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Modification of fluorene and fluorenone core *via* C–H functionalization

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We report the modification of fluorene and fluorenone cores, and the assembly of 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 bioactive compounds. In this work, the C–H bonds of fluorene and fluorenone were subjected to C–H arylation, alkylation, benzylation, alkoxylation, and annulation reactions to afford modified fluorenes/fluorenones. Alternatively, various functionalized fluorenes/fluorenones were 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 couples, fluorene–carbazole couples, 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* a 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.* (Fig. 1).[4,5]

While synthetically derived fluorenes and fluorenones are widespread in materials chemistry, several fluorene- and fluorenone-based natural products are also well known (Fig. 1).[1] Some fluorene- or fluorenone-based compounds are 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 have been 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] Notably, 9-fluorenyl-

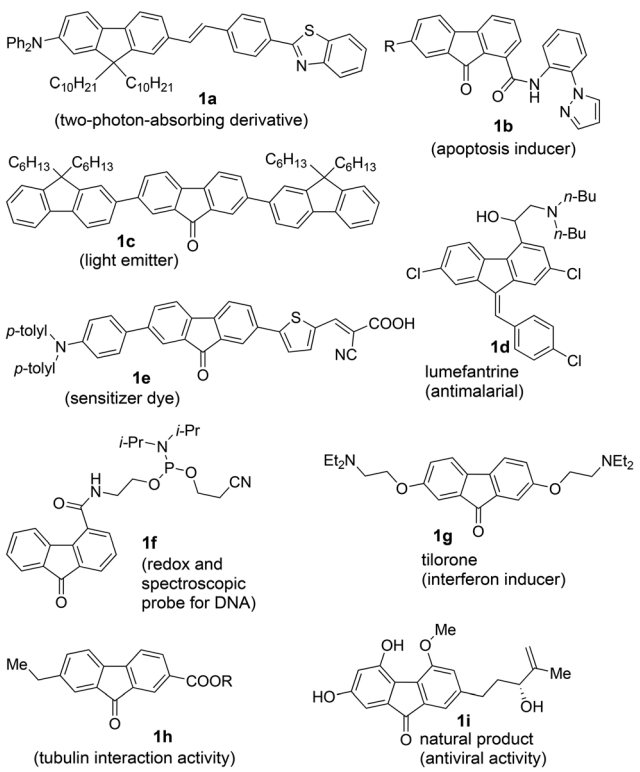

Fig. 1 Representative fluorene and fluorenone molecules with applications in materials and medicinal chemistry.

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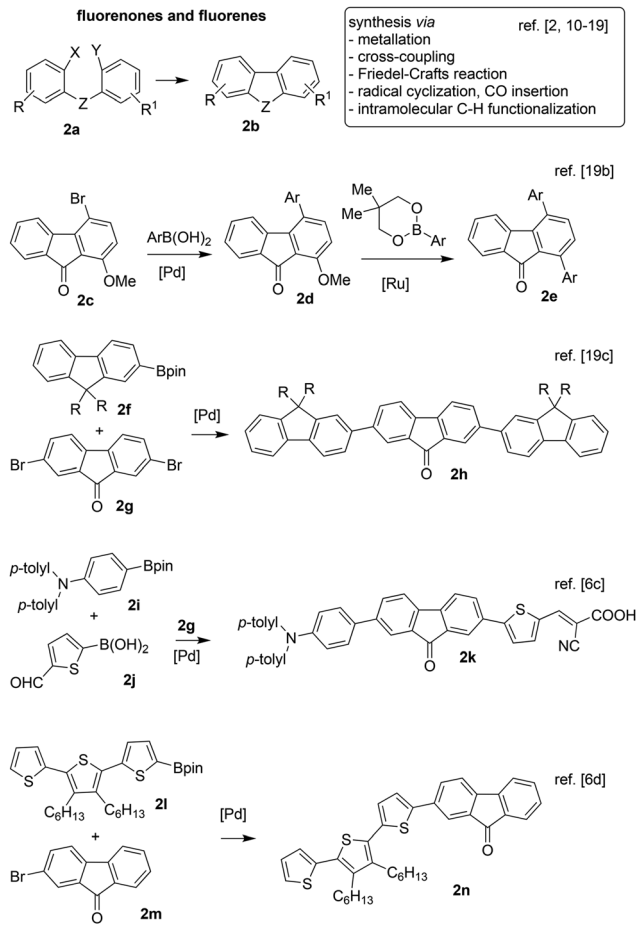
methoxycarbonyl (Fmoc)-group-based molecules play a pivotal role in amino acid/peptide chemistry.[9]

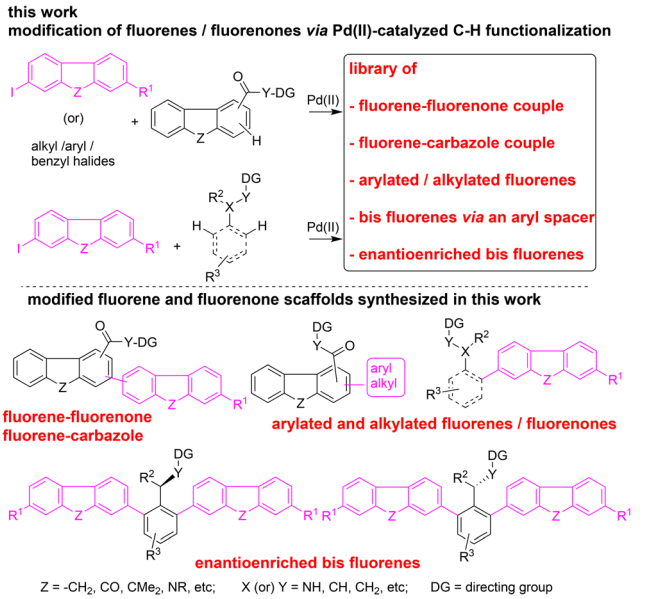
Given their applications and pivotal roles in developing functional materials and medicinally or biologically active agents, various synthetic routes have been designed for synthesizing the core structures of fluorenes and fluorenones.[10–19]

Functionalized fluorenone- or fluorene-based monomers are generally synthesized *via* traditional cross-coupling reactions (Scheme 1).[19,20] Some 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] Fluorene skeletons have been constructed *via* the Friedel–Crafts reaction,[16] gold-catalyzed C–C bond-forming reactions,[17] intramolecular C–H functionalization, *etc.*[18]

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



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



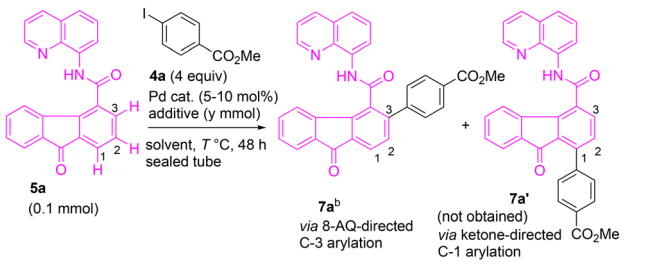
Scheme 2 Modification of fluorene and fluorenone core *via* C–H functionalization and expansion of their library.

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] In particular, transition-metal-catalyzed, directing-group-assisted C–C bond-forming reactions leading to biaryls *via* direct C–H coupling constitute a powerful alternative to traditional cross-coupling tactics. Taking impetus from the contributions of Pd(II)-catalyzed, directing-group-aided sp^2 C–H arylation reactions in expanding the library of privileged skeletons,[22–24] we envisaged the direct functionalization of C–H bonds in fluorenes and fluorenones to construct a library of modified fluorene and fluorenone motifs (Scheme 2). This process has enabled the assembly of a variety of fluorene and fluorenone monomeric motifs, which are expected to show scope in the development of materials and medicinal chemistry.

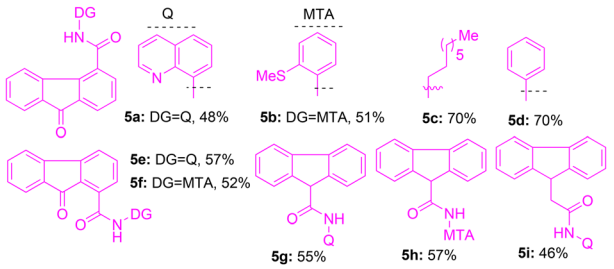
Results and discussion

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** with 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*-

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.

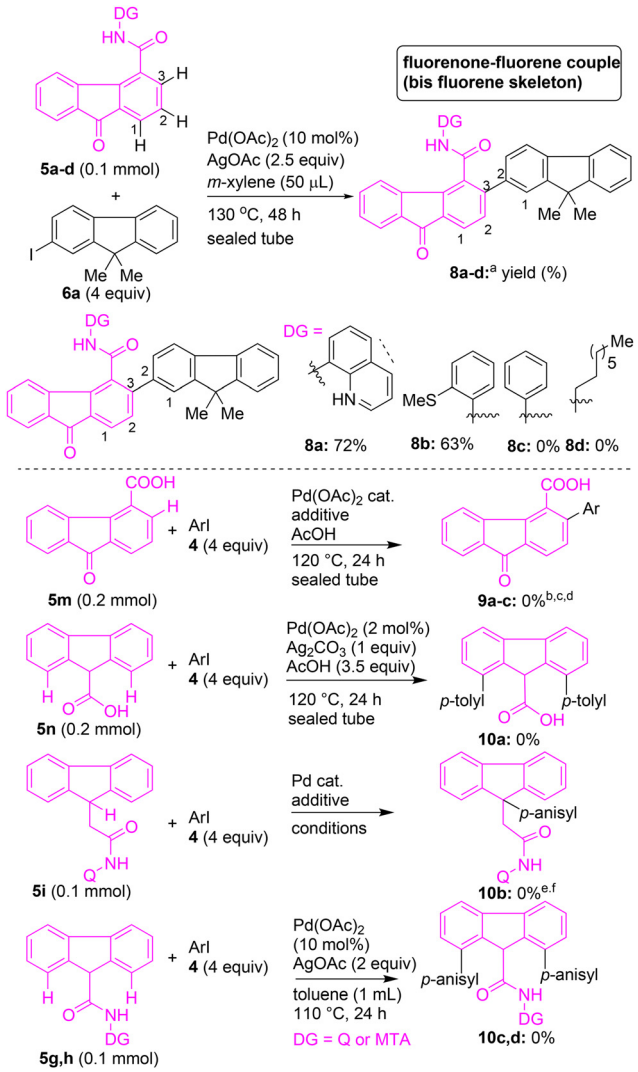
fluorene-1-carboxylic acid with 8-AQ and MTA directing groups (Table 1). We also assembled fluorene-based carboxamides **5g–i** from their corresponding fluorene carboxylic acid and 8-AQ or MTA using standard procedures (Table 1).

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 an 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 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 or 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 fluorene-4-carboxamide **5a** was attempted using methyl 4-iodobenzoate (**4a**, 4 equiv.) in the presence of $Pd(OAc)_2$ (10 mol%) and K_2CO_3 (2 equiv.) in *o*-xylene at 130 °C for 48 h (entry 1, Table 1). This reaction afforded 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.) under neat conditions afforded 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 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 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 other expected 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 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 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



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** is 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 the 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).

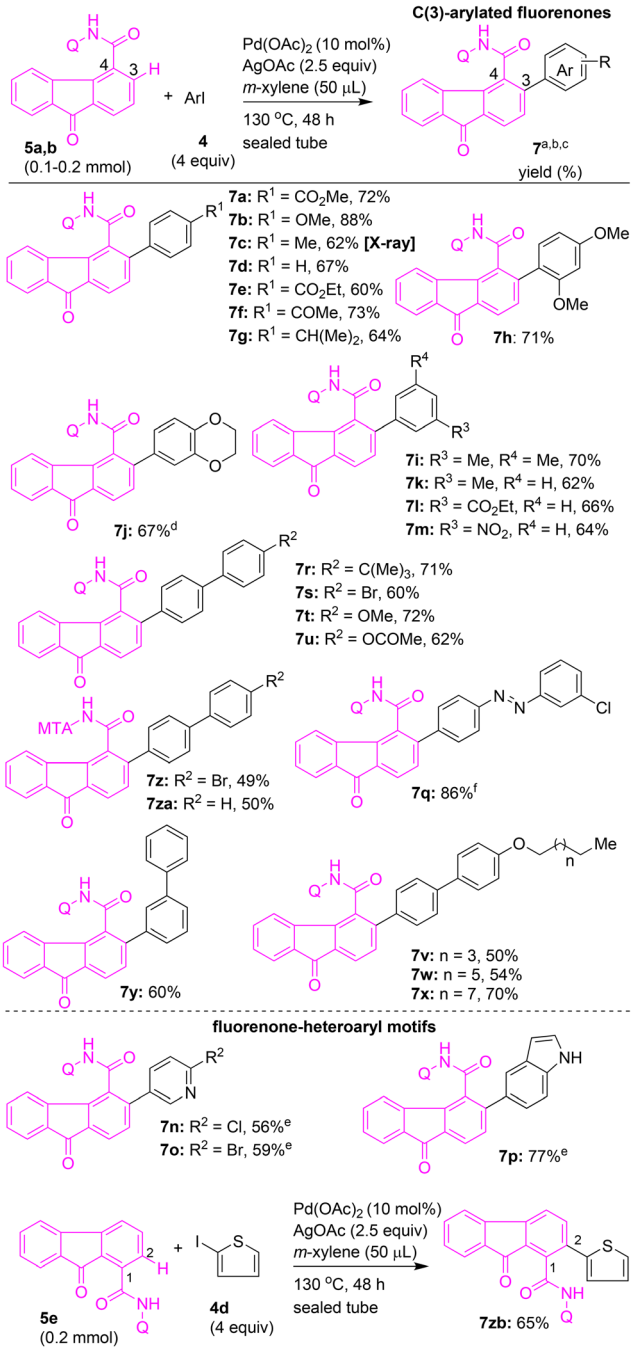
accomplishing the β-C(sp^2)–H arylation of fluorenone carboxamide **5a**/**5b**. This confirmed that the corresponding bidentate directing group 8-AQ in **5a** or MTA in **5b** provides the required chelation assistance during the β-C(sp^2)–H activation in the proposed Pd^{II}–Pd^{IV} catalytic cycle,[22,23a] enabling the site-selective C(3)–H arylation of **5a** or **5b**.

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** to prepare a wide range of π-extended fluorenone-4-carboxamides (Scheme 4). The Pd(II)-catalyzed C(3)–H arylation of **5a** was attempted using various aryl iodides containing electron-donating or electron-withdrawing substituents at the *para* or *meta* position (*e.g.*, OMe, alkyl, COMe, COOR, or NO_2) and phenyl iodide in the presence of $Pd(OAc)_2$ 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 (Fig. 2).

Next, fluorene-4-carboxamide **5a** was subjected to 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 substituents 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** possessing MTA as the DG with iodobiaryls yielded the corresponding fluorenone–biaryl motifs **7z** and **7za** in 49–50% yields (Scheme 4).

Having introduced the aryl group at the C(3)–H of the fluorenone-4-carboxamide motif and obtained the modified fluorenone–aryl systems **7a–z** and **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** with 8-AQ DG were subjected to (*ortho*) C–H arylation with various iodofluorenes/iodofluorenones **6a–d**.



Scheme 4 Expansion of the 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 conditions. [e] The reaction was carried out in *m*-xylene (1 mL). [f] Toluene (1 mL) as solvent at 110 °C.

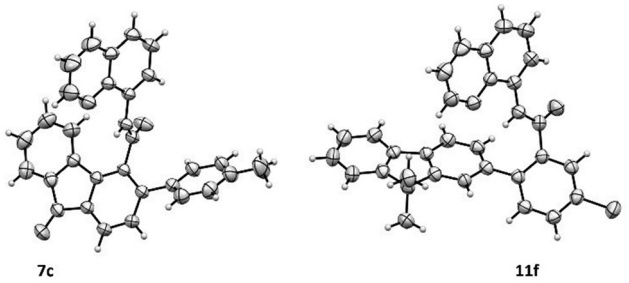
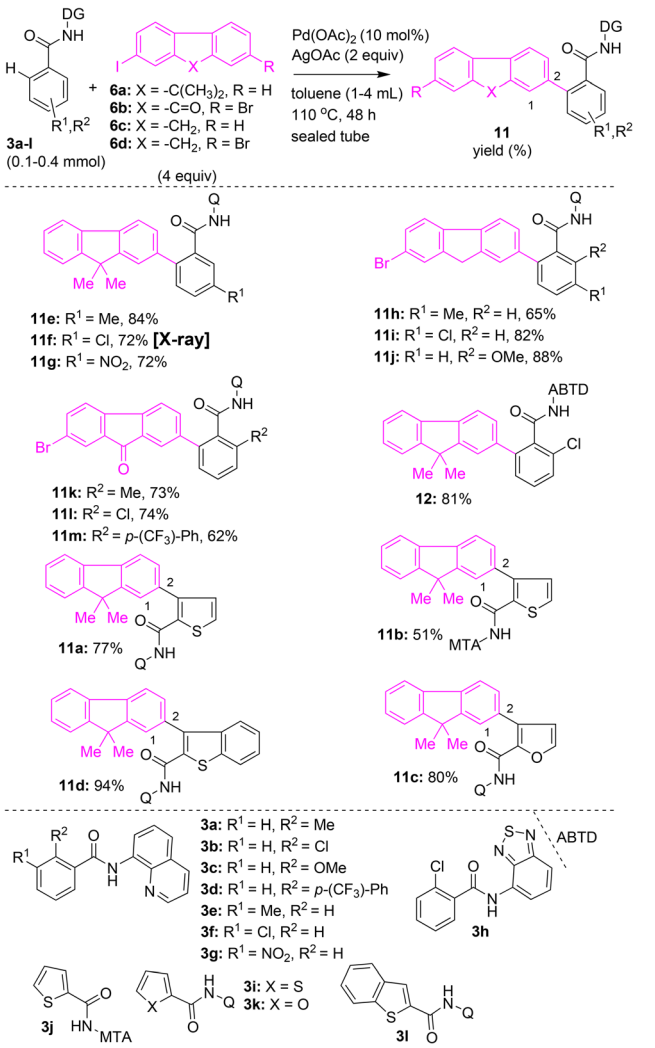


Fig. 2 X-ray (ORTEP) structures of compounds **7c** and **11f**.



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.

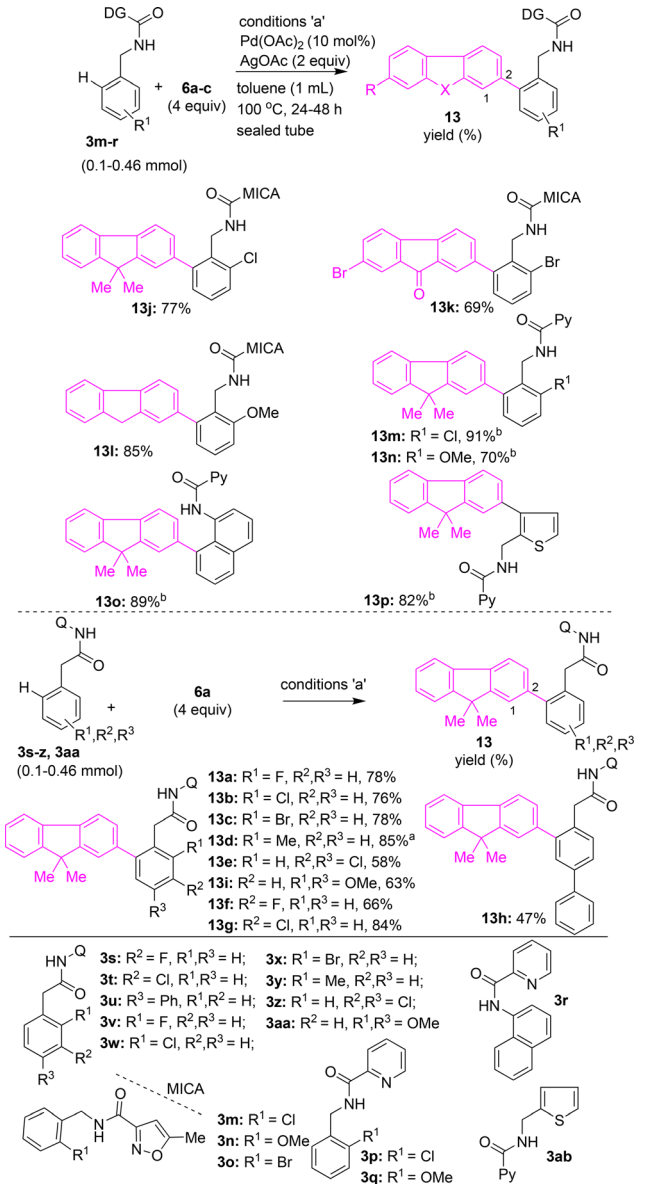
The Pd(II)-catalyzed C–H arylation of benzamides **3a–g** with 2-iodo-9,9-dimethyl-9*H*-fluorene (**6a**) or 2-bromo-7-iodo-9*H*-fluoren-9-one (**6b**) or 2-bromo-7-iodo-9*H*-fluorene (**6d**) under the optimized conditions yielded the corresponding fluorene–benzamide or fluorenone–benzamide coupled motifs **11e–m** in 62–88% yields (Scheme 5). The structure of compound **11f** was confirmed by X-ray structure analysis (Fig. 2). As corresponding *meta*-substituted benzamides **3e–g** contain two *ortho* β-C–H

bonds, arylation occurred selectively at the least hindered *ortho* β-C–H bond in **3e–g**, thereby affording the corresponding mono β-C–H arylation products **11e–g**. This observation is in accordance with the earlier reports of directing-group-aided C(sp^2)–H arylation of *meta*-substituted benzamides.[22,23h,j,s,t] Benzamide substrate **3h** possessing ABTD as the DG with **6a** under the optimized reaction conditions, gave fluorene–aryl coupled moiety **12** in 81% yield (Scheme 5).

Several functional materials used in organic field effect transistors feature a chemical design based on fluorenone–thiophene coupled motifs. Taking impetus from the applications of fluorenone–thiophene motifs, we attempted the synthesis of fluorenone–thiophene and fluorine–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**, possessing 8-AQ DG, was subjected to Pd(II)-catalyzed C(3)–H arylation with 2-iodofluorene **6a** to afford fluorene–thiophene motif **11a** in 77% yield (Scheme 5). Thiophene-2-carboxamide **3j**, possessing 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** with 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).

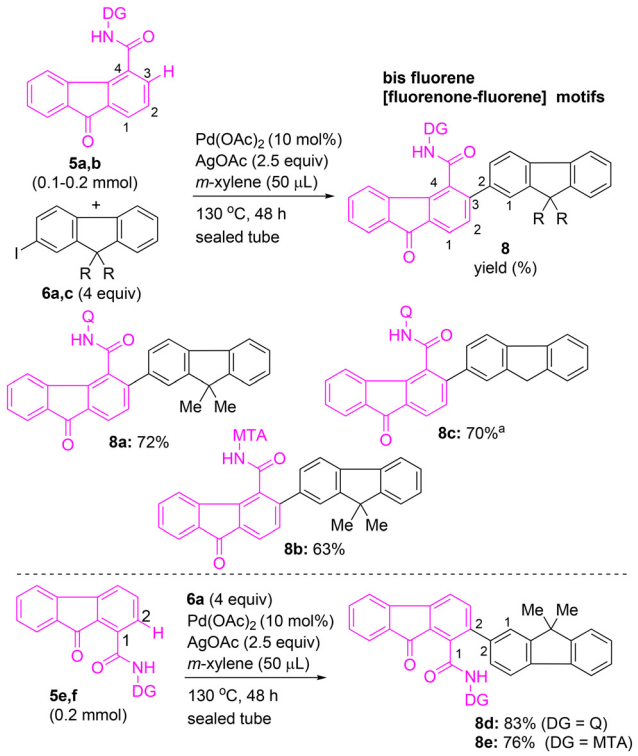
Next, arylacetamides possessing 8-AQ DG were subjected to the (*ortho*) γ-C(sp^2)–H arylation with iodofluorene **6a**. Arylacetamides **3s**, **3t**, **3v–z** and **3aa** with substitutions at the *ortho*- or *meta*- or *para*-positions were heated with **6a** in the presence of $Pd(OAc)_2$ and AgOAc in toluene. These attempts yielded the corresponding fluorene–arylacetamide motifs (π-extended fluorenes) **13a–g** and **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 these lines, benzylamine substrates possessing 5-methylisoxazole-3-carboxamide DG **3m–o** were subjected to Pd(II)-catalyzed (*ortho*) γ-C(sp^2)–H arylation conditions with iodofluorenes **6a**, **6b**, and **6c**, which afforded the corresponding fluorene–benzylamine coupled motifs **13j–l** in 69–85% yields (Scheme 6). Further, benzylamines possessing picolinamide DG, **3p** and **3q**, or naphthylamine **3r** with 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 C(3)–H arylation with **6a**, which afforded thiophene–fluorene motif **13p** in 82% yield (Scheme 6).

We then intended to expand the scope of this method by synthesizing fluorenones with enhanced conjugation, *viz.*, fluorenone–fluorene motifs (Scheme 7). Towards this, heating fluorene-4-carboxamide **5a** with 8-AQ DG with **6a** in the presence of $Pd(OAc)_2$ and AgOAc in *m*-xylene (50 μL) at 130 °C for

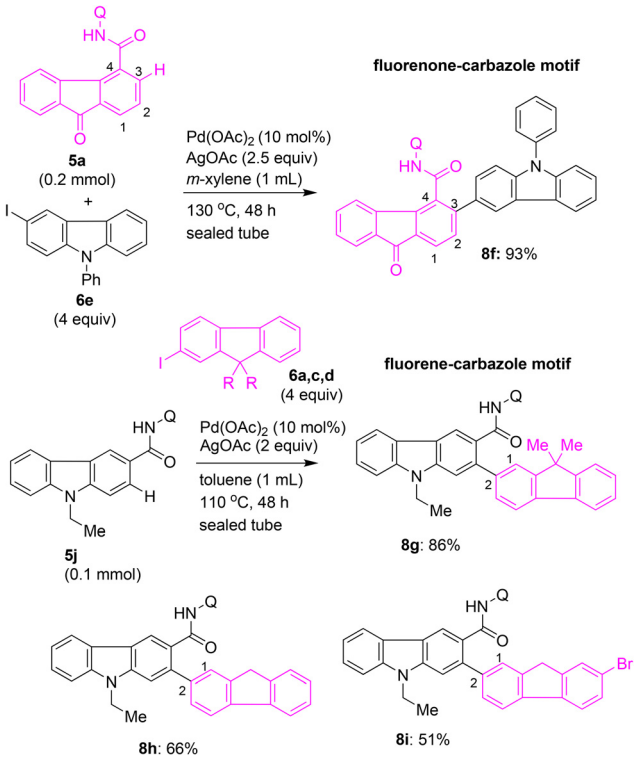


Scheme 6 Expansion of the library of C(2) arylated, π-extended fluorenones or fluorenes through the coupling of the *ortho* γ-C(sp^2)–H bond of aryl acetamides and benzylamines with iodofluorenes or iodofluorenones. [a] **13d** is from substrate **3y** and **6a** (4 equiv.), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (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).

48 h afforded fluorenone–fluorene coupled motif **8a** in 72% yield *via* C(3)–H arylation (Scheme 7). Next, the same reaction was performed using fluorene-4-carboxamide **5b** with MTA DG, to afford fluorenone–fluorene coupled motif **8b** in 63% yield. Further, treatment of **5a** with 2-iodofluorene **6c** afforded the fluorenone–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 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** and **5f** towards the synthesis of bis fluorene (fluorenone–fluorene coupled) motifs. [a] Chlorobenzene (1 mL) was used as a solvent.



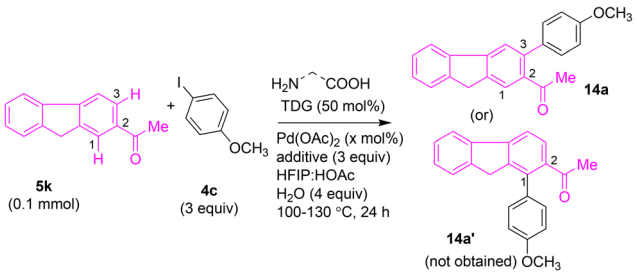
Scheme 8 Synthesis of fluorenone–carbazole and fluorene–carbazole coupled motifs *via* the Pd(II)-catalyzed C–H arylation of fluorenone-4-carboxamide **5a** and carbazole-3-carboxamide **5j**.

Along these lines, 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 fluorenone–carbazole coupled skeleton **8f** in 93% yield (Scheme 8). Alternatively, we treated carbazole-3-carboxamide **5j** possessing 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 C2 position of the carbazole unit, affording the corresponding carbazole–fluorene motifs **8g–i** in 51–86% yields (Scheme 8).

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 C(3)–H arylated fluorene **14a** in 30–53% yields (entries 1 and 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 and 5, Table 2). 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, Table 2). The same reaction in AcOH : H_2O yielded **14a** in 44% yield (entry 7, 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, Table 2). We then attempted 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-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** with maximum 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 C(1)–H arylation is a sluggish process compared to arylation at the C(3)–H position of **5k**.

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



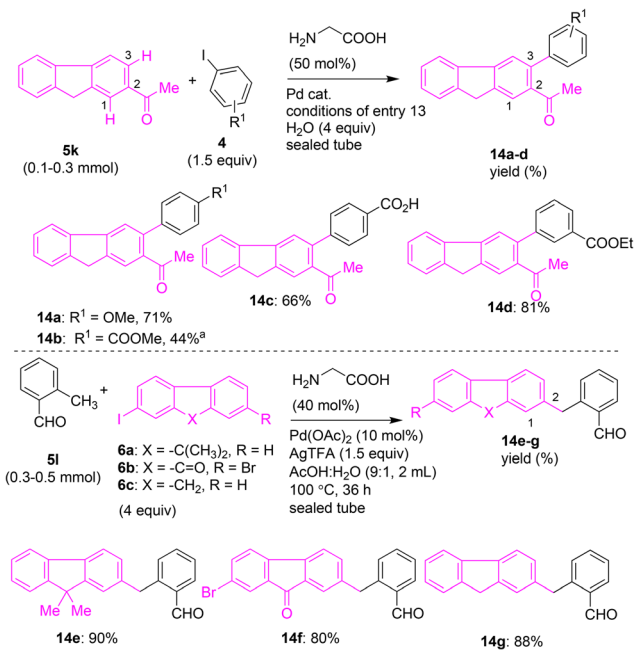
Entry	Catalyst (10 mol%)	Additive (x equiv.)	Solvent (mL)	TDG (50 mol%)	**14a:** yield[a] (%)
1	$Pd(PPh_3)_2Cl_2$	AgOAc (2)	HFIP : AcOH (9 : 1, 1 mL)	Glycine	53
2	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3 (2)	HFIP : AcOH (9 : 1, 1 mL)	Glycine	30
3[b]	$Pd(PPh_3)_2Cl_2$	AgTFA (1.5)	TFA (1 mL)	Glycine	0
4	$Pd(OAc)_2$	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 (1 mL). [c] Using 1.5 equiv. of ArI.

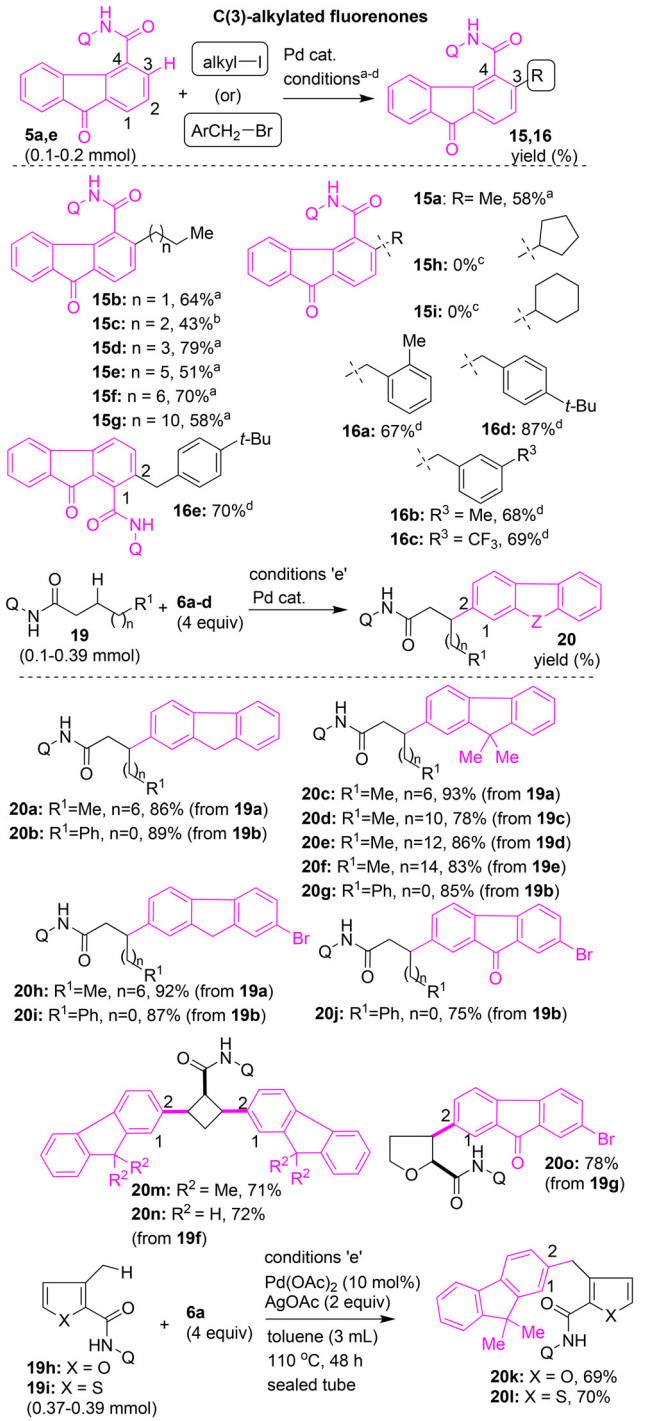
This observation is in accordance with earlier work dealing with C–H arylation of a similar type of substrate (*e.g.*, 2-acetylnapthalene), which predominantly afforded the corresponding least hindered *ortho* C–H functionalized product.[26d]

With the optimized reaction conditions in hand, we then performed the β-C(3)–H arylation of 2-acetylfluorene **5k** with different aryl iodides containing electron-donating or electron-withdrawing substituents (*e.g.*, OMe, COOH, COOMe, COOEt) in the presence of glycine, $Pd(OAc)_2$, AgOAc, H_2O (4 equiv.), or HFIP : AcOH. These attempts successfully afforded the corresponding fluorene–aryl coupled skeletons **14a–d** in 44–81% yields (Scheme 9). Along these lines, 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** using the reported conditions,[26c] involving Pd(OAc), glycine, $Pd(OAc)_2$, AgTFA, and 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).

We then explored the synthesis of alkylated fluorenones and fluorenes *via* β-C(sp^2)–H alkylation and benzylation of the fluorene core. In this direction, we initially performed the 8-AQ DG-assisted β-C(sp^2)–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, and PivOH in *t*-amylOH at 130 °C for 48 h. This reaction successfully afforded 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, and PivOH in *t*-amylOH (2 mL) at 130 °C for 48 h to afford the corresponding



Scheme 9 Pd(II)-catalyzed transient directing group (TDG)-promoted C–H arylation of 2-acetylfluorene (**5k**) and *o*-tolualdehyde (**5l**). [a] 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).



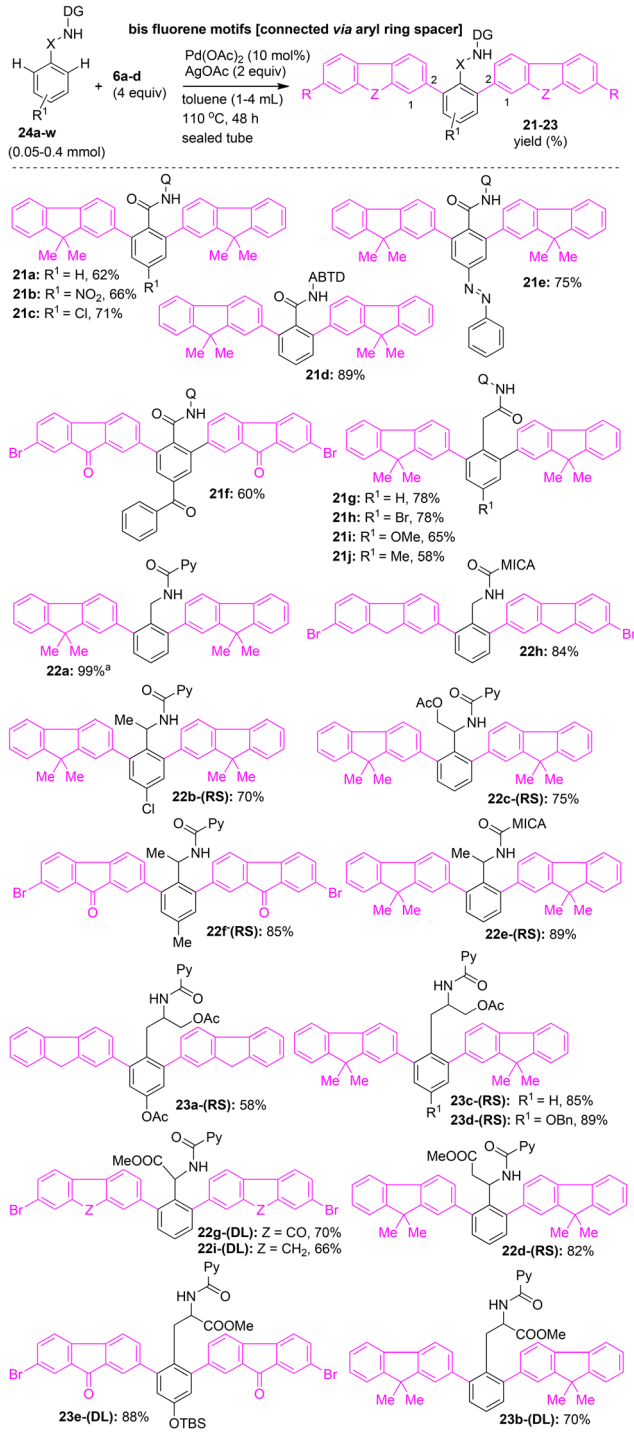
Scheme 10 Synthesis of alkylated fluorenones/fluorenes. [a] Compounds **15a**, **15b** and **15d–g** are from substrate **5a** using corresponding R-I (4 equiv.) and conditions $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 equiv.), PivOH (20 mol%), *t*-amylOH (2 mL), 130 °C, 48 h, sealed tube (purged with N_2 atm). [b] 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] Compounds **15h** and **15i** were detected as an inseparable mixture. [d] Compounds **16a–d** and **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). Product **20** was obtained from the respective carboxamide **19**.

β-C(3)–H alkylated fluorenone scaffolds **15b** and **15d–g** in 43–79% yields (Scheme 10) Compound **15c** was obtained from **5a** and *n*-BuI using conditions which included $Pd(OAc)_2$, $CuBr_2$, K_2CO_3, H_2O (1.5 mL), 110 °C, and 48 h. The expected β-C(3)–H alkylated fluorenone scaffolds **15h** and **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.

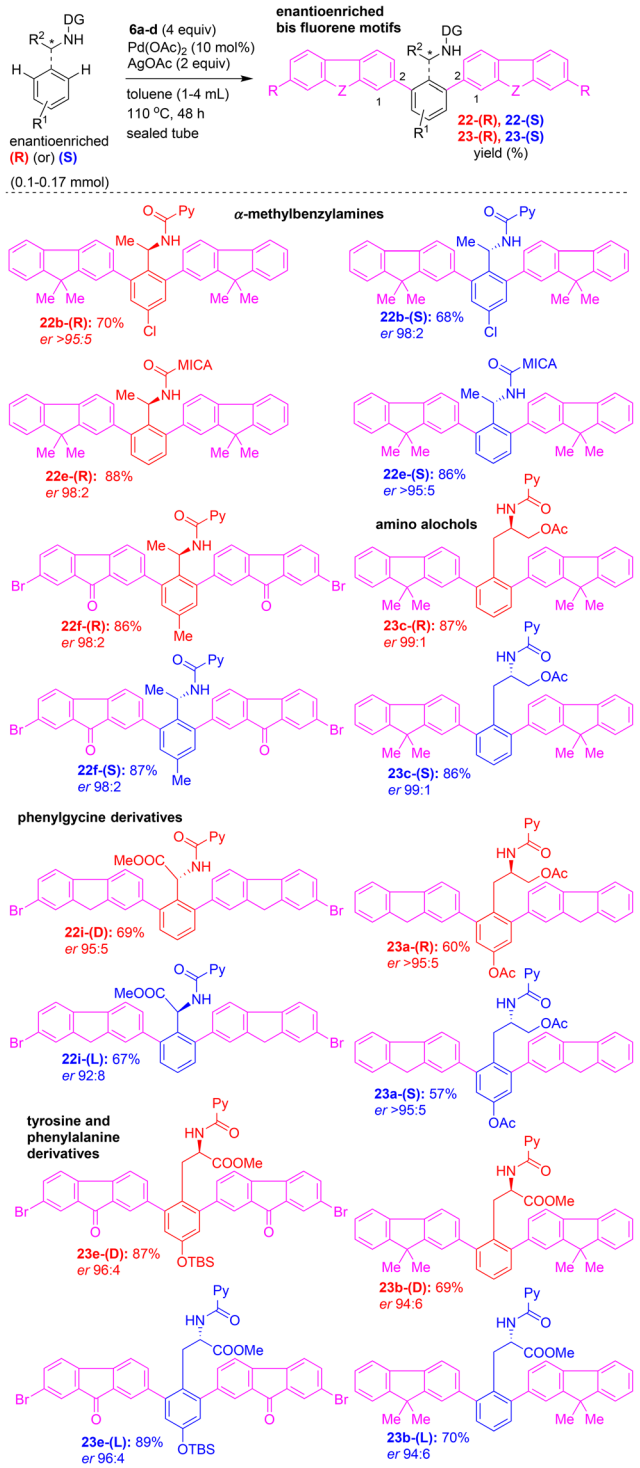
Having introduced the alkyl group at the C(3)–H of the fluorenone-4-carboxamide motif and obtained the modified fluorene–alkyl motifs **15a–g** (Scheme 10), alternatively, we ventured into the synthesis of fluorene–alkyl motifs **20** *via* arylation of the β-C(sp^3)–H of aliphatic/alicyclic carboxamides. Accordingly, aliphatic carboxamides possessing 8-AQ DG **19a–e** were subjected to β-C(sp^3)–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 possessing 8-AQ DG, **17** and **18**, were subjected to Pd(II)-catalyzed β-C(sp^3)–H arylation with iodofluorenes **6a–c**. These attempts afforded the corresponding fluorene-appended alicyclic motifs **20m–o** in 71–78% yields (Scheme 10). In agreement with reports in the literature,[24n,o] the corresponding products **20m–o** are believed to have *cis* stereochemistry *via* arylation of the diastereotopic β-C(sp^3)–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 these lines, 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, arylation of the methyl γ-C(sp^3)–H bond of thiophene-2-carboxamide or furan-2-carboxamide, **19h** and **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 a bis fluorene motif with 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(sp^2)–H arylation of benzamides with iodofluorenes and iodofluorenones to obtain the targeted bis fluorene motifs with an aryl ring spacer unit. At first, benzamide **24a** possessing 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** with an aryl ring spacer unit *via* the double C–H arylation of **24a** (see Scheme S2 in SI for the structures of



Scheme 11 Construction of π-extended bis fluorenes with 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 Scheme S2 in SI for the structures of starting materials **24a–w**. [a] 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).



Scheme 12 Construction of enantioenriched π-extended bis fluorenes with 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 Scheme S2 in SI for the structures of starting materials used in this scheme.

starting materials **24a–w** relevant to Scheme 11). Benzamides **24c** and **24d** were then reacted with **6a** to afford bis fluorenes **21b** and **21c** in 66–71% yields (Scheme 11). Benzamide **24e** linked with the ABTD directing group reacted with **6a** to afford 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 Pd(II)-catalyzed double *ortho* C(sp^2)–H arylation with iodofluorene **6a** to afford target bis fluorene motifs **21g–j** with an aryl ring spacer unit in 58–78% yields (Scheme 11).

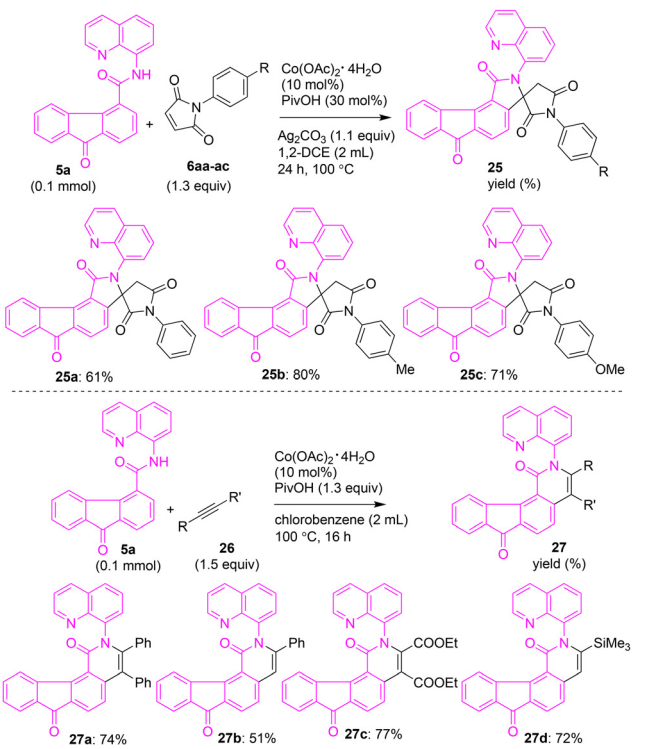
Benzylamine or α-methylbenzylamine substrates **24s**, **24u-(*RS*)**, **24r-(*RS*)**, **24t-(*RS*)** and **24q** with picolinamide or 5-methylisoxazole-3-carboxamide directing groups were subjected to Pd(II)-catalyzed double *ortho* C(sp^2)–H arylation with iodofluorenes **6a**, **6d** or iodofluorenone **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** was 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*)** and **23d-(*RS*)** were obtained. Furthermore, we subjected aromatic amino acid derivatives, such as phenylglycine, phenylalanine, and tyrosine substrates, to 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)** and **22i-(DL)**, phenylalanine-based bis fluorene motif **23b-(DL)**, β-phenylalanine-based bis fluorene motif **22d-(*RS*)**, and 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 with an aryl ring spacer unit (Scheme 12). Accordingly, enantioenriched α-methylbenzylamine substrates **24u-(*R*)**, **24u-(*S*)**, **24r-(*R*)**, **24r-(*S*)**, **24t-(*R*)**, and **24t-(*S*)** possessing picolinamide or MICA DG were subjected to 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*)** and **22f-(*S*)** in good yields with good enantiopurity (see Scheme S2 in SI for the structures of starting materials relevant to Scheme 12).

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

Having obtained arylated and alkylated fluorene/fluorenone scaffolds, we shifted our attention toward synthesizing modified fluorenones *via* ring annulation on fluorenones. Taking inspiration from reported cobalt-catalyzed oxidative cyclization, we treated maleimides **6aa–ac** with fluorenone-4-carboxamide **5a** using the reported conditions (Scheme 13),[27a] involving $Co(OAc)_2{\cdot}H_2O$, 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 SI for the proposed mechanism of formation of **25a–c**). Additionally, we heated acetylenes (symmetrical or unsymmetrical) with fluorene-4-carboxamide **5a** under the reported conditions[27b] involving $Co(OAc)_2{\cdot}H_2O$ and PivOH in chlorobenzene. These attempts gave the corresponding fluorenone-based isoquinolone derivatives **27a–d** in 51–77% yields (Scheme 13).

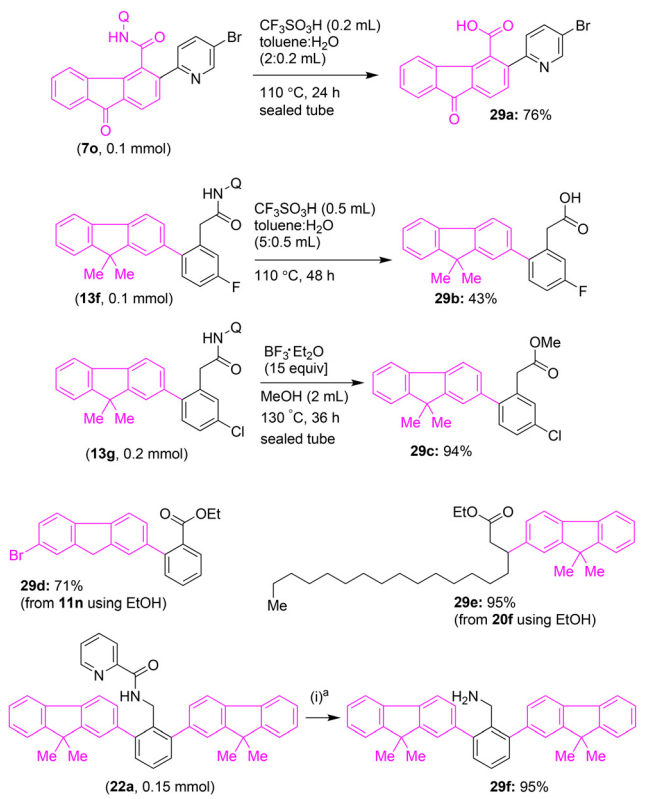
Next, we intended to show the utility and removal of the bidentate directing group[28b] after performing Pd(II)-catalyzed C–H arylation reactions affording functionalized fluorenes/



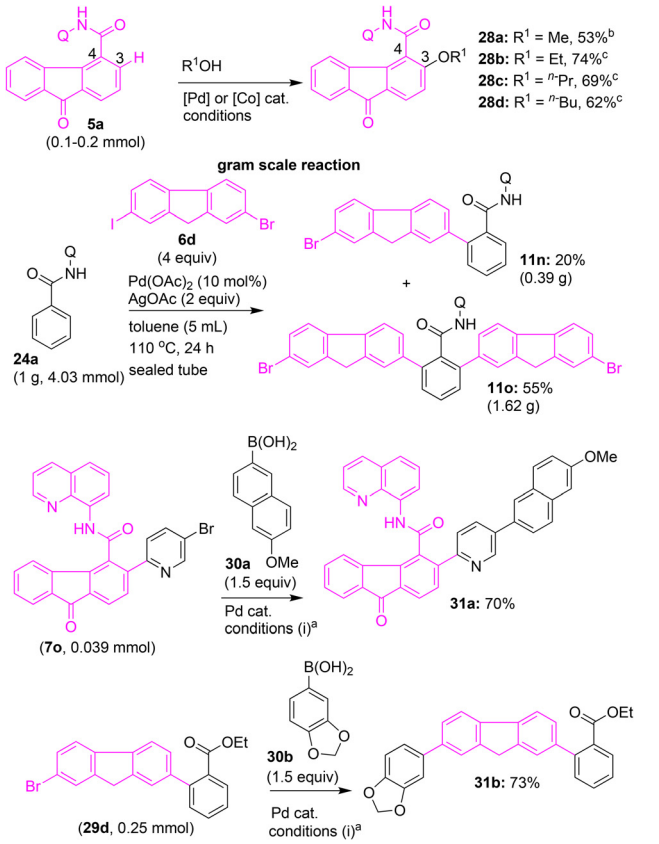
Scheme 13 Cobalt-catalyzed 8-aminoquinoline-directed oxidative cyclization of fluorenone carboxamide **5a** with maleimides and alkynes.

fluorenones (Scheme 14). We subjected the C(3)-arylated fluorenone carboxamide **7o** or fluorenone-arylacetamide **13f** to triflic-acid-mediated amide hydrolysis to afford 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 $BF_3{\cdot}OEt_2$-mediated direct amide to ester conversion method. Accordingly, fluorene-arylacetamide **13g**, fluorene–benzamide **11n**, and aliphatic carboxamide **20f** containing 8-AQ DG were subjected to the $BF_3{\cdot}OEt_2$-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).

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 *ortho* β-C–H arylation with **6d** in the presence of $Pd(OAc)_2$ and AgOAc. This reaction afforded fluorene–aryl motif **11n** (20%) and bis fluorene motif **11o** (55%). Given that this reaction was performed on a gram scale, it may be sluggish. Hence, we



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.



Scheme 15 Synthetic transformations, gram-scale C–H arylation of carboxamide and synthesis of C–H alkoxylated fluorenones and π-extended fluorene motifs *via* a 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] 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] Compounds **28b–d** are from substrate **5a** using Co $(OAc)_2{\cdot}4H_2O$ (20 mol%), NaOAc (2 equiv.), Ag_2O (1 equiv.), ROH (2 mL), 80 °C, 24 h, sealed tube (purged with ambient air).

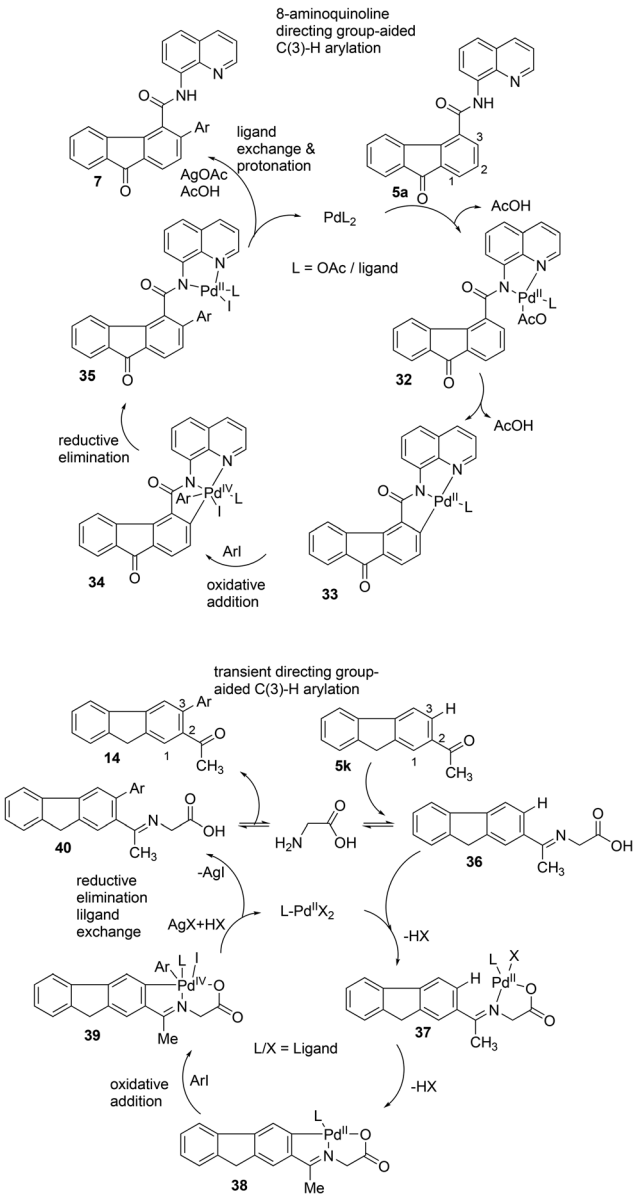
observed fluorene–aryl motif **11n** in considerable yield *via* mono C–H arylation. Notably, on a small scale, C–H arylation of **24a** with **6a** predominantly afforded bis fluorene motif **21a** (Scheme 11). As fluorene and fluorenone compounds are vital components in material chemistry, we wished 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 end, we intended to perform the cross-coupling reaction between the bromo functionality in fluorenone–aryl motifs **7o** and **29d** with boronic acids **30a** and **30b** under 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 the compounds (see Charts A–V in SI 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 SI 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 an 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 SI). Emission spectra of **31b** in different concentrations in MeCN (8.2, 16.5, 22.1, 27.6, and 55.2 μM) were recorded at an excitation wavelength of 260 nm (see Chart W in SI). Preliminary examination of the emission spectra of **31b** in different concentrations indicated that emission is constantly increasing with an increase in concentration, and no quenching of fluorescence due to intermolecular interaction was observed (see Chart W in SI). Additional work has 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 structures of representative C(3)-arylated fluorenone-4-carboxamide motif **7c** and fluorene–benzamide motif **11f** were unambiguously ascertained from the single-crystal X-ray structure analysis (Fig. 2). The X-ray structures divulged that 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 compounds **7c**/**11f**, NMR and HRMS analysis data and in agreement with the reports in the literature[22–24] the structures of all other compounds were ascertained.

In agreement with reports in the literature,[22–24] the mechanism of the Pd(II)-catalyzed, bidentate-directing-group-8-AQ-assisted C–H arylation of the *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 concerted metalation deprotonation (CMD), generating five-membered Pd(II) species **33** *via* **32**. Oxidative addition of Pd(II) species **33** with an aryl iodide yields 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 protonolysis, affording 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 reports in the literature,[26] a plausible mechanism for the transient directing group (TDG)-assisted arylation of the 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 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 β-C(sp^2)–H arylated product **14** and the 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 agreement with the reports in the literature.[22,23a,26a]

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, bioactive and drug molecules, *etc.*). Thus, synthesizing modified fluorenes and fluorenones (monomers) is considered a worthwhile effort. In this work, the C–H bonds of the fluorene or fluorenone core were subjected to directing-group-aided arylation, alkylation, benzyla-

tion, 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 with 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 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 prepared 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 $^{13}C\{^1H\}$ 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 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 are reported, and the yields have not been optimized. The UV-vis absorption spectra of the compounds were recorded at a concentration (c) = 0.02 g per 100 mL in CH_3CN.

We performed HPLC analysis of the starting material (substrates) used and fluorene- and fluorenone-based motifs synthesized in this work *via* C–H functionalization (see the SI). 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), and **24o-(*S*)** (er 98 : 2) were ascertained from HPLC analysis. Next, the HPLC analysis patterns of the synthesized racemic fluorene- and fluorenone-based motifs **22b-(*RS*)**, **22e-(*RS*)**, **22f-(*RS*)**, **22i-(DL)**, **23a-(*RS*)**, **23c-(*RS*)**, **23b-(DL)** and **23e-(DL)** 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)

To an 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), were added DMF (1 to 2 drops) and $(COCl)_2$ (1.2 equiv.) under a flow of nitrogen atm and the reaction was prolonged for 5 h at rt. After completion of reaction, the solvent was evaporated to afford the corresponding acid chloride of fluorenone or fluorene derivative, and vacuum dried. Next, to an RB flask containing the appropriate amine (8-aminoquinoline or 2-(methylthio)aniline or aniline or 1-octyl amine) in anhydrous DCM (2–10 mL) was added Et_3N (1.2 equiv.). Then, to this flask, the requisite acid chloride of fluorenone or fluorene derivative (dissolved in anhydrous DCM) was added 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 using silica gel column chromatography (EtOAc : hexane) 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 a 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 to a sealed tube (purged with N_2 atm) and the reaction mixture was heated at 130 °C for 48 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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

A mixture of an appropriate carboxamide containing a 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 to a sealed tube (purged with N_2 atm), and the reaction mixture was heated at 130 °C for 48 h. After the completion of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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 a directing group (1 equiv.), an appropriate aryl iodide (4 equiv.), $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (10 mol%), and CsOAc (4 equiv.), in *t*-amylOH (1–3 mL) was added to a sealed tube (purged with N_2 atm) and the reaction mixture was heated at 130 °C for 36 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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.) were added $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv.), glycine (50 mol%), and H_2O (4 equiv.) in HFIP : AcOH [5 : 1] and the reaction was heated at 130 °C for 24 h in a sealed tube (purged with N_2 atm). At the end of the reaction, the crude reaction mixture was cooled to rt and the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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.) were added $Pd(OAc)_2$ (10 mol%), AgTFA (1.5 equiv.), glycine (40 mol%), and AcOH : H_2O [9 : 1] and the reaction was heated at 100 °C for 36 h in a sealed tube (purged with N_2 atm). At the end of the reaction, the crude reaction mixture was cooled to rt and the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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) were added to a sealed tube (purged with N_2 atm) and the reaction mixture was heated at 130 °C for 48 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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.) were added $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv.), $CuBr_2$ (20 mol%), and H_2O (1.5 mL) at 110 °C for 48 h in a sealed tube (filled with ambient air). At the end of the reaction, 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/hexane 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 to a sealed tube (purged with N_2 atm) and the reaction mixture was heated at 100 °C for 36 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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

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.), and $Pd(OAc)_2$ (10 mol%) in toluene or *p*-xylene was heated at 110 or 130 °C 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 : hexane) 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

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.), and toluene : MeOH (1 : 1, 2 mL) was reacted at rt in a sealed tube (purged with ambient air) for 48 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) to afford the corresponding C–H methoxylated fluorenone carboxamide **28a** (see the respective table/scheme for the specific entry).

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

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.) was added to a sealed tube (purged with ambient air) and the reaction mixture was heated at 80 °C for 24 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) to afford the corresponding C–H alkoxylated fluorenone carboxamide (see the respective table/scheme for specific entries).

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

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.), $Co(OAc)_2{\cdot}4H_2O$ (10 mol%), Ag_2CO_3 (1.1 equiv.), PivOH (30 mol%), and 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. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) to afford the corresponding isoindolone-spiro-succinimides 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

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 disubstituted alkynes (1.3 equiv.), $Co(OAc)_2{\cdot}4H_2O$ (10 mol%), PivOH (1.3 equiv.), and chlorobenzene (2 mL) was heated in a sealed tube (filled with ambient air) at 100 °C for 24 h. At the end of the reaction, the crude was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) 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.) was added CF_3SO_3H (0.2 mL) in toluene : H_2O [10 : 1] and heated at 110 °C for 24 h in a sealed tube (filled with ambient air). At the end of the reaction, the crude reaction mixture was cooled to rt and quenched by slowly adding a saturated solution of Na_2CO_3 (5 mL) and then 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 : hexane) to afford the corresponding product (see the respective scheme for the 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 the specific entry).

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

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%), and 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). At the end of the reaction, the crude reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc : hexane) to afford the corresponding product (see the respective scheme for the specific entry).

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

Methyl 4-(9-oxo-4-(quinolin-8-ylcarbamoyl)-9*H*-fluoren-3-yl) benzoate (7a). Compound **7a** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 20 : 80) as a yellow-colored solid (70 mg, 72%, 0.2 mmol scale); R_f (20% EtOAc/hexane) 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). Compound **7c** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 20 : 80) as a yellow-colored solid (55 mg, 62%, 0.2 mmol scale); R_f (20% EtOAc/hexane) 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). Compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 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). Compound **8f** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 30 : 70) as a yellow-colored solid (55 mg, 93%, 0.1 mmol scale); R_f (20% EtOAc/hexane) 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, 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). Compound **11f** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (120 mg, 72%, 0.35 mmol scale); R_f (10% EtOAc/hexane) 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). Compound **14a** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (22 mg, 71%, 0.1 mmol scale); R_f (20% EtOAc/hexane) 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). Compound **20a** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (131 mg, 86%, 0.33 mmol scale); R_f (10% EtOAc/hexane) 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). Compound **20b** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (39 mg, 89%, 0.1 mmol scale); R_f (10% EtOAc/hexane) 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). Compound **21a** was obtained after purification by

column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (158 mg, 62%, 0.4 mmol scale); R_f (10% EtOAc/hexane) 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*)).** Compound **22b-(*RS*)** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (45 mg, 70%, 0.1 mmol scale); R_f (10% EtOAc/hexane) 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 compound **22b-(*RS*)** was determined using a Daicel Chiralpak IB column, hexane/i-PrOH (98 : 02), flow rate 0.5 mL min^{-1}, 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*)). Compound **22b-(*R*)** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (45 mg, 70%, 0.1 mmol scale); R_f (10% EtOAc/hexane) 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. $[\alpha]_D^{25}$ = −35.00 (c = 0.02 g mL^{-1}, $CHCl_3$). The enantiomeric ratio (er = >95 : 5) of compound **22b-(*R*)** was determined by HPLC using a Daicel Chiralpak IB column, hexane/i-PrOH (98 : 02), flow rate 0.5 mL min^{-1}, 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*)). Compound **22b-(*S*)** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (44 mg, 68%, 0.1 mmol scale); R_f (10% EtOAc/hexane) 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. $[\alpha]_D^{25}$ = +33.00 (c = 0.02 g mL^{-1}, $CHCl_3$). The enantiomeric ratio (er = 98 : 2) of compound **22b-(*S*)** was determined by HPLC using a Daicel Chiralpak IB column, hexane/i-PrOH (98 : 02), flow rate 0.5 mL min^{-1}, 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). Compound **29a** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 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). Compound **29b** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 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-F} = 247.3), 153.8, 153.7, 139.0 (d, J_{C-F} = 3.1 Hz), 138.8, 138.7, 138.5, 133.1 (d, J_{C-F} = 7.9 Hz), 131.7 (d, J_{C-F} = 8.2 Hz), 128.1, 127.4, 127.0, 123.7, 122.6, 120.1, 119.8, 117.5 (d, J_{C-F} = 21.7 Hz), 114.4 (d, J_{C-F} = 20.8 Hz), 46.9, 38.6, 27.0. $^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): 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). Compound **29c** was obtained after purification by column chromatography on silica gel (EtOAc : hexane = 10 : 90) as a colorless solid (71 mg, 94%, 0.2 mmol scale); R_f (10% EtOAc/hexane) 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.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data are available within the article or its supplementary information (SI). Brief crystal data of compounds **7c**/**11f**, a proposed mechanism relevant to formation of compound **25** and

structures of relevant starting materials, experimental proceduers, characterization data of all compounds, plots of absorption and emission spectra of compounds, copies of ^{1}H and ^{13}C NMRs and HPLC charts are provided in supplementary information. See DOI: https://doi.org/10.1039/d5ob01242b.

CCDC 2416200 (**7c**) and 2416201 (**11f**) contain the supplementary crystallographic data for this paper.[29a,b]

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