a** with **4a** in the presence of $Pd(OAc)_2$ and Ag_2CO_3 (2 equiv) in neat condition afforded the C(3)–H arylated product **7a** in 30% yield (entry 2, Table 1). Performing the same reaction using AgOAc as an additive in *o*-xylene or toluene or HFIP afforded **7a** in 48-50% yields (entries 3-5, Table 1). Next, we heated **5a** with **4a** in the presence of $Pd(OAc)_2$, AgOAc, and $(BnO)_2PO_2H$ (20 mol%) or PivOH (20 mol%) as additional additives in toluene at 110 °C, and these reactions gave **7a** in 45-48% yields (entries 6 and 7, Table 1).

Next, the same reaction using $Pd(TFA)_2$ or $Pd(MeCN)_2Cl_2$ and AgOAc or Cs_2CO_3 as an additive in *o*-xylene at 130 °C gave the product **7a** in a decreased yield (20-33%, entries 8 and 9, Table 1). The reaction using $Pd(OAc)_2$ catalyst and AgOAc in *m*-xylene solvent afforded the product **7a** in 50% yield (entry 10, Table 1). Next, the reaction of **5a** and **4a** in the presence of $Pd(OAc)_2$ and AgOAc in a minimal amount of solvent *m*-xylene (50 µL), gave **7a** in an improved yield (72% entry 11, Table 1). The arylation of **5a** using reduced equiv of **4a** (2 equiv) in the presence of $Pd(OAc)_2$ and AgOAc in *m*-xylene (50 µL) gave **7a** in low yield (32%, entry 12, Table 1). The arylation of **5a** using 4 equiv of aryl iodide **4a** in the presence of 5 mol% of $Pd(OAc)_2$ and AgOAc in *m*-xylene (50 µL) gave **7a** in 50% yield (entry 13, Table 1). The arylation of **5a** using 4 equiv of aryl iodide **4a** in the presence of 10 mol% of $Pd(OAc)_2$ and AgOAc in *m*-xylene (50 µL) for 24 h instead of 48 h gave **7a** in 60% yield (entry 14, Table 1). In addition to the 8-AQ DG-assisted C(3)–H arylation of fluorenone **5a**, which afforded **7a** as the product, there was no indication of C(1)–H arylation directed by the inherent ketone functionality in fluorenone **5a**, and the expected other product **7a'** was not obtained (Table 1).

Having examined the arylation of fluorene-4-carboxamide **5a**, we intended to explore the competence of different directing groups for accomplishing the C(3)–H arylation of 9-oxo-9*H*-fluorene-4-carboxamides **5a-d** (Scheme 3). Heating a mixture of **5a** possessing 8-AQ as the DG with iodofluorene **6a** in the presence of $Pd(OAc)_2$ and AgOAc in *m*-xylene at 130 °C for 48 h afforded the fluorenone-fluorene dyad **8a** in 72% yield *via* the C(3)–H arylation of **5a** (Scheme 3). The Pd(II)-catalyzed arylation of **5b**, possessing MTA as the DG, with **6a**, afforded the fluorenone-fluorene dyad **8b** in 63% yield *via* the C(3)–H arylation of **5b**. The Pd(II)-catalyzed C–H arylation of fluorenone carboxamide **5d** or **5c** possessing a simple amide as the DG with **6a** did not afford the corresponding expected fluorenone-fluorene skeleton **8c** or **8d** (Scheme 3). These attempts suggested that a bidentate directing group is necessary for accomplishing the *β*-C(sp^2)–H arylation of fluorenone carboxamide **5a**/**5b**. This confirmed that the corresponding bidentate directing group 8-AQ in **5a** or MTA in **5b** provides the required chelation assistance during

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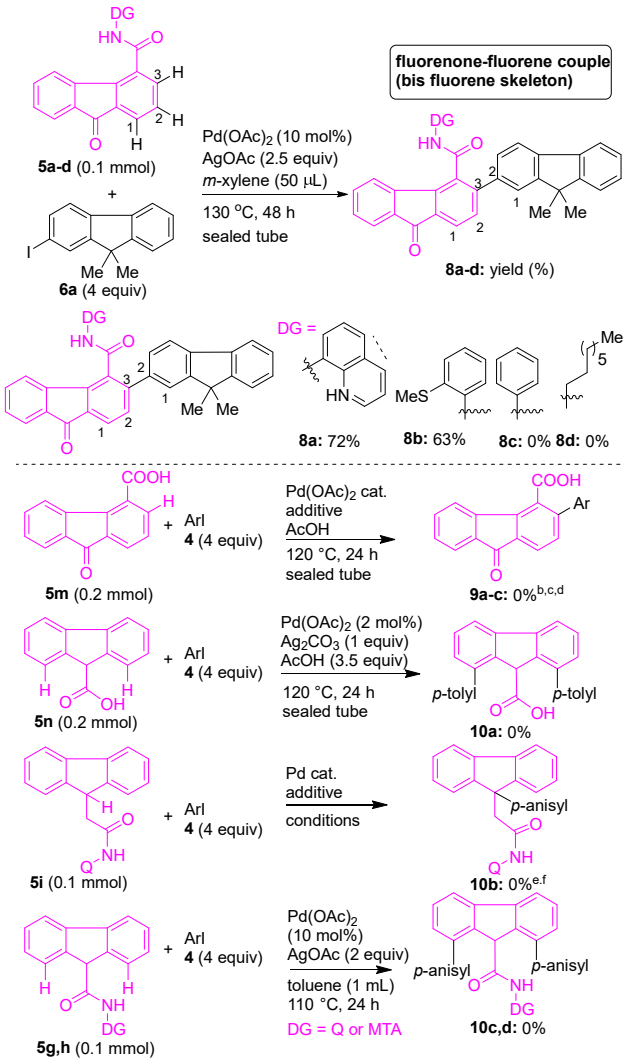
the *β*-C(sp²)–H activation in the proposed Pd^{II}–Pd^{IV} catalytic cycle,[22,23a] enabling the site-selective C(3)–H arylation of **5a** or **5b**.



Scheme 3. Pd(II)-catalyzed modification of fluorenone/fluorene core *via* C-H arylation using different directing groups. [a] Products **8a-d** are from the corresponding fluorenone carboxamides **5a-d**. [b] Product **9a** is from **5m** using **4a** (4 equiv), $Pd(OAc)_2$ (6 mol%), NMe_4Cl (1.3 equiv), KOAc (1.5 equiv) and AcOH (1.5 equiv). [c] Product **9b** is from **5m** using 1-iodo-4-methylbenzene (**4b**, 4 equiv), $Pd(OAc)_2$ (2 mol%), Ag_2CO_3 (1 equiv), KOAc (1.5 equiv) and AcOH (3.5 equiv). [d] Product **9c** from **5m** using 2-iodo-9,9-dimethyl-9*H*-fluorene (**6a**, 4 equiv), $Pd(OAc)_2$ (6 mol%), NMe_4Cl (1.3 equiv), KOAc (1.5 equiv) and AcOH (1.5 equiv). [e] Using conditions of entry 4 of Table 1 and *p*-anisyl iodide (**4c**). [f] Using **4c**, $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.5 equiv), KOAc (1.2 equiv) in HFIP: AcOH (3:7), 110 °C, 24 h, sealed tube (purged with N_2 atm).

Next, we intended to attempt the native carboxylic acid group-mediated C-H arylation of fluorene carboxylic acid **5m** or **5n** (Scheme 3). We tried the Pd(II)-catalyzed C(3)–H arylation of **5m** with aryl iodides **4a** or **4b** or iodofluorene **6a** under different reaction conditions. These reactions did not afford the expected C(3)–H arylated fluorene-4-carboxylic acid **9a-c** (Scheme 3). We then attempted the C(1)–H arylation of 9*H*-fluorene-9-carboxylic acid **5n** with *p*-tolyl iodide in the presence of $Pd(OAc)_2$ and Ag_2CO_3 in AcOH at 130 °C for 24 h. This reaction did not yield the expected C(1)–H arylated fluorene **10a** (Scheme 3). We continued testing the C-H arylation of additional fluorene substrates. The Pd(II)-catalyzed *β*-C–H arylation of carboxamide **5i**, possessing 8-AQ as the DG with *p*-anisyl iodide, did not yield the expected C(9)–H arylated fluorene **10b** (Scheme 3). The *γ*-C–H arylation of fluorene-9-carboxamide **5g** possessing 8-AQ DG with *p*-anisyl iodide did not give the expected C(1)–H arylated product **10c**. Similarly, the *γ*-C–H arylation of fluorene-9-carboxamide **5h** possessing MTA DG did not provide the expected bis C(1)–H arylated product **10d** (Scheme 3).

Having obtained the optimal reaction conditions for the site-selective C-H arylation of fluorenone-4-carboxamide **5a**, we then intended to expand the scope of C–H arylation of **5a** and prepare a wide range of π-extended fluorenone-4-carboxamides (Scheme 4). The Pd(II)-catalyzed C(3)–H arylation of **5a** was attempted by using various aryl iodides containing electron-donating or electron-withdrawing substituent at the *para* or *meta* position (e.g., OMe, alkyl, COMe, COOR, NO_2, etc) and phenyl iodide in the presence of the $Pd(OAc)_2$ and AgOAc in *m*-xylene (50 μL) at 130 °C for 48 h. These reactions afforded the corresponding C(3)–H arylated, π-extended fluorenones **7a-g** and **7k-m** in 60–88% yields (Scheme 4). The structure of compound **7c** was confirmed by X-ray structure analysis (Figure 2).

Next, fluorene-4-carboxamide **5a** was subjected to the Pd(II)-catalyzed arylation with various disubstituted aryl iodides to afford the corresponding C(3)–H arylated fluorenones **7h-j** in 67-71% yields (Scheme 4). The C(3)–H arylation of **5a** using heteroaryl iodides such as iodopyridyls and 5-iodoindole afforded the corresponding fluorenone-heteroaryl motifs **7n-p** in 56-77% yields. Treatment of **5a** with azobenzene-based aryl iodide afforded fluorenone-azobenzene motif **7q** in 86% yield. Treatment of various biaryl iodides containing electron-donating or electron-withdrawing substituent at the *para* position (e.g., OMe, alkyl, Br, *O*-alkyl, OAc) with **5a** yielded the corresponding fluorenone-biaryl motifs (π-extended fluorenones) **7r-x** in 50-72% yields (Scheme 4). The reaction of 3-iodobiphenyl with **5a** afforded the fluorenone-biaryl motif **7y** in 60% yield (Scheme 4). Additionally, treatment of fluorene-4-carboxamide **5b** having the MTA as the DG with iodobiaryls yielded the corresponding fluorenone-biaryl motifs **7z** and **7za** in 49-50% yields (Scheme 4).

Having done the introduction of the aryl group at the C(3)-H of the fluorenone-4-carboxamide motif and obtained the modified fluorenone-aryl systems **7a-z**, **7za** (Scheme 4), alternatively, we ventured into the synthesis of C(2) arylated π-extended fluorenones **11** and **12** *via* the *ortho* C-H arylation of aromatic carboxamides (Scheme 5). Accordingly, benzamides **3a-g** having 8-AQ DG were subjected to the (*ortho*) C-H arylation with various iodofluorenes/iodofluorenones **6a-d**.

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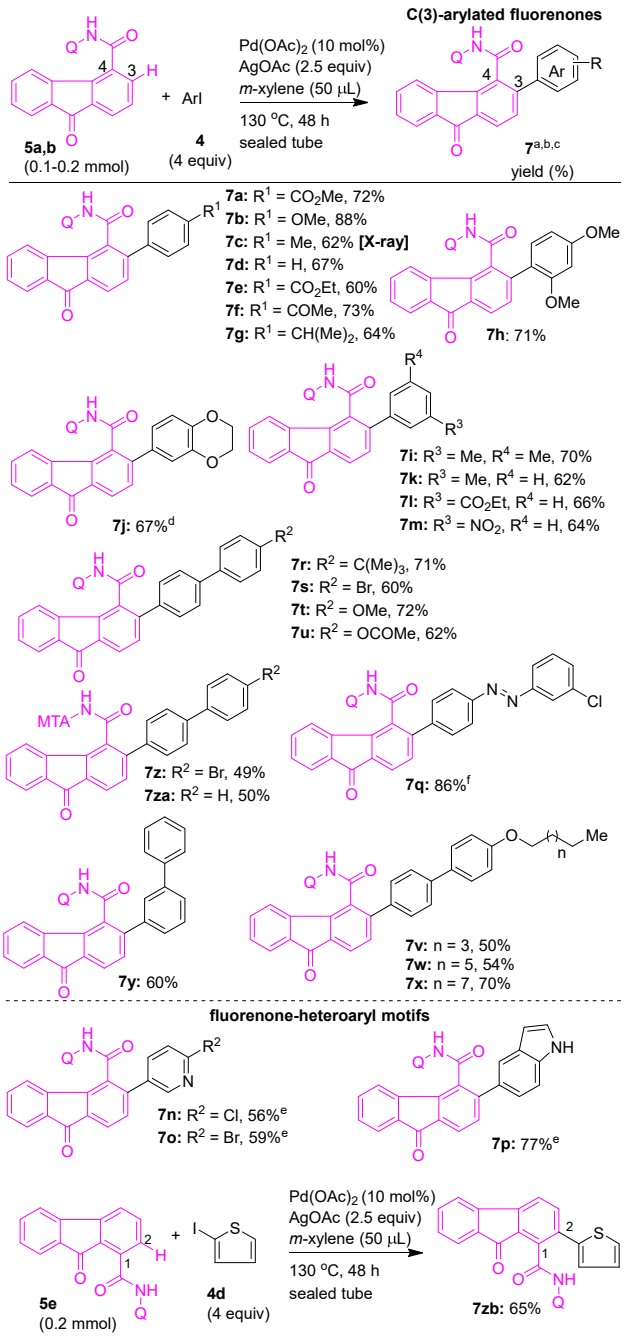
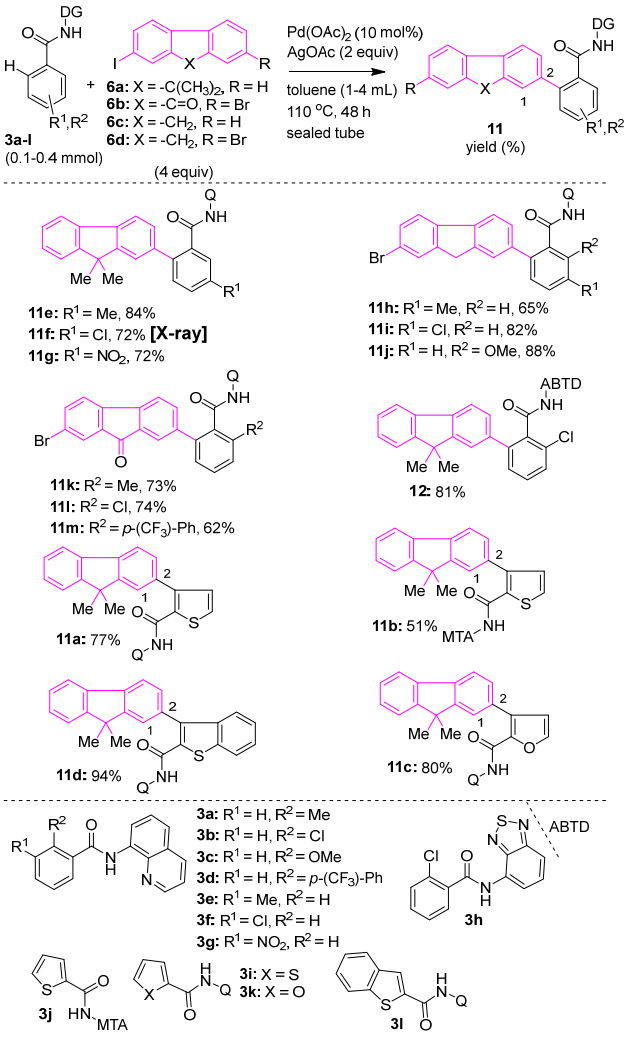


Scheme 4. Expansion of library of C(3) or C(2) arylated, π-extended fluorenones *via* Pd(II)-catalyzed C-H arylation of fluorenone-4-carboxamide **5a** **5b** and **5e**. [a] The reactions were carried out using 8-aminoquinoline DG and 2-methylthioaniline DG-linked substrates. [b] Compounds **7a–y** were obtained from **5a**. [c] Compounds **7z** and **7za** were obtained from **5b**. [d] The reaction was carried out under neat condition. [e] The reaction was carried out in *m*-xylene (1 mL). [f] Toluene (1 mL) as solvent at 110 °C.



Scheme 5. Expansion of the library of C(2) arylated, π-extended fluorenones or fluorenes through the coupling of the C-H bond of benzamides and heteroaryl carboxamides with iodofluorenes or iodofluorenones.

The Pd(II)-catalyzed C-H arylation of benzamides **3a-g** with 2-iodo-9,9-dimethyl-9*H*-fluorene (**6a**) or 2-bromo-7-iodo-9*H*-fluoren-9-one (**6b**) or 2-bromo-7-iodo-9*H*-fluorene (**6d**) under the optimized conditions yielded the corresponding fluorene-benzamide or fluorenone-benzamide coupled motifs **11e-m** in 62-88% yields (Scheme 5). The structure of compound **11f** was confirmed by X-ray structure analysis (Figure 2). Since corresponding *meta*-substituted benzamides **3e-g** contain two *ortho* *б*-C-H bonds, the arylation selectively occurred at the least hindered *ortho* *б*-C-H bond in **3e-g**, thereby affording the corresponding mono *б*-C-H arylation products **11e-g**. This observation is in accordance with the earlier reports of directing group-aided C(sp^2)-H arylation *meta*-substituted benzamides.[22,23h,j,s,t] Benzamide substrate **3h** having ABTD as the DG with **6a** under the optimized reaction conditions, gave the fluorene-aryl coupled moiety **12** in 81% yield (Scheme 5).

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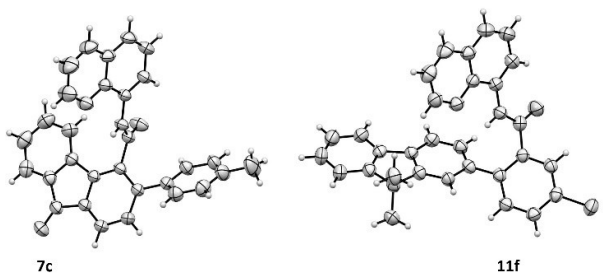
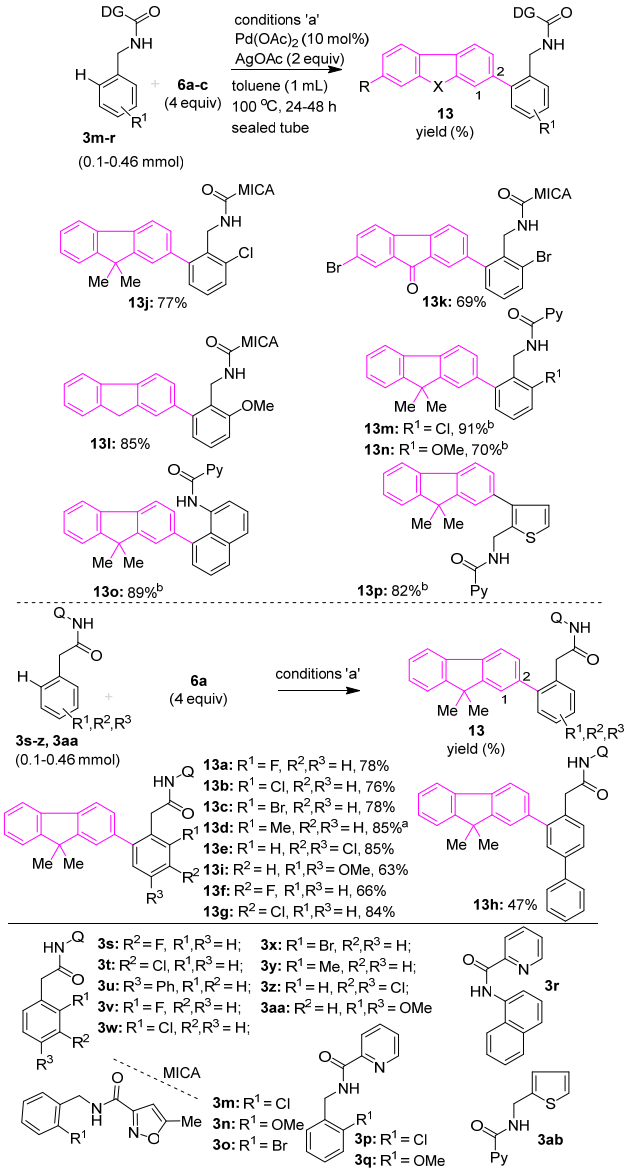


Figure 2. X-ray (ORTEP) structures of compounds **7c** and **11f**.

Several functional materials used in organic field effect transistors possess the chemical design of fluorenone-thiophene coupled motifs. Taking an impetus from the applications of fluorenone-thiophene motifs, we attempted the synthesis of fluorenone-thiophene and fluorene-thiophene coupled molecules. Accordingly, Pd(II)-catalyzed reaction of fluorene-1-carboxamide **5e** with 2-iodothiophene afforded the fluorenone-thiophene coupled motif **7zb** in 65% yield (Scheme 4). Alternatively, thiophene-2-carboxamide **3i** having the 8-AQ DG was subjected to the Pd(II)-catalyzed C(3)–H arylation with 2-iodofluorene **6a** to afford the fluorene-thiophene motif **11a** in 77% yield (Scheme 5). Thiophene-2-carboxamide **3j** having MTA DG with **6a**, also afforded the fluorene-thiophene coupled motif **11b** in 51% yield (Scheme 5). Subsequently, we treated furan-2-carboxamide **3k** and benzothiophene-2-carboxamide **3l** having 8-AQ DG with **6a** under standard reaction conditions to afford the corresponding fluorene-furan motif **11c** and fluorene-benzothiophene motif **11d** in 80-94% yields (Scheme 5).

Next, arylacetamides having 8-AQ DG were subjected to the (*ortho*) *γ*-C(sp^2)-H arylation with iodofluorene **6a**. Arylacetamides **3s**, **3t**, **3v-z** and **3aa** having substitutions at the *ortho*- or *meta*- or *para*-positions were heated with **6a** in the presence of $Pd(OAc)_2$ and AgOAc in toluene. These attempts yielded the corresponding fluorene-arylacetamide motifs (π-extended fluorenes) **13a-g**, **13i** in 58-85% yields (Scheme 6). Biaryl acetamide **3u** with **6a** yielded the fluorene-biaryl coupled moiety **13h** in 47% yield (Scheme 6). Along this line, benzylamine substrates possessing 5-methylisoxazole-3-carboxamide DG **3m-o** were subjected to the Pd(II)-catalyzed (*ortho*) *γ*-C(sp^2)-H arylation conditions with iodofluorenes **6a**, **6b**, **6c**, which afforded the corresponding fluorene-benzylamine coupled motifs **13j-l** in 69-85% yields (Scheme 6). Further, benzylamines possessing picolinamide DG **3p**, **3q**, or naphthylamine **3r** having the picolinamide DG were treated with **6a** in the presence of $Pd(OAc)_2$, $CuBr_2$, and CsOAc in *t*-amylOH.[25a] These attempts yielded the corresponding fluorene-benzylamine and fluorene-naphthylamine coupled motifs **13m-o** in 70-91% yields (Scheme 6). Additionally, thiophen-2-ylmethanamine substrate **3ab** possessing a picolinamide directing group was subjected to the C(3)–H arylation with **6a**, which afforded the thiophene-fluorene motif **13p** in 82% yield (Scheme 6).



Scheme 6. Expansion of the library of C(2) arylated, π-extended fluorenones or fluorenes through the coupling of *ortho γ*-C(sp^2)-H bond of aryl acetamides and benzylamines with iodofluorenes or iodofluorenones. [a] **13d** is from substrate **3y** and **6a** (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), *p*-xylene (1 mL), 48 h sealed tube (purged with N_2 atm). [b] **13m-p** are from their corresponding substrates using conditions **6a** (4 equiv), $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (10 mol%), CsOAc (4 equiv), *t*-amylOH (1-3 mL), 130 °C, 36 h sealed tube (purged with N_2 atm).

We then intended to expand the scope of this method by synthesizing fluorenones having enhanced conjugation, *viz.*, fluorenone-fluorene motifs (Scheme 7). Towards this, heating fluorene-4-carboxamide **5a** having 8-AQ DG with **6a** in the presence of $Pd(OAc)_2$ and AgOAc in *m*-xylene (50 µL) at 130 °C for 48 h afforded the fluorenone-fluorene coupled motif **8a** in 72% yield *via* the C(3)–H arylation (Scheme 7). Next, the same reaction was performed using fluorene-4-carboxamide **5b** having MTA DG, to afford the fluorenone-fluorene coupled motif **8b** in 63% yield. Further, treatment of **5a** with 2-iodofluorene **6c** afforded the fluorenone-

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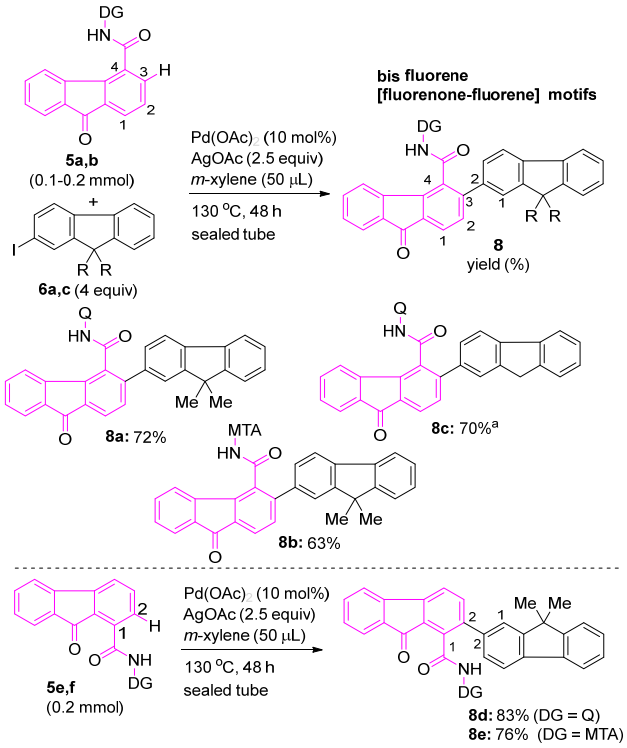
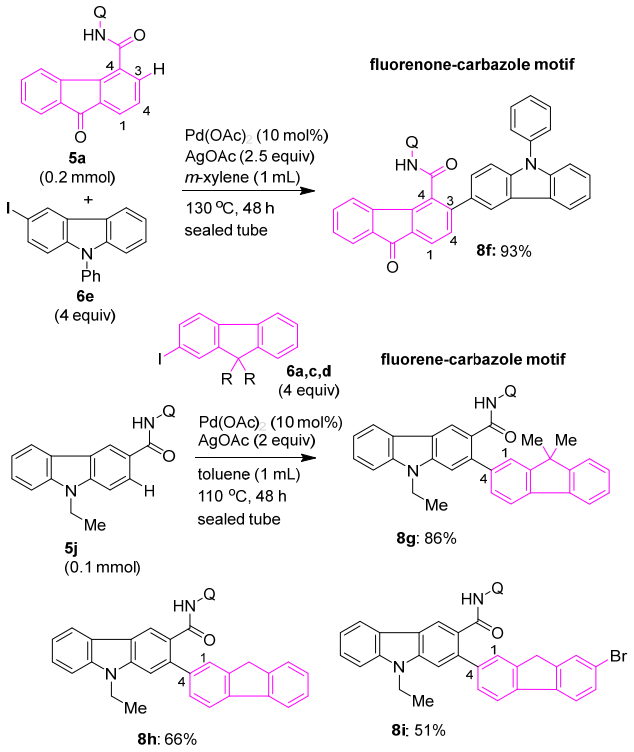
fluorene coupled motif **8c** in 70% yield. Subsequently, the C(2)–H arylation of fluorene-1-carboxamides **5e** or **5f** with **6a** in the presence of $Pd(OAc)_2$ and AgOAc yielded the corresponding fluorenone-fluorene coupled motifs **8d** and **8e** in 76-83% yields (Scheme 7).



Scheme 7. Pd(II)-catalyzed C-H arylation of fluorenone-4-carboxamides **5a**, **5b** and fluorenone-1-carboxamides **5e**, **5f** towards the synthesis of bis fluorene (fluorenone-fluorene coupled) motifs. [a] Chlorobenzene (1 mL) was used as a solvent.

Along this line, we envisioned preparing fluorenone-carbazole and fluorene-carbazole coupled scaffolds. Toward this, we heated fluorene-4-carboxamide **5a** with 3-iodocarbazole **6e** (4 equiv) as the coupling partner in the presence of $Pd(OAc)_2$ and AgOAc in *m*-xylene. This reaction afforded the fluorenone-carbazole coupled skeleton **8f** in 93% yield (Scheme 8). Alternatively, we treated carbazole-3-carboxamide **5j** having the 8-AQ DG with iodofluorenes **6a**, **6c** and **6d** as the coupling partners in the presence of $Pd(OAc)_2$ and AgOAc in toluene at 110 °C for 48 h. These attempts resulted in the fusion of the C2 position of the fluorene unit with the C3 position of the carbazole unit affording the corresponding carbazole-fluorene motifs **8g-i** in 51-86% yields (Scheme 8).



Scheme 8. Synthesis of fluorenone-carbazole and fluorene-carbazole coupled motifs *via* the Pd(II)-catalyzed C-H arylation of fluorenone-4-carboxamide **5a** and carbazole-3-carboxamide **5j**.

We then wished to adopt the transient directing group-assisted (TDG) *β*-C-H functionalization strategy[26a] to functionalize fluorene moiety **5k** and obtain C–H arylated fluorene motif **14a** or **14a'**. Table 2 describes the screening of reaction conditions for the Pd(II)-catalyzed, transient directing group-aided direct *β*-C(sp^2)–H arylation of 2-acetylfluorene (**5k**) with *p*-anisyl iodide. We commenced the optimization studies by evaluating the significance of glycine as a TDG to functionalize the C(1)-H or C(3)-H bond of 2-acetylfluorene (**5k**). We attempted the *β*-C(sp^2)–H arylation of **5k** with **4c** (3 equiv) in the presence of glycine (50 mol%), $Pd(PPh_3)_2Cl_2$, AgOAc or Ag_2CO_3 as an additive and H_2O (4 equiv) in HFIP:AcOH (9:1). This reaction afforded the C(3)–H arylated fluorene **14a** in 30-53% yields (entries 1, 2, Table 2). The same reaction in TFA solvent did not yield **14a** (entry 3, Table 2).

The C–H arylation of **5k** with **4c** using $Pd(OAc)_2$ or $PdCl_2$ as the catalyst instead of $Pd(PPh_3)_2Cl_2$ yielded **14a** in 30-40% yields (entries 4, 5 and Table 2). The C–H arylation of **5k** with **4c** in the presence of glycine, $Pd(OAc)_2$, AgTFA as an additive, and H_2O in HFIP:AcOH yielded **14a** in 55% yield (entry 6 and Table 2). The same reaction in AcOH:H_2O yielded **14a** in 44% yield (entry 7 and Table 2). Then, the C–H arylation of **5k** with **4c** in the presence of glycine, $Pd(TFA)_2$, AgTFA and H_2O in HFIP:AcOH yielded **14a** in 50% yield (entry 8 and Table 2). We then tried to perform the C–H arylation of **5k** with **4c** by using other amino acids as the transient directing group (TDG). We attempted the Pd(II)-catalyzed arylation of **5k** with **4c** in the presence of *β*-

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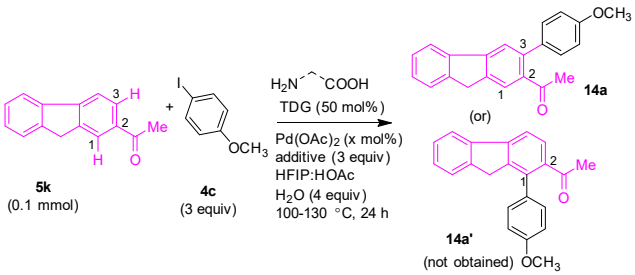
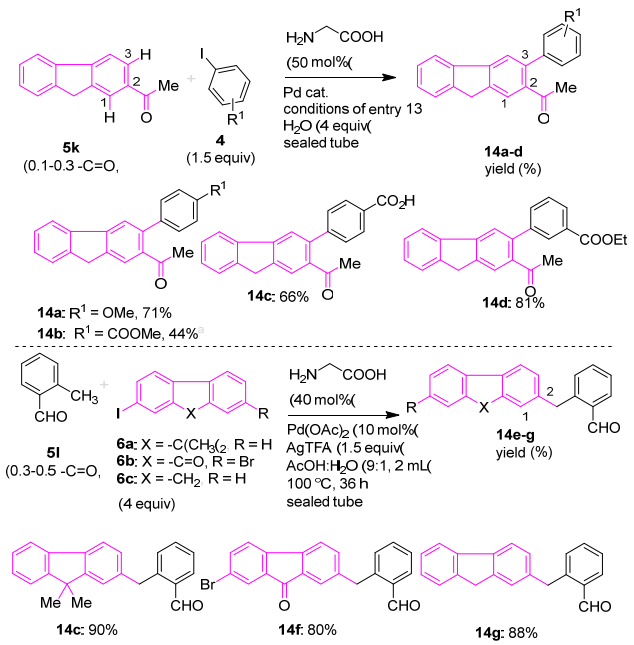
alanine or phenylglycine or DL-alanine or 2-aminoisobutyric acid as the TDG. These reactions were not fruitful, and product **14a** was obtained in low yields (entries 9-12, Table 2). This trend suggested that glycine is a suitable TDG to perform the *β*-C(sp^2)–H arylation of **5k** with **4c**. Accordingly, another reaction condition[26b] involving the *β*-C(sp^2)–H arylation of **5k** with **4c** (1.5 equiv) in the presence of glycine, $Pd(OAc)_2$, AgOAc and H_2O (4 equiv) in HFIP:AcOH afforded **14a** in a maximum of 71% yield (entry 13, Table 2). While the expected product **14a** was obtained, we did not obtain **14a'** in characterizable amounts. The C(1)-H bond in **5k** is relatively hindered, and presumably the C(1)-H arylation is a sluggish process when compared to the arylation at the C(3)-H position of **5k**. This observation is in accordance with the earlier work dealing with C-H arylation of a similar type of substrate (e.g., 2-acetylnapthalene), which predominantly afforded the corresponding least hindered *ortho* C-H functionalized product.[26d]

Table 2. Pd(II)-catalyzed transient directing group-aided modification of fluorene motif **5k** *via* C-H arylation



entry	catalyst (10 mol%)	additive (x equiv)	solvent (mL)	TDG (50 mol%)	**14a**: yield (%)[a]
1	$Pd(PPh_3)_2Cl_2$	AgOAc (2)	HFIP:AcOH (9:1, 1 mL)	glycine	53
2	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3 (2)	HFIP:AcOH (9:1, 1 mL)	glycine	30
3[b]	$Pd(PPh_3)_2Cl_2$	AgTFA (1.5)	TFA (1 mL)	glycine	0
4	$Pd(OAc)_2$	AgOAc (2)	HFIP:AcOH (9:1, 1 mL)	glycine	40
5	$PdCl_2$	AgOAc (2)	HFIP:AcOH (9:1, 1 mL)	glycine	30
6	$Pd(OAc)_2$	AgTFA (2.5)	HFIP:AcOH (9:1, 1 mL)	glycine	55
7[b]	$Pd(OAc)_2$	AgTFA (1.5)	AcOH:H_2O (9:1, 1 mL)	glycine	44
8	$Pd(TFA)_2$	AgTFA (1.5)	HFIP:AcOH (9:1, 1 mL)	glycine	50
9	$Pd(PPh_3)_2Cl_2$	AgOAc (2)	HFIP:AcOH (9:1, 1 mL)	*β*-alanine	25
10	$Pd(PPh_3)_2Cl_2$	AgOAc (2)	HFIP:AcOH (9:1, 1 mL)	phenylglycine	10
11	$Pd(PPh_3)_2Cl_2$	AgOAc (2)	HFIP:AcOH (9:1, 1 mL)	DL-alanine	10
12	$Pd(OAc)_2$	AgTFA (1.5)	HFIP:AcOH (9:1, 1 mL)	2-aminoisobutyric acid	0
13[c]	$Pd(OAc)_2$	AgOAc (2)	HFIP:AcOH (5:1, 1 mL)	glycine	71

[a] Isolated yield. [b] Reaction temperature = 100 °C and H_2O (1mL). [c] Using 1.5 equiv of ArI.



Scheme 9. Pd(II)-catalyzed transient directing group (TDG)-promoted C–H arylation of 2-acetylfluorene (**5k**) and *o*-tolualdehyde (**5l**). [a] The compound **14b** was obtained from substrate **5k** using reaction conditions including **4a** (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol%), AgOAc (2 equiv), HFIP:HOAc (9:1), 130 °C, 36 h, sealed tube (purged with N_2 atm).

Having an optimized reaction condition in our hand, we then performed the *β*-C(3)–H arylation of 2-acetylfluorene **5k** with different aryl iodides containing electron-donating or electron-withdrawing substituent (e.g., OMe, COOH, COOMe, COOEt) in the presence of glycine, $Pd(OAc)_2$, AgOAc, H_2O (4 equiv), HFIP:AcOH. These attempts successfully afforded the corresponding fluorene-aryl coupled skeletons **14a-d** in 44-81% (Scheme 9). Along this line, we attempted the transient directing group-assisted arylation of methyl C(sp^3)-H bond of *o*-tolualdehyde **5l** with iodofluorenes **6a** or **6c** or iodofluorenone **6b** by using the reported conditions,[26c] involving Pd(OAc), glycine, $Pd(OAc)_2$, AgTFA, AcOH:H_2O (9:1). These attempts were successful in affording the fluorene- and fluorenone-based diarylmethanes **14e-g** in 80-90% yield using TDG methodology (Scheme 9).

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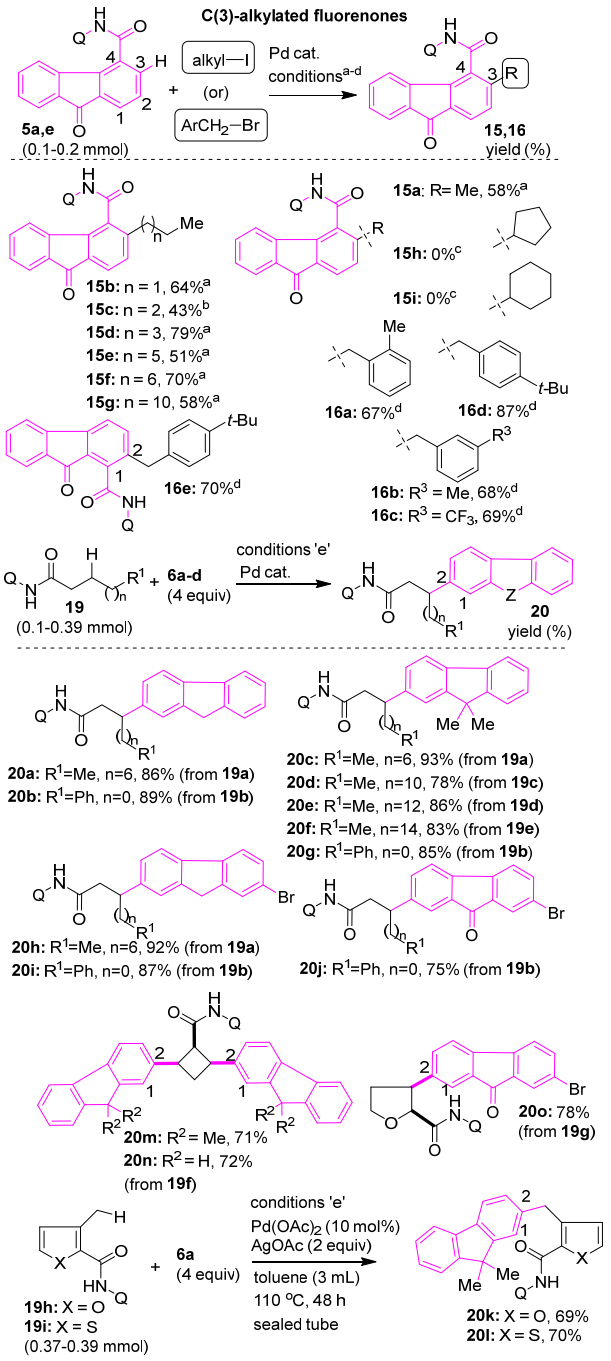
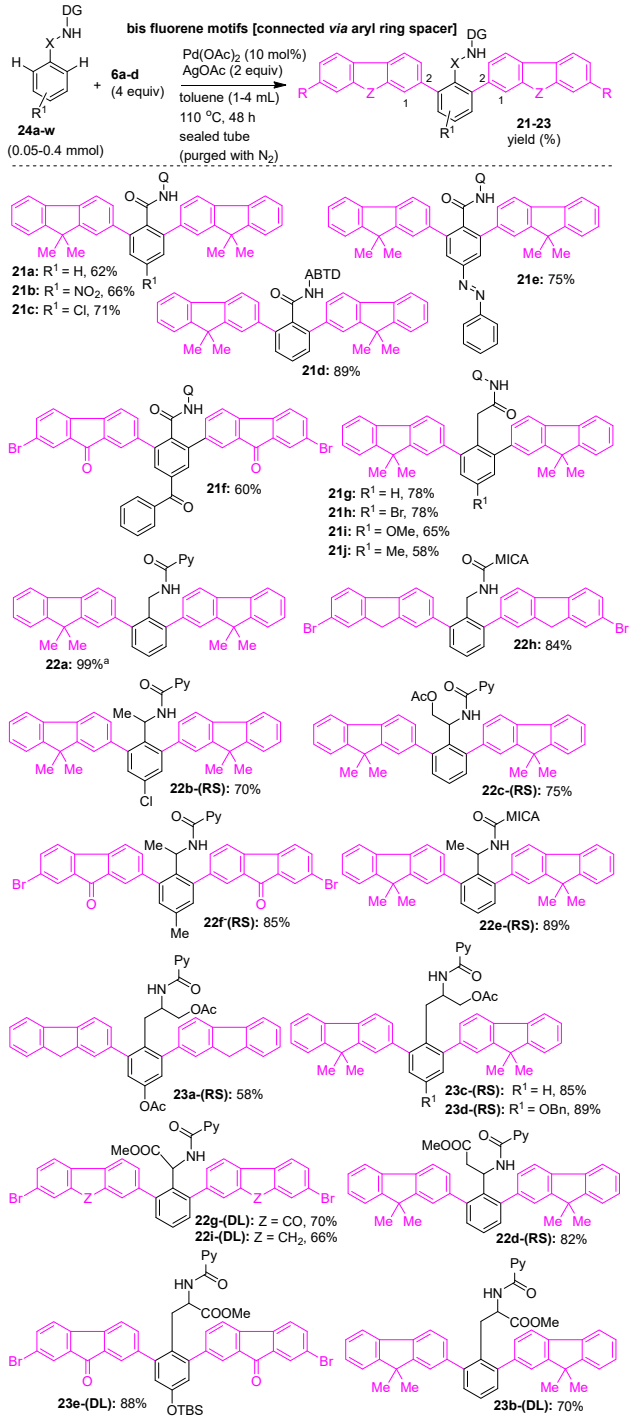


Scheme 10. Synthesis of alkylated fluorenones/fluorenes. [a] The compounds **15a**, **15b**, **15d-g** are from substrate **5a** using corresponding R-I (4 equiv) and conditions $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 equiv), PivOH (20 mol%), *t*-amylOH (2 mL), 130 °C, 48 h, sealed tube (purged with N_2 atm). [b] The compound **15c** is from substrate **5a** using conditions *n*-BuI (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), $CuBr_2$ (20 mol%), H_2O (1.5 mL), 110 °C, 48 h, sealed tube (filled with ambient air). [c] The compounds **15h** and **15i** were detected as an inseparable mixture. [d] The compounds **16a-d**, **16e** are from substrates **5a** and **5e** respectively, using conditions BnBr (3 equiv), $Pd(OAc)_2$ (5 mol%), KOAc (2 equiv), 1,4-dioxane (2 mL), 100 °C, 36 h, sealed tube (purged with N_2 atm). The product **20** was obtained from the respective carboxamide **19**.



Scheme 11. Construction of π-extended bis fluorenes having an aryl spacer *via* the *ortho* C(sp^2)-H arylation of benzamide, arylacetamide, benzylamine, amino alcohol and amino acid carboxamides using iodofluorenes and iodofluorenones. See the Scheme S2 in Supporting Information for the structures of starting materials **24a-w**. [a] The compound **22a** was obtained from substrate **24s** using **6a** (4 equiv), $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (10 mol%), CsOAc (4 equiv), *t*-amylOH (2 mL), 130 °C, 36 h, sealed tube (purged with N_2 atm).

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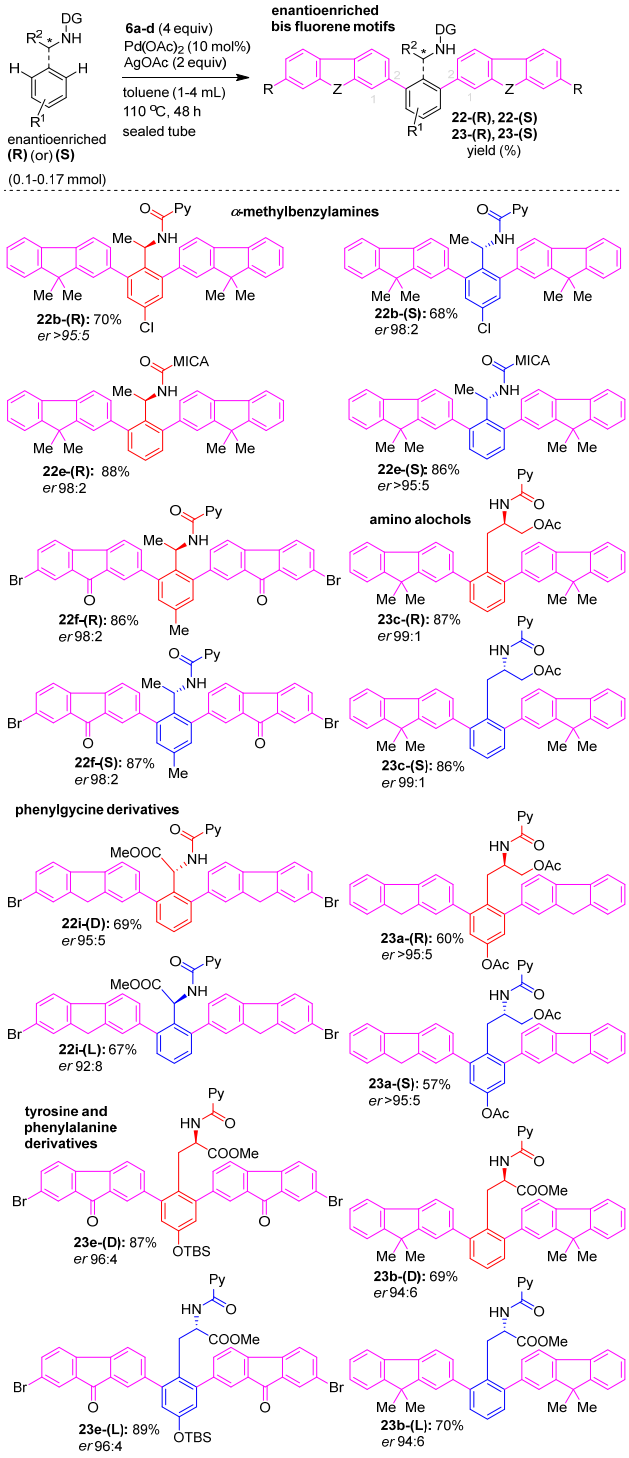

Scheme 12. Construction of enantioenriched π-extended bis fluorenes having an aryl spacer *via* the *ortho* C(sp²)-H arylation of benzamide, arylacetamide, benzylamine, amino alcohol, and amino acid carboxamides using iodofluorenes and iodofluorenones. See the Scheme S2 in Supporting Information for the structures of starting materials used in this Scheme.

We then explored the synthesis of alkylated fluorenones and fluorenes *via* *β*-C(sp²)–H alkylation and benzylation of the fluorene core. In this direction, we initially performed the 8-AQ DG-assisted *β*-C(sp²)–H alkylation of fluorenone-4-carboxamide **5a**. Substrate **5a** was treated with MeI (4 equiv) in the presence of $Pd(OAc)_2$, K_2CO_3, PivOH in *t*-amylOH at 130 °C for 48 h. This reaction successfully afforded the *β*-C(3)–H methylated fluorenone scaffold **15a** in 67% yield (Scheme 10). Successively, **5a** was treated with various primary alkyl iodides (4 equiv) in the presence of $Pd(OAc)_2$, K_2CO_3, PivOH in *t*-amylOH (2 mL) at 130 °C for 48 h to afford the corresponding *β*-C(3)–H alkylated fluorenone scaffolds **15b**, **15d-g** in 43-79% yields (Scheme 10) Compound **15c** was obtained from **5a** and *n*-BuI using conditions including $Pd(OAc)_2$, $CuBr_2$, K_2CO_3, H_2O (1.5 mL), 110 °C, 48 h. The expected *β*-C(3)–H alkylated fluorenone scaffolds **15h**, **15i** were not obtained when alkylation of **5a** was attempted using the corresponding secondary alkyl iodides. An inseparable mixture of starting material and unidentified products was obtained in these cases.

Having done the introduction of the alkyl group at the C(3)-H of the fluorenone-4-carboxamide motif and obtained the modified fluorene-alkyl motifs **15a-g** (Scheme 10), alternatively, we ventured into the synthesis of fluorene-alkyl motifs **20** *via* arylation of *β*-C(sp³)-H of aliphatic/alicyclic carboxamides. Accordingly, aliphatic carboxamides having 8-AQ DG **19a-e** were subjected to the *β*-C(sp³)-H arylation with various iodofluorenes **6a-d** in the presence of $Pd(OAc)_2$ and AgOAc in toluene. These attempts afforded the corresponding fluorene-alkyl motifs **20a-j** in 75-93% yields (Scheme 10). Then, alicyclic carboxamides having 8-AQ DG **17**, **18** were subjected to the Pd(II)-catalyzed *β*-C(sp³)-H arylation with iodofluorenes **6a-c**. These attempts afforded the corresponding fluorene-appended alicyclic motifs **20m-o** in 71-78% yields (Scheme 10). In concurrence with the literature reports,[24q,r] the corresponding products **20m-o** are believed to have *cis* stereochemistry *via* the arylation of the diastereotopic *β*-C(sp³)-H bond of the corresponding alicyclic carboxamides (Scheme 10).

Next, fluorene-4-carboxamide **5a** was treated with benzyl bromide (3 equiv) in the presence of $Pd(OAc)_2$ and KOAc in 1,4-dioxane at 100 °C to afford the corresponding *β*-C(3)–H benzylated fluorenone (fluorenone-based diarylmethane) scaffold **16a** in 67% yield (Scheme 10). Along this line, using the corresponding benzyl bromides, fluorenone-based diarylmethane scaffolds **16b-d** were obtained in 68-87% yields from C(3)-H benzylation of **5a**. Additionally, the Pd(II)-catalyzed C-H benzylation of fluorene-1-carboxamide **5e** with 1-bromo-4-(*tert*-butyl)benzene afforded the corresponding *β*-C(2)–H benzylated fluorenone (fluorenone-based diarylmethane) scaffold **16e** in 70% yield (Scheme 10). Successively, the arylation of methyl *γ*-C(sp³)-H bond of thiophene-2-carboxamide or furan-2-carboxamide **19h**, **19i** with iodofluorene **6a** in the presence of $Pd(OAc)_2$ and AgOAc in toluene afforded the corresponding fluorenone-based diarylmethane scaffolds **20k** and **20l** in 69-70% yields (Scheme 10).

Given the importance of π-extended fluorene motifs in materials science, we envisioned assembling bis fluorene motif having an aryl ring spacer unit and enantioenriched π-extended fluorene motif (Schemes 11 and 12). Towards this end, we planned to perform the double *ortho* *β*-C(sp²)-H arylation of benzamides with iodofluorenes

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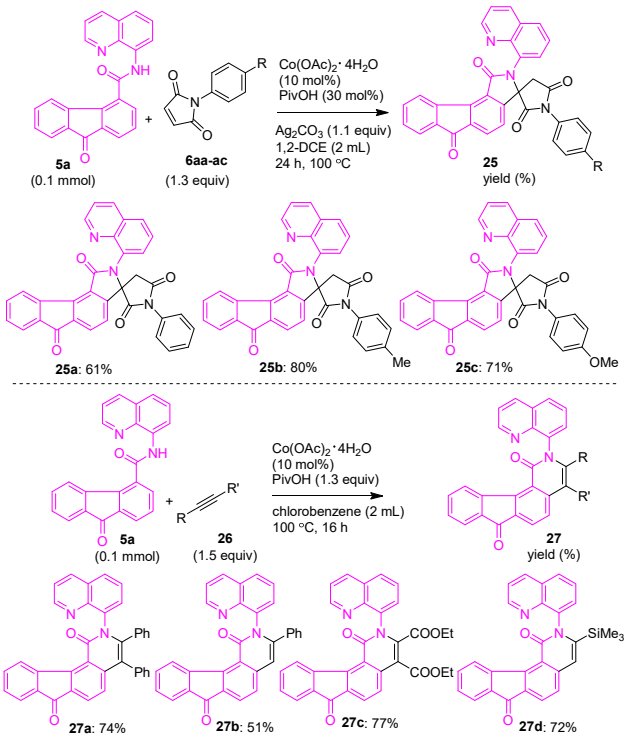
and iodofluorenones to obtain the targeted bis fluorene motifs having an aryl ring spacer unit. At first, the benzamide **24a** having the 8-AQ DG was reacted with iodofluorene **6a** in the presence of $Pd(OAc)_2$ and AgOAc in toluene. This reaction successfully afforded the expected bis fluorene motif **21a** having an aryl ring spacer unit *via* the double C-H arylation of **24a** (see the Scheme S2 in Supporting Information for the structures of starting materials **24a-w** relevant to Scheme 11). Benzamides **24c** and **24d** were then reacted with **6a** to afford the bis fluorenes **21b**, and **21c** in 66-71% yields (Scheme 11). Benzamide **24e** linked with the ABTD directing group reacted with **6a** to afford the bis fluorene **21d** in 89% yield (Scheme 11). Treatment of azobenzene-based benzamide **24f** with **6a** yielded the azobenzene-based bis fluorene motif **21e** in 75% yield (Scheme 11). Treatment of benzophenone-based carboxamide **24b** with **6b** yielded the benzophenone-based bis fluorenone motif **21f** in 60% yield. Then, arylacetamides **24h-k** were subjected to the Pd(II)-catalyzed double *ortho* C(sp^2)-H arylation with iodofluorene **6a** to afford the targeted bis fluorene motifs **21g-j** having an aryl ring spacer unit in 58-78% yields (Scheme 11).

Benzylamine or *α*-methylbenzylamine substrates **24s**, **24u-(RS)**, **24r-(RS)**, **24t-(RS)** and **24q** having picolinamide or 5-methylisoxazole-3-carboxamide directing groups were subjected to the Pd(II)-catalyzed double *ortho* C(sp^2)-H arylation with iodofluorenes **6a**, **6d** or iodofluorenone **6b**. These attempts yielded the corresponding targeted benzylamine-based bis fluorene motifs **22a**, **22b-(RS)**, **22e-(RS)**, **22f-(RS)** and **22h** in 70-99% yields (Scheme 11). Similarly, the Pd(II)-catalyzed picolinamide DG-assisted double *ortho* C(sp^2)-H arylation of substrates **24v-(RS)**, **24n-(RS)**, **24o-(RS)** and **24p-(RS)** with iodofluorene **6a** or **6c** were performed. The corresponding phenyl glycinol-based bis fluorene motif **22c-(RS)**, phenyl alaninol-based bis fluorene motif **23c-(RS)** and tyrosinol-based bis fluorene motifs **23a-(RS)**, **23d-(RS)** were obtained. Furthermore, we subjected aromatic amino acid derivatives such as phenylglycine, phenylalanine, and tyrosine substrates to the Pd(II)-catalyzed picolinamide DG-assisted double *ortho* C(sp^2)-H arylation with iodofluorenes **6a**, **6b** and **6d**. Accordingly, phenylglycine-based bis fluorene motifs **22g-(DL)**, **22i-(DL)**, phenylalanine-based bis fluorene motif **23b-(DL)**, *β*-phenylalanine-based bis fluorene motif **22d-(RS)**, tyrosine-based bis fluorene motif **23e-(DL)** were obtained from their corresponding substrates **24g-(DL)**, **24l-(DL)**, **24w-(RS)** and **24m-(DL)** (Scheme 11).

Subsequently, we wished to prepare an enantioenriched bis fluorene motif having an aryl ring spacer unit (Scheme 12). Accordingly, enantioenriched *α*-methylbenzylamine substrates **24u-(R)**, **24u-(S)**, **24r-(R)**, **24r-(S)**, **24t-(R)**, **24t-(S)** having picolinamide or MICA DG were subjected to the Pd(II)-catalyzed double *ortho* C(sp^2)-H arylation with iodofluorenes **6a** or iodofluorenone **6b**. These attempts yielded the corresponding enantioenriched *α*-methylbenzylamine-based bis fluorene motifs **22b-(R)**, **22b-(S)**, **22e-(R)**, **22e-(S)**, **22f-(R)**, **22f-(S)** in good yields with good enantiopurity (see the Scheme S2 in Supporting Information for the structures of starting materials relevant to Scheme 12).

We conducted the Pd(II)-catalyzed picolinamide DG-assisted double *ortho* C(sp^2)-H arylation of enantioenriched phenyl alaninol substrates **24n-(R)**, **24n-(S)**, tyrosinol substrates **24o-(R)**, **24o-(S)** with iodofluorene **6a** or **6c**. These attempts yielded the corresponding enantioenriched phenylalaninol-based bis fluorene motifs **23c-(R)**, **23c-(S)** and tyrosinol-based bis fluorene motifs **23a-(R)**, **23a-(S)** in good yields and enantiopurity (Scheme 12). Furthermore, we conducted the Pd(II)-catalyzed picolinamide DG-assisted double *ortho* C(sp^2)-H arylation of enantioenriched aromatic amino acid substrates such as phenylglycine **24g-(D)**, **24g-(L)**, tyrosine **24m-(D)**, **24m-(D)** and phenylalanine **24l-(D)**, **24l-(L)** with iodofluorene **6d** or **6b** or **6a**. These attempts yielded the corresponding enantioenriched phenylglycine-based bis fluorene motifs **22i-(D)**, **22i-(L)**, tyrosine-based bis fluorene motifs **23e-(D)**, **23e-(L)** and phenylalanine-based bis fluorene motifs **23b-(D)**, **23b-(L)** in good yields and enantiopurity (Scheme 12).



Scheme 13. Cobalt-catalyzed 8-aminoquinoline directed oxidative cyclization of fluorenone carboxamide **5a** with maleimides and alkynes.

Having obtained arylated and alkylated fluorene/fluorenone scaffolds, we shifted our attention toward synthesizing modified fluorenones *via* ring annulation on fluorenones. Taking inspiration from the reported cobalt-catalyzed oxidative cyclization, we treated maleimides **6aa-ac** with fluorenone-4-carboxamide **5a** by using the reported conditions (Scheme 13),[27a] involving $Co(OAc)_2·H_2O$, PivOH and Ag_2CO_3 in 1,2-DCE. These attempts afforded the corresponding fluorenone-based spiro succinimides **25a-c** in 61-80% yields (see Scheme S1 in Supporting Information for proposed mechanism of formation of **25a-c**). Additionally, we heated acetylenes (symmetrical or unsymmetrical) with fluorene-4-carboxamide **5a** under the

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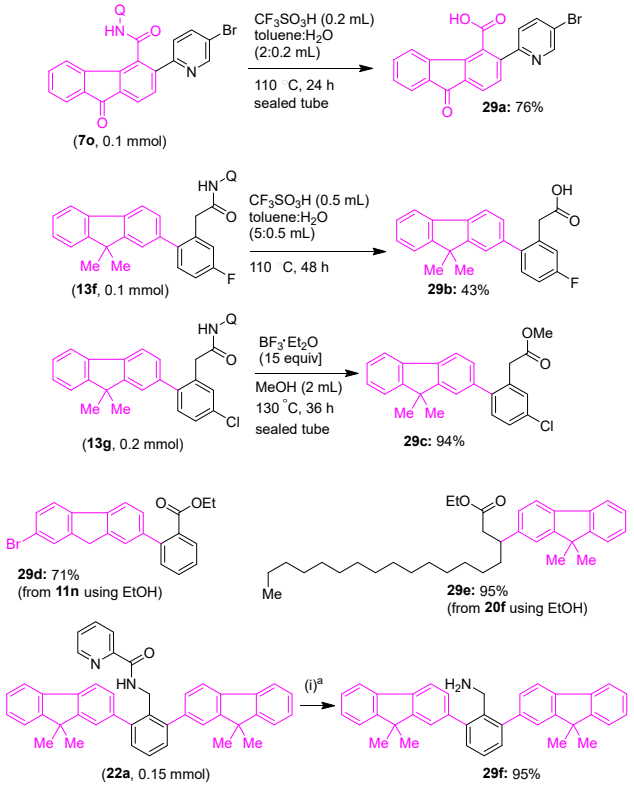
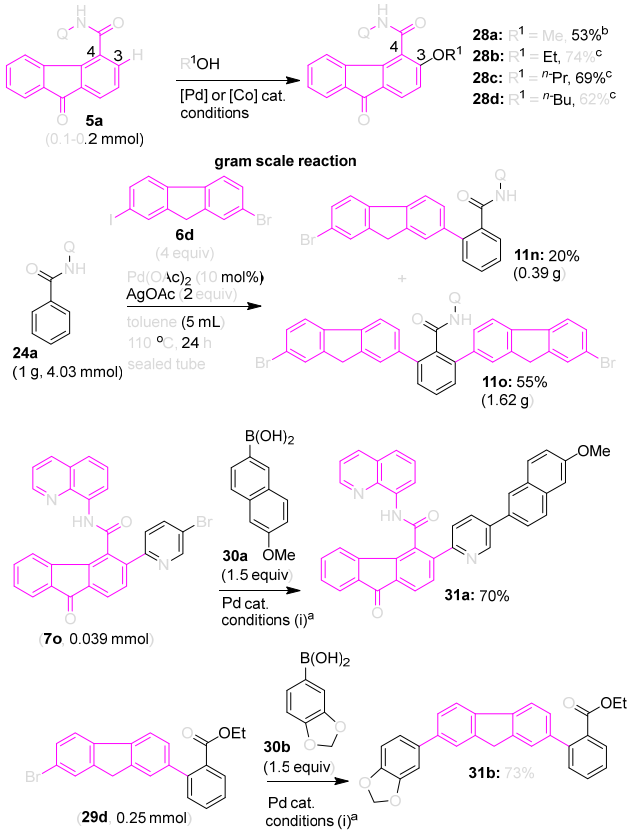
reported conditions[27b] involving $Co(OAc)_2·H_2O$, PivOH in chlorobenzene. These attempts gave the corresponding fluorenone-based isoquinolone derivatives **27a-d** in 51-77% yields (Scheme 13).



Scheme 14. Synthetic transformations. Removal of the directing groups. [a] Conditions (i): Zn dust (15 equiv), HCl (0.4 mL), THF:H_2O (1:1), 12 h, open flask.

Next, we intended to show the utility and removal of the bidentate directing group[28b] after performing the Pd(II)-catalyzed C-H arylation reactions affording functionalized fluorenes/fluorenones (Scheme 14). We subjected the C(3)-arylated fluorenone carboxamide **7o** or fluorenone-arylacetamide **13f** to triflic acid-mediated amide hydrolysis to afford the C(3)-arylated fluorenone carboxylic acid **29a** or fluorenone-arylacetic acid **29b** (Scheme 14). In another attempt, we succeeded in removing the 8-aminoquinoline DG *via* the $BF_3·OEt_2$-mediated direct amide to ester conversion method. Accordingly, fluorene-arylacetamide **13g**, fluorene-benzamide **11n**, and aliphatic carboxamide **20f** containing the 8-AQ DG were subjected to the $BF_3·OEt_2$-mediated amide to ester conversion. These reactions afforded the corresponding fluorene motifs **29c**, **29d**, and **29e** (Scheme 14). We also succeeded in removing the picolinoyl group from benzylamine-based bis fluorene motif **22a** by using the reported conditions, involving Zn dust and 12 N HCl in a mixture of THF/H_2O at rt for 12 h.[28a] This process gave the benzylamine-based bis fluorene motif **29f** (Scheme 14).



Scheme 15. Synthetic transformations, a gram-scale C-H arylation of carboxamide and synthesis of C-H alkoxylated fluorenones and π-extended fluorene motifs *via* cross-coupling reaction. [a] Conditions (i): $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (3 equiv), toluene:EtOH:H_2O (2:1:1), 110 °C, 24 h sealed tube (purged with N_2 atm). [b] The compound **28a** is obtained from substrate **5a** using $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (1.5 equiv), toluene:MeOH (1:1, 2 mL), rt, 48 h, sealed tube (purged with ambient air). [c] The compounds **28b-d** are from substrate **5a** using $Co(OAc)_2·4H_2O$ (20 mol%), NaOAc (2 equiv), Ag_2O (1 equiv), ROH (2 mL), 80 °C, 24 h, sealed tube (purged with ambient air).

Furthermore, the palladium-catalyzed or cobalt-catalyzed C-H alkoxylation[25b] of the *β*-C(3)–H bond of fluorene-4-carboxamide **5a** using primary alcohols afforded the corresponding *β*-C(3)–H alkoxylated fluorenone scaffolds **28a-d** (Scheme 15). We then attempted a gram-scale synthesis of a modified fluorene scaffold. Accordingly, benzamide **24a** was subjected to the *ortho β*-C-H arylation with **6d** in the presence of $Pd(OAc)_2$ and AgOAc. This reaction afforded the fluorene-aryl motif **11n** (20%) and the bis fluorene motif **11o** (55%). Given that this reaction was performed on a gram-scale, it may be sluggish. Hence, we observed the fluorene-aryl motif **11n** in considerable yield *via* the mono C-H arylation. Notably, on a small scale, the C-H arylation of **24a** with **6a** predominantly afforded the bis fluorene motif **21a** (Scheme 11). Since fluorene and fluorenone compounds are vital components in material chemistry, we wished to further extend the synthetic utility of this work by attempting the synthesis of a few analogues of fluorene and fluorenone, which hold significance in material chemistry. Towards this, we intended to perform the cross-coupling reaction between the bromo functionality in the fluorenone-

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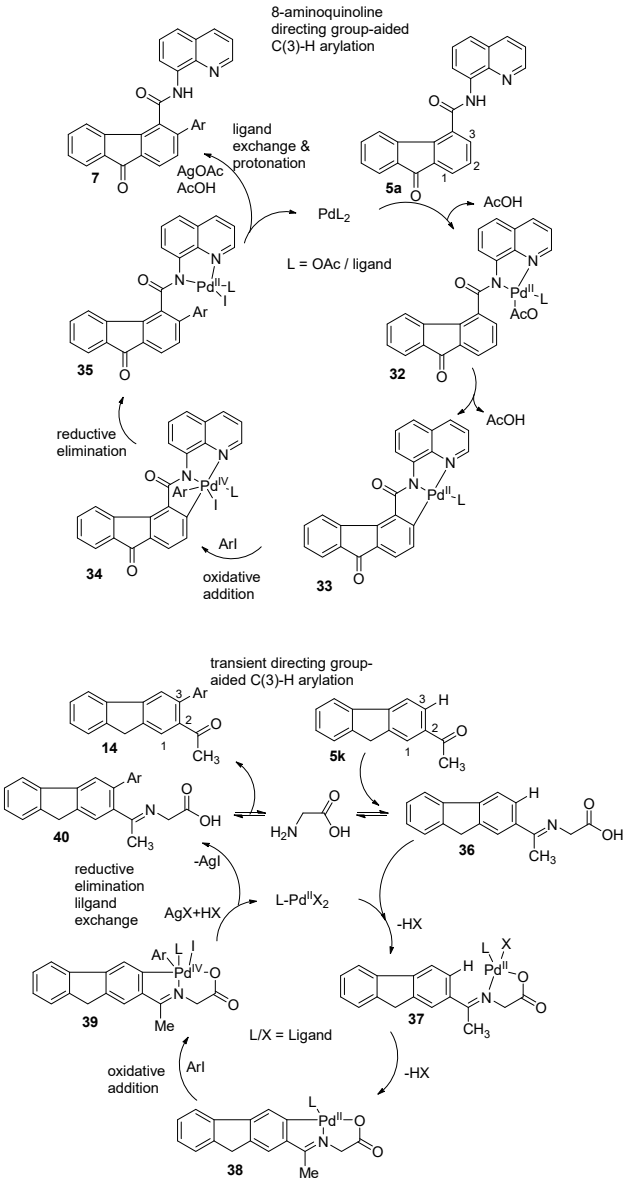
aryl motifs **7o** and **29d** with boronic acids **30a** and **30b** under the Suzuki coupling reaction conditions. These attempts enabled the synthesis of π-extended fluorene-aryl motifs **31a** and **31b** (Scheme 15).

We recorded the UV-Vis absorption spectra (λ_{max} (absorption)) of compounds (see Charts A-V in Supporting Information for the plots of UV-Vis absorption spectra), and we also obtained the preliminary fluorescence emission spectra of representative modified fluorene scaffolds prepared in this work (see Chart X in Supporting Information for the plots of fluorescence emission spectra). Emission spectra of **7q**, **8a**, **8c**, **8f**, **8g**, **27a**, **29f** and **31b** were recorded in MeCN (concentration of solutions = 27.6 μM) at the excitation wavelength of 260 nm. Two compounds **29f** and **31b** were found to show fluorescence (λ_{max} (emission) (nm) **29f**: 342, **31b**: 438) (see Chart X in Supporting Information). Emission spectra of **31b** in different concentrations in MeCN (8.2, 16.5, 22.1, 27.6, and 55.2 μM) were recorded at the excitation wavelength of 260 nm (see Chart W in Supporting Information). The preliminary examination of the emission spectra of **31b** in different concentrations indicated that the emission is constantly increasing with an increase in the concentration, and no quenching of fluorescence due to intermolecular interaction was observed (see Chart W in Supporting Information). Additional work is yet to be carried out to explore the fluorescence properties and application of other compounds synthesized in this work.

The NMR spectra and HRMS data established the structures of all the modified fluorenes and fluorenones obtained via the C-H functionalization process. In addition to this, the structure of representative C(3)-arylated fluorenone-4-carboxamide motif **7c** and fluorene-benzamide motif **11f** was unambiguously ascertained by the single-crystal X-ray structure analysis (Figure 2). The X-ray structures divulged that the Pd(II)-catalyzed bidentate directing group-aided, chelation-assisted C-H functionalization has occurred at the *ortho* β-C(sp^2)-H bond in the corresponding carboxamides **5a** and **3f** *via* a well-known Pd(II)/Pd(IV) redox cycle.[22,23a,26a] Based on the X-ray structure of these representative compound **7c**/**11f**, NMR and HRMS analysis data and in concurrence with the literature reports[22-24] the structures of all other compounds were ascertained.

In concurrence with the literature reports,[22-24] the mechanism of the Pd(II)-catalyzed, bidentate directing group-8-AQ-assisted C-H arylation *ortho* C(sp^2)-H bond of fluorenone-4-carboxamide **5a** is proposed (Scheme 16). The coordination of the 8-AQ moiety in fluorenone-4-carboxamide **5a** to the Pd(II) metal center is followed by a concerted metalation deprotonation (CMD), generating the five-membered Pd(II) species **33** *via* **32**. Oxidative addition of the Pd(II) species **33** with an aryl iodide yields the Pd(IV) species **34**, which then embarks on reductive elimination to generate a new C–C bond in compound **35**. Next, halide removal occurs with the help of a halide ion scavenger, followed by the protonolysis, affording the C(3)-arylated fluorenone-4-carboxamide motif **7** and the active Pd(II) species is regenerated in the catalytic cycle (Scheme 16). Similarly, based on the literature reports,[26] a plausible mechanism for the transient directing group (TDG)-assisted arylation of β-C(sp^2)-H bond of 2-acetylfluorene **5k** is illustrated. The *in-situ* installation of the glycine directing group with the aromatic ketone generates intermediate **36**. The coordination of the TDG in **36** to the Pd(II) metal center is followed by CMD, which affords **38** *via* **37**. Oxidative addition of **38** with an aryl iodide generates the Pd(IV) species **39**. Then, intermediate **39** undergoes reductive elimination (generating a new C–C bond in **40**) and subsequent halide removal by a halide ion scavenger, elimination of the TDG affords the β-C(sp^2)-H arylated product **14** and active Pd(II) species is regenerated.



Scheme 16. The proposed mechanism of Pd(II)-catalyzed, bidentate directing group-8-AQ-assisted or transient directing group-assisted C-H arylation in concurrence with the literature reports.[22,23a,26a]

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Conclusions

In summary, we reported the modification of fluorene and fluorenone core through the C-H functionalization route and assembling a library of modified fluorenes and fluorenones. Fluorene and fluorenone motifs are versatile components in functional materials and have found various applications (e.g., in oligomers, polymers, and as fluorophores, components for OLEDs, liquid crystals, bio-active and drug molecules, etc). Thus, synthesizing modified fluorenes and fluorenones (monomers) is considered a worthwhile effort. In this work, the C-H bonds of fluorene or fluorenone core were subjected to the directing group-aided arylation, alkylation, benzylation, alkoxylation, and annulation to afford several new examples of modified fluorenes and fluorenones. We also performed cobalt-catalyzed oxidative cyclization of fluorenone substrates, affording the corresponding fluorenone-moiety appended spiro compounds and quinolones. The synthesis of C(1), C(2), C(3), and C(4) functionalized fluorenes or fluorenones was accomplished depending on the starting substrates using bidentate directing group- or transient directing group-assisted C(sp^2)-H and C(sp^3)-H functionalization strategies. Alternatively, the functionalized fluorenes or fluorenones were also obtained by reacting the C-H bonds of aryl or alkyl carboxamide substrates with iodofluorenes or iodofluorenones. Overall, we have shown the synthesis of a wide range of fluorene-fluorenone, fluorene-carbazole, π-extended bis fluorenes having an aryl spacer, enantioenriched π-extended bis fluorenes, and arylated or alkylated fluorenes and fluorenones. We have also shown the removal of the directing group after performing the C-H functionalization in the fluorenone or fluorene core. We have obtained the UV-Vis absorption spectra of the synthesized compounds. Preliminary fluorescence emission spectra of representative modified fluorene scaffolds prepared in this work were ascertained. Given the importance of fluorene- and fluorenone-based motifs in materials and medicinal chemistry, this work contributes to augmenting the library of modified fluorene and fluorenone scaffolds *via* the C-H activation/functionalization method.

Experimental

General. The reagents used are commercially available and used without purification. The TLC analyses were performed on silica gel 60 F254 pre-coated plates or preparative alumina TLC plates and visualized by observation under irradiation with a UV lamp or iodine vapour. Column chromatography separation of crude reaction mixtures/samples was carried out on silica gel (100-200 mesh). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on 400 and ~101 MHz spectrometers, respectively (with TMS as an internal standard). The HRMS analysis data were obtained from a QTOF mass analyzer using the electrospray ionization (ESI) method. The IR spectra were recorded as neat samples / thin films, using KBr to prepare pellets for solid samples, or in a solvent. The required anhydrous solvents were prepared under standard solvent drying procedures, and reactions were carried out under a nitrogen atmosphere or in ambient air in RB flasks or in the sealed tubes as mentioned in the respective Schemes/Tables. Organic layers obtained from the work-up procedure were dried using anhydrous Na_2SO_4. Isolated yields of products were reported, and yields have not been optimized. The UV-Vis absorption spectra of compounds were recorded at a concentration (*c*) = 0.02 g/100 mL in CH_3CN.

We have performed the HPLC analysis of the starting material (substrates) used and fluorene- and fluorenone-based motifs synthesized in this work *via* C-H functionalization (see the supporting information). Initially, the HPLC analysis patterns of the racemic substrates **24g-(DL)**, **24l-(DL)**, **24m-(DL)**, **24n-(RS)**, **24o-(RS)**, **24r-(RS)**, **24t-(RS)** and **24u-(RS)** were determined. Subsequently, the enantiopurity of substrates **24t-(R)** (*er* 99:2), **24t-(S)** (*er* 98:2), **24u-(R)** (*er* 99:4), **24u-(S)** (*er* 99:4), **24r-(R)** (*er* 99:1), **24r-(S)** (*er* 99:4), **24g-(D)** (*er* 95:5), **24g-(L)** (*er* 92:8), **24l-(D)** (*er* 98:2), **24l-(L)** (*er* 99:1), **24m-(D)** (*er* 98:2), **24m-(L)** (*er* 99:1), **24n-(R)** (*er* 99:1), **24n-(S)** (*er* 99:1), **24o-(R)** (*er* 98:2), **24o-(S)** (*er* 98:2) were ascertained from HPLC analysis. Next, the HPLC analysis patterns of the racemic fluorene- and fluorenone-based motifs **22b-(RS)**, **22e-(RS)**, **22f-(RS)**, **22i-(DL)**, **23a-(RS)**, **23c-(RS)**, **23b-(DL)** and **23e-(DL)** synthesized were ascertained. Then, the HPLC analysis patterns of the enantioenriched fluorene- and fluorenone-based motifs **22b-(R)**, **22b-(S)**, **22e-(R)**, **22e-(S)**, **22f-(R)**, **22f-(S)**, **22i-(D)**, **22i-(L)**, **23a-(R)**, **23a-(S)**, **23c-(R)**, **23c-(S)**, **23b-(D)**, **23b-(L)**, **23e-(D)** and **23e-(L)** were ascertained.

General procedure for synthesizing fluorenone carboxamides (5a-f) and fluorene carboxamides (5g-i).

In a RB flask, containing 9-oxo-9*H*-fluorene-4-carboxylic acid (1-5 mmol, 1 equiv) or 9-oxo-9*H*-fluorene-1-carboxylic acid (1 mmol, 1 equiv) or 9*H*-fluorene-9-carboxylic acid (1-2 mmol, 1 equiv) or 2-(9*H*-fluoren-9-yl)acetic acid (2 mmol, 1 equiv) in anhydrous DCM (2-10 mL) is added DMF (1 to 2 drops) and $(COCl)_2$ (1.2 equiv) under a flow of nitrogen atm and the reaction is prolonged for 5 h at rt. After the reaction period is over, the solvent is evaporated to afford the corresponding acid chloride of fluorenone or fluorene derivative, and is vacuum dried. Next, to an RB flask containing appropriate amine (8-aminoquinoline or 2-(methylthio)aniline or aniline or 1-octyl amine) in anhydrous DCM (2-10 mL) is added Et_3N (1.2 equiv). Then, to this flask, the requisite acid chloride of fluorenone or fluorene derivative (dissolved in anhydrous DCM) is dropped dropwise under a nitrogen atm. The resulting reaction mixture was allowed to stir at rt for 36 h. Thereafter, the reaction mixture was diluted with DCM (10-15 mL) and washed with a saturated solution of $NaHCO_3$ (15 mL, three times). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the corresponding crude reaction mixture, which was then purified on silica gel column chromatography (EtOAc:hexanes) to give the corresponding fluorenone and fluorene carboxamide.

General procedure for the Pd(II)-catalyzed C-H arylation of fluorenone-4-carboxamide 5a,b and fluorenone-1-carboxamide 5e.

A mixture of an appropriate fluorenone-4-carboxamide **5a** or **5b** or fluorenone-1-carboxamide **5e** containing directing group (1 equiv), an appropriate aryl iodide (4 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.5 equiv) in *m*-xylene (50 µL) was added in a sealed tube (purged with N_2 atm) and reaction mixture was heated at 130 °C for 48 h. After the completion of the reaction time, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H arylated fluorenone carboxamide (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H arylation of carboxamides 3a-o, 3s-x, 3z, 3aa, 5j, 19a-i, 17, 18, 24a-w.

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A mixture of an appropriate carboxamide containing directing group (1 equiv), an appropriate aryl iodide (4 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) in toluene (1-4 mL) was added in a sealed tube (purged with N_2 atm) and reaction mixture was heated at 130 ℃ for 48 h. After the completion of the reaction time, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H arylated fluorenone or fluorene carboxamide (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H arylation of carboxamides 3p-r/3ab in the presence of $CuBr_2$.

A mixture of an appropriate carboxamide containing directing group (1 equiv), an appropriate aryl iodide (4 equiv), $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (10 mol%), CsOAc (4 equiv), in *t*-amylOH (1-3 mL) was added in a sealed tube and reaction mixture was heated at 130 ℃ for 36 h in a sealed tube (purged with N_2 atm). After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H arylated fluorenone or fluorene carboxamide (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H arylation of 2-acetylfluorene 5k.

To a mixture of substrate 2-acetyl fluorene **5k** (1 equiv) and appropriate aryl iodide (1.5 equiv) was added $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), glycine (50 mol%), H_2O (4 equiv) in HFIP:AcOH [5:1] and the reaction was heated at 130 ℃ for 24 h in a sealed tube (purged with N_2 atm). After the reaction period was over, the crude reaction mixture was cooled to rt and the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H arylated fluorene derivative (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H arylation of *o*-tolualdehyde 5l.

To a mixture of substrate *o*-tolualdehyde **5l** (1 equiv) and appropriate aryl iodide (4 equiv) was added $Pd(OAc)_2$ (10 mol%), AgTFA (1.5 equiv), glycine (40 mol%), AcOH:H_2O [9:1] and the reaction was heated at 100 ℃ for 36 h in a sealed tube (purged with N_2 atm). After the reaction time period was over, the crude reaction mixture was cooled to rt and the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H arylated fluorene derivative (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H alkylation of fluorenone-4-carboxamide 5a.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (1 equiv), a required alkyl iodide (4 equiv), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 equiv) and PivOH (20 mol%) in *t*-amylOH (1-2 mL) was added in a sealed tube (purged with N_2 atm) and reaction mixture was heated at 130 ℃ for 48 h. After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H alkylated fluorenone carboxamide (see the respective Table/Scheme for specific entries).

Typical procedure for the Pd(II)-catalyzed C-H alkylation of fluorenone-4-carboxamide 5a with *n*-BuI.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (1 equiv) and *n*-BuI (4 equiv) was added $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), $CuBr_2$ (20 mol%), H_2O (1.5 mL) at 110 ℃ for 48 h in a sealed tube (filled with ambient air). After the reaction time was over, the crude reaction mixture was cooled to rt and extracted with EtOAc (5-7 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel (EtOAc/Hexanes as eluent) to afford the corresponding C-H butylated fluorenone carboxamide **15c** (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H benzylation of fluorenone-4-carboxamide 5a or fluorenone-1-carboxamide 5e.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** or fluorenone-1-carboxamide **5e** containing 8-aminoquinoline as the directing group (1 equiv), a required benzyl bromide (3 equiv), $Pd(OAc)_2$ (5 mol%) and KOAc (2 equiv) in 1,4-dioxane (1-2 mL) was added in a sealed tube (purged with N_2 atm) and reaction mixture was heated at 100 ℃ for 36 h. After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H benzylated fluorenone carboxamide (see the respective Table/Scheme for specific entries).

General procedure for the Pd(II)-catalyzed C-H halogenation of fluorenone-4-carboxamide 5a.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (1 equiv), a required halogen source NIS or NCS (4 equiv), $Pd(OAc)_2$ (10 mol%) in toluene or *p*-xylene was heated at 110 or 130 ℃ for 48 h in a sealed tube (purged with N_2 atm). After the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H halogenated fluorenone carboxamide (see the respective Scheme for specific entries).

Typical procedure for the Pd(II)-catalyzed C-H methoxylation of fluorenone-4-carboxamide 5a.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (1 equiv), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (1.5 equiv), toluene:MeOH (1:1, 2 mL) at rt in a sealed tube (purged with ambient air) for 48 h. After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H methoxylated fluorenone carboxamide **28a** (see the respective Table/Scheme for specific entry).

General procedure for the Co(II)-catalyzed C-H alkoxylation of fluorenone-4-carboxamides 5a.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (1 equiv), a required aliphatic alcohol (2 mL), $Co(OAc)_2{\cdot}4H_2O$ (20 mol%), Ag_2O (1 equiv) and NaOAc (2 equiv) in a sealed tube (purged with ambient air) and reaction mixture was heated at 80 ℃ for 24 h. After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding C-H alkoxylated fluorenone carboxamide (see the respective Table/Scheme for specific entries).

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General procedure for the Co(II)-catalyzed 8-aminoquinoline-directed oxidative cyclization of fluorenone carboxamide 5a with maleimides 6aa-ac.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (0.1 mmol, 1 equiv), a required maleimide (1.3 equiv), $Co(OAc)_2.4H_2O$ (10 mol%), Ag_2CO_3 (1.1 equiv), PivOH (30 mol%), 1,2-DCE (2 mL) was heated in a sealed tube (filled with ambient air). The reaction mixture was heated at 100 °C for 24 h. After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding isoindolone-spirosuccinimides unit-linked fluorenone carboxamide (see the respective Table/Scheme for specific entries).

General procedure for the Co(II)-catalyzed 8-aminoquinoline-directed cyclization of fluorenone carboxamide 5a with substituted alkynes 26.

To a mixture of an appropriate fluorenone-4-carboxamide **5a** containing 8-aminoquinoline as the directing group (0.1 mmol, 1 equiv), a required mono or di-substituted alkynes (1.3 equiv), $Co(OAc)_2.4H_2O$ (10 mol%), PivOH (1.3 equiv), chlorobenzene (2 mL) was heated in a sealed tube (filled with ambient air) at 100 °C for 24 h. After the reaction time was over, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding isoquinolone unit-containing fluorenone carboxamide (see the respective Table/Scheme for specific entries).

Typical procedure for the triflic acid-mediated amide hydrolysis of C-H arylated compounds 7o/13f (removal of the 8-aminoquinoline directing group).

To a mixture of a C-H arylated carboxamide **7o** or **13f** (0.1 mmol, 1 equiv), CF_3SO_3H (0.2 mL) in toluene:H_2O [10:1] was added at 110 °C for 24 h in a sealed tube (filled with ambient air). After the reaction period, the crude reaction mixture was cooled to rt and quenched by slowly adding a saturated solution of Na2CO3 (5 mL) and washed with ethyl acetate. The aq. layer was acidified with 12 N HCl to pH 2 and extracted with EtOAc (15 mL). The combined organic layers were concentrated and dried over anhydrous Na_2SO_4 to form the free carboxylic acid containing fluorenone and phenyl acetic acid derivative, which was purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding product (see the respective scheme for specific entry).

General procedure for removing the 8-aminoquinoline directing group from 13g/11n/20f.

A mixture of an appropriate arylated carboxamide (1 equiv), $BF_3{\cdot}Et_2O$ (15 equiv), and anhydrous MeOH/EtOH (2-4 mL) in a screw-capped sealed tube containing a magnetic bead was stirred and heated at 130 °C for 36 h. Then, the reaction mixture was allowed to attain rt and concentrated under reduced pressure to afford the corresponding crude reaction mixture, which was purified by column chromatography to afford the corresponding ester derivative (see the respective scheme for specific entry).

Typical procedure for the Pd(II)-catalyzed Suzuki-Miyaura cross-coupling reaction on C-H arylated carboxamide 7o/29d.

To a mixture of a C-H arylated carboxamide or ester derivative **7o** or **29d** (1 equiv), a required boronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (3 equiv) in toluene:EtOH:H_2O [2:1:1] was heated at 110 °C for 24 h in a sealed tube (purged with N_2 atm). After the reaction period, the crude reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexanes) to afford the corresponding product (see the respective scheme for specific entry).

Characterization (analytical) data of all compounds are provided in the Supporting Information. Characterization (analytical) data of representative compounds are given below.

Methyl 4-(9-oxo-4-(quinolin-8-ylcarbamoyl)-9*H*-fluoren-3-yl)benzoate (7a): The compound **7a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a yellow colored solid (70 mg, 72%, 0.2 mmol scale); R_f (20% EtOAc/hexanes) 0.5; mp: 187-189 °C; IR (DCM): 2925, 1672, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (s, 1H), 8.85 (dd, J_1 = 7.0, J_1 = 1.8 Hz, 1H), 8.59 (dd, J_1 = 4.2, J_1 = 1.5 Hz, 1H), 8.11 (dd, J_1 = 8.3, J_1 = 1.5 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.71-7.65 (m, 4H), 7.59-7.53 (m, 2H), 7.42-7.26 (m, 4H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 192.5, 166.2, 166.0, 148.3, 144.7, 143.5, 142.5, 141.7, 138.2, 136.2, 135.2, 134.4, 134.1, 133.7, 131.2, 130.8, 129.8, 129.7, 129.6, 128.5, 127.8, 127.2, 125.0, 124.3, 123.2, 122.5, 121.7, 116.8, 52.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{21}N_2O_4$: 485.1501 found, 485.1500.

9-Oxo-*N*-(quinolin-8-yl)-3-(*p*-tolyl)-9*H*-fluorene-4-carboxamide (7c): The compound **7c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a yellow colored solid (55 mg, 62%, 0.2 mmol scale); R_f (20% EtOAc/hexanes) 0.5; mp: 219-221 °C; IR (DCM): 2921, 1712, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.91 (s, 1H), 8.89 (d, J = 7.3 Hz, 1H), 8.61-8.60 (m, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.67 (dd, J_1 = 9.8, J_2 = 7.7 Hz, 2H), 7.60-7.55 (m, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.41-7.24 (m, 4H), 7.07 (d, J = 7.8 Hz, 2H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 192.7, 166.5, 148.2, 146.0, 142.8, 141.6, 138.3, 138.1, 136.1, 136.0, 135.1, 134.6, 134.0, 133.3, 131.3, 130.9, 129.3, 129.1, 128.2, 127.8, 127.2, 124.9, 124.1, 123.1, 122.3, 121.6, 116.7, 21.0. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{21}N_2O_2$: 441.1603 found, 441.1616.

9,9-Dimethyl-9'-oxo-*N*-(quinolin-8-yl)-9*H*,9'*H*-[2,3'-bifluorene]-4'-carboxamide (8a): The compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a yellow colored solid (78 mg, 72%, 0.2 mmol scale); R_f (20% EtOAc/hexanes) 0.5; mp: 222-224 °C; IR (DCM): 2924, 1670, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.92 (s, 1H), 8.90 (dd, J_1 = 7.5, J_2 = 1.2 Hz, 1H), 8.55 (dd, J_1 = 4.2, J_2 = 1.6 Hz, 1H), 8.01 (dd, J_1 = 8.3, J_2 = 1.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.76-7.63 (m, 4H), 7.59-7.43 (m, 5H), 7.36 (td, J_1 = 7.6, J_2 = 1.2 Hz, 1H), 7.31-7.22 (m, 5H), 1.22 (s, 6H). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 192.8, 166.6, 153.8, 153.7, 148.1, 146.4, 142.8, 141.9, 139.2, 138.4, 138.2, 137.9, 136.1, 135.1, 134.6, 134.0, 133.5, 131.4, 130.9, 129.4, 127.7, 127.4, 127.4, 127.0, 126.8, 124.9, 124.2, 123.2, 122.7, 122.5, 122.3, 121.6, 120.1, 120.0, 116.6, 46.7, 26.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{27}N_2O_2$: 543.2073 found, 543.2068.

9-Oxo-3-(9-phenyl-9*H*-carbazol-3-yl)-*N*-(quinolin-8-yl)-9*H*-fluorene-4-carboxamide (8f): The compound **8f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow colored solid (55 mg, 93%, 0.1 mmol scale); R_f (20% EtOAc/hexanes) 0.5; mp: 150-152 °C; IR (DCM): 2925, 1671, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (s, 1H), 8.86 (d, J = 7.6 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.37 (d, J = 1.4 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 7.5 Hz,

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1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.60 (dd, J_1 = 8.5, J_2 = 1.7 Hz, 1H), 7.52-7.45 (m, 4H), 7.41-7.19 (m, 10H), 7.16-7.13 (m, 1H). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 192.8, 166.9, 148.0, 146.7, 142.8, 141.8, 141.0, 140.4, 138.1, 137.1, 135.9, 135.0, 134.6, 134.0, 133.0, 131.5, 131.2, 130.8, 129.7, 129.3, 127.6, 127.4, 127.1, 126.7, 126.4, 126.1, 124.9, 124.1, 123.5, 123.1, 122.1, 121.4, 120.5, 120.2, 120.1, 116.8, 109.7, 109.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{26}N_3O_2$: 592.2025 found, 592.2026.

5-Chloro-2-(9,9-dimethyl-9*H*-fluoren-2-yl)-*N*-(quinolin-8-yl)benzamide (11f): The compound **11f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (120 mg, 72%, 0.35 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 201-203 °C; IR (DCM): 2924, 1665, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.73 (s, 1H), 8.79 (d, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 3.7 Hz, 1H), 7.95-7.93 (m, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.57-7.37 (m, 6H), 7.26-7.23 (m, 3H), 7.17 (dd, J_1 = 8.2, J_2 = 4.2 Hz, 1H), 1.09 (s, 6H). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 166.5, 153.9, 153.7, 147.7, 139.1, 138.8, 138.4, 138.2, 137.5, 137.4, 135.9, 134.1, 133.7, 131.9, 130.6, 129.5, 127.9, 127.6, 127.3, 127.1, 126.8, 123.3, 122.4, 121.7, 121.3, 120.1, 119.9, 116.4, 46.6, 26.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{24}ClN_2O$: 475.1577 found, 475.1594.

1-(3-(4-Methoxyphenyl)-9*H*-fluoren-2-yl)ethan-1-one (14a): The compound **14a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (22 mg, 71%, 0.1 mmol scale); R_f (20% EtOAc/hexanes) 0.5; mp: 137-139 °C; IR (DCM): 1679, 1609, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.82-7.73 (m, 3H), 7.57 (d, *J* = 7.1 Hz, 1H), 7.41-7.25 (m, 4H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 2H), 3.87 (s, 3H), 2.03 (s, 3H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 205.1, 159.5, 144.3, 144.2, 141.7, 140.5, 139.7, 139.3, 133.6, 130.1, 127.7, 127.0, 125.2, 124.6, 121.5, 120.5, 114.1, 55.3, 36.7, 30.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}O_2$: 315.1385 found, 315.1381.

3-(9*H*-Fluoren-2-yl)-*N*-(quinolin-8-yl)decanamide (20a): The compound **20a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (131 mg, 86%, 0.33 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 100-102 °C; IR (DCM): 2924, 1684, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (s, 1H), 8.73 (d, *J* = 7.5 Hz, 1H), 8.58 (dd, J_1 = 4.2, J_2 = 1.5 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.67-7.64 (m, 2H), 7.46-7.20 (m, 8H), 3.79 (d, *J* = 21.7 Hz, 1H), 3.72 (d, *J* = 21.8 Hz, 1H), 3.39-3.32 (m, 1H), 2.91-2.81 (m, 2H), 1.85-1.69 (m, 2H), 1.25-1.18 (m, 10H), 0.82 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 147.8, 143.6, 143.1, 141.6, 140.0, 138.1, 136.0, 134.3, 127.7, 127.2, 126.5, 126.2, 126.1, 124.8, 124.1, 121.3, 121.2, 119.8, 119.5, 116.3, 46.1, 42.8, 36.7, 36.3, 31.7, 29.5, 29.1, 27.5, 22.5, 14.0. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{35}N_2O$: 463.2749 found, 463.2730.

3-(9*H*-Fluoren-2-yl)-3-phenyl-*N*-(quinolin-8-yl)propanamide (20b): The compound **20b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (39 mg, 89%, 0.1 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 152-154 °C; IR (DCM): 2924, 1684, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.80 (s, 1H), 8.75 (d, *J* = 7.3 Hz, 1H), 8.71 (dd, J_1 = 4.2, J_2 = 1.6 Hz, 1H), 8.10 (dd, J_1 = 8.3, J_2 = 1.5 Hz, 1H), 7.83-7.20 (m, 15H), 4.90 (t, *J* = 7.7 Hz, 1H), 3.85 (d, *J* = 21.9 Hz, 1H), 3.79 (d, *J* = 21.7 Hz, 1H), 3.40 (d, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 147.9, 143.9, 143.7, 143.2, 142.4, 141.4, 140.2, 138.1, 136.2, 134.2, 128.6, 127.7, 127.7, 127.3, 126.6, 126.5, 126.4, 124.9, 124.5, 121.4, 121.4, 120.1, 119.9, 119.6, 116.4, 47.3, 44.6, 36.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{25}N_2O$: 441.1967 found, 441.1964.

2,6-Bis(9,9-dimethyl-9*H*-fluoren-2-yl)-*N*-(quinolin-8-yl)benzamide (21a): The compound **21a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (158 mg, 62%, 0.4 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 253-257 °C; IR (DCM): 2923, 1672, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (s, 1H), 8.63-8.60 (m, 2H), 7.96 (dd, J_1 = 8.3, J_2 = 1.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.69-7.63 (m, 7H), 7.38-7.26 (m, 9H), 1.29 (s, 12H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 153.7, 153.5, 147.7, 140.8, 139.4, 138.7, 138.3, 138.2, 136.4, 135.9, 134.0, 129.2, 127.6, 127.5, 127.0, 126.9, 126.8, 123.0, 122.4, 121.4, 121.2, 119.9, 119.8, 116.5, 46.6, 26.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{46}H_{37}N_2O$: 633.2906 found, 633.2915.

***N*-(1-(4-Chloro-2,6-bis(9,9-dimethyl-9*H*-fluoren-2-yl)phenyl)ethyl)picolinamide (22b-(RS)):** The compound **22b-(RS)** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (45 mg, 70%, 0.1 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 145-147 °C; IR (DCM): 2923, 1673, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.05 (d, *J* = 7.8 Hz, 1H), 7.94-7.20 (m, 20H), 5.62-5.55 (m, 1H), 1.60 (s, 12H), 1.47 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.5, 153.7, 153.5, 149.5, 147.5, 143.9, 140.1, 138.8, 138.4, 137.8, 136.8, 131.2, 130.3, 127.9, 127.3, 127.0, 125.6, 123.5, 122.6, 121.7, 120.0, 119.7, 46.9, 46.3, 27.3, 26.8, 23.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{44}H_{38}ClN_2O$: 645.2673 found, 645.2672. The HPLC of the compound **22b-(RS)** was determined using the Daicel Chiralpak IB column, hexane/*i*-PrOH (98:02), flow rate 0.5 mL/min, UV detection at 254 nm, t_R = 15.11 min, t_S = 16.54 min.

***(R)*-*N*-(1-(4-Chloro-2,6-bis(9,9-dimethyl-9*H*-fluoren-2-yl)phenyl)ethyl)picolinamide (22b-(R)):** The compound **22b-(R)** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (45 mg, 70%, 0.1 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 141-143 °C; IR (DCM): 2923, 1680, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.05 (d, *J* = 7.8 Hz, 1H), 7.93-7.19 (m, 20H), 5.61-5.54 (m, 1H), 1.59 (s, 12H), 1.46 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.6, 153.7, 153.5, 149.5, 147.5, 143.9, 140.1, 138.8, 138.4, 137.7, 136.8, 131.2, 130.3, 127.9, 127.3, 127.0, 125.6, 123.5, 122.6, 121.7, 120.0, 119.7, 46.9, 46.3, 27.3, 26.7, 23.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{44}H_{38}ClN_2O$: 645.2673 found, 645.2678. $[\alpha]^{25}_D$ = -35.00 (*c* = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (*er* = >95:5) of the compound **22b-(R)** was determined by HPLC using the Daicel Chiralpak IB column, hexane/*i*-PrOH (98:02), flow rate 0.5 mL/min, UV detection at 254 nm, t_R = 15.06 min, t_S = 16.70 min.

***(S)*-*N*-(1-(4-Chloro-2,6-bis(9,9-dimethyl-9*H*-fluoren-2-yl)phenyl)ethyl)picolinamide (22b-(S)):** The compound **22b-(S)** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (44 mg, 68%, 0.1 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 142-144 °C; IR (DCM): 2923, 1679, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.05 (d, *J* = 7.8 Hz, 1H), 7.93-7.19 (m, 20H), 5.61-5.54 (m, 1H), 1.59 (s, 12H), 1.46 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.5, 153.7, 153.5, 149.5, 147.5, 143.9, 140.2, 138.8, 138.5, 137.8, 136.8, 131.2, 130.3, 128.0, 127.3, 127.0, 125.6, 123.5, 122.6, 121.7, 120.0, 119.7, 46.9, 46.3, 27.3, 26.7, 23.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{44}H_{38}ClN_2O$: 645.2673 found, 645.2676. $[\alpha]^{25}_D$ = +33.00 (*c* = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (*er* = 98:2) of the compound **22b-(S)** was

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DOI: 10.1039/D5OB01242B

determined by HPLC using the Daicel Chiralpak IB column, hexane/*i*-PrOH (98:02), flow rate 0.5 mL/min, UV detection at 254 nm, t_R = 15.49 min, t_S = 16.83 min.

3-(5-Bromopyridin-2-yl)-9-oxo-9*H*-fluorene-4-carboxylic acid (29a): The compound **29a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 90:10) as a yellow colored solid (29 mg, 76%, 0.1 mmol scale); R_f (EtOAc) 0.5; mp: 197-199 °C; IR (DCM): 2925, 1715, 771 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6): δ_H 8.79 (d, J = 2.2 Hz, 1H), 8.21 (dd, J_1 = 8.4, J_2 = 2.3 Hz, 1H), 7.79-7.64 (m, 6H), 7.46 (t, J = 7.4 Hz, 1H), 3.55 (br. s, 1H). (The proton signal corresponding to COOH is broad); $^{13}C\{^1H\}$ NMR (~101 MHz, DMSO-d^6): δ_C 192.1, 169.5, 155.1, 150.2, 142.6, 142.4, 140.4, 136.1, 134.2, 134.2, 130.9, 130.5, 129.8, 125.0, 124.9, 124.7, 123.3, 120.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{11}BrNO_3$: 379.9922 found, 379.9912.

2-(2-(9,9-Dimethyl-9*H*-fluoren-2-yl)-5-fluorophenyl)acetic acid (29b): The compound **29b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 90:10) as a colorless solid (15 mg, 43%, 0.1 mmol scale); R_f (EtOAc) 0.5; mp: 86-88 °C; IR (DCM): 2924, 1708, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (d, J = 7.6 Hz, 2H), 7.45-7.43 (m, 1H), 7.37-7.31 (m, 4H), 7.25-7.22 (m, 1H), 7.13-7.04 (m, 2H), 3.64 (s, 2H), 1.47 (s, 6H). (The proton signal corresponding to COOH is not identified); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 177.2, 161.9 (d, $J_{C\text{-}F}$ = 247.3), 153.8, 153.7, 139.0 (d, $J_{C\text{-}F}$ = 3.1 Hz), 138.8, 138.7, 138.5, 133.1 (d, $J_{C\text{-}F}$ = 7.9 Hz), 131.7 (d, $J_{C\text{-}F}$ = 8.2 Hz), 128.1, 127.4, 127.0, 123.7, 122.6, 120.1, 119.8, 117.5 (d, $J_{C\text{-}F}$ = 21.7 Hz), 114.4 (d, $J_{C\text{-}F}$ = 20.8 Hz), 46.9, 38.6, 27.0.$^{19}F\{^1H\}$ NMR (~376 MHz, CDCl3): δ_F = -115.12. HRMS (ESI): *m/z* $[M-H]^+$ calcd for $C_{23}H_{18}FO_2$: 345.1291 found, 345.1289.

Methyl 2-(5-chloro-2-(9,9-dimethyl-9*H*-fluoren-2-yl)phenyl)acetate (29c): The compound **29c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colorless solid (71 mg, 94%, 0.2 mmol scale); R_f (10% EtOAc/hexanes) 0.5; mp: 70-72 °C; IR (DCM): 2925, 1736, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.74 (m, 2H), 7.46-7.44 (m, 1H), 7.38-7.22 (m, 7H), 3.64 (s, 3H), 3.60 (s, 2H), 1.49 (s, 6H); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 153.7, 153.7, 141.3, 138.8, 138.6, 138.5, 133.5, 133.1, 131.4, 130.4, 127.9, 127.4, 127.3, 127.0, 123.5, 122.6, 120.1, 119.8, 52.0, 46.8, 38.7, 27.0. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{24}H_{21}ClNaO_2$: 399.1128 found, 399.1113.

Data availability

The data are available within the article or its ESI.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgments

S. A. B. thanks IISER Mohali for funding this research work. We thank IISER Mohali for its analytical (NMR, HRMS, and X-ray) facilities. S. B. thanks IISER Mohali for the PhD fellowship. The authors also thank the Departmental NMR facility supported by DST-FIST (SR/FST/CS-II/2019/94 (TPN No. 32545)).

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Data availability

The data are available within the article or its ESI.