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Air-Stable Pd Catalytic Systems for Sequential One-Pot Synthesis of Challenging Unsymmetrical Aminoaromatics

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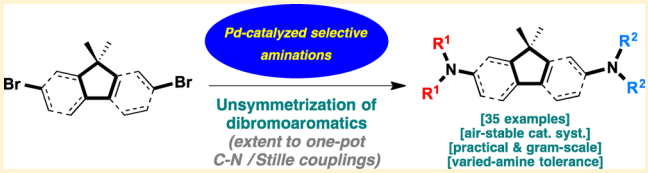
Supporting Information

ABSTRACT: The selective functionalization of dibromoaromatic scaffolds using air-stable palladium catalytic systems was carried out. This methodology involved rapid mono and diselective Buchwald-Hartwig aminations via microwave irradiation. The conditions were optimized to couple sequentially different moieties in one pot. Couplings with a wide scope of amines allowed accessing a new library of symmetrical and unsymmetrical derivatives (35 examples). Using this versatile method, a near-IR push−pull sensor was prepared installing the electron-donating and -withdrawing groups through a multicomponent reaction. These conditions revealed to be gram-scalable and adaptable to various groups; hence, promoting facile use in synthetic chemistry.



INTRODUCTION

Paralleled by the growing number of applications in material sciences (electronics, photonics) and therapeutics (natural products, pharmaceuticals),[1] selective functionalization of aromatic compounds has received broad considerations. Numerous palladium-catalyzed methodologies have emerged as reliable avenues to generate such aromatic products.[2] However, controlled couplings have been limited to a narrow array of substrates based on the halogen selectivities (Br/Cl or I/Br).[3] Indeed, selective couplings of simple dihalogenated aromatic scaffolds are seldom reported in the literature.[4]

Considering fluorene in particular for its significant applications,[1a] Pd-catalyzed monoamination of 2,7-dibromofluorenes was limited to aryl amines (Scheme 1).[5] Long routes engaging harsh conditions as nitrations and Ullmann-type couplings are hitherto used to synthesize aminofluorene derivatives.[6] Such conventional routes might still be preferred due to the overestimation of the role of glovebox in Buchwald−Hartwig C−N couplings. The endless list of costly palladium sources, ligands, and bases also complicates the choice of suitable catalytic systems for synthetic chemists.[7] Hence, we were encouraged to investigate the development of robust catalytic conditions to generate diverse amino-aromatic libraries and synthesize products inaccessible by classical aminations.

Our group recently reported a library of fluorescent fluorene probes.[8] During our initial study, we developed a convenient Pd-catalyzed methodology for the preparation of push−pull dyes starting from 7-bromo-9,9-dimethylfluorene-2-carbaldehyde. We now wish to report an appendage diversity-oriented synthesis (DOS)[2c,3d,9] of functionalized aromatic compounds using air-stable palladium catalytic systems (Scheme 1).

This methodology involves MW-assisted mono and diamination of easily accessible dibromoaromatic scaffolds. An extent of the latter provides sequential one-pot C−N/C−N and C−N/Stille couplings. Scope and limitations have been tested with dibrominated 2,7-fluorenes, 2,7-naphthalenes, 2,6-pyridines, and 2,5-thiophenes. This work permits the access to a variety of useful symmetrical and unsymmetrical aromatic compounds. For example, 2-amino-7-vinylfluorenes are important intermediates for numerous applications. The vinyl group is amenable to polymerization in light-harvesting materials, metathesis, Mizoroki−Heck cross-coupling, and oxidative cleavage to form push−pull sensors.[10] The amino moiety is beneficial for biomedical research and nanoparticles functionalization.[11] Using these conditions, a near-IR probe **PP** (Scheme 1) was prepared by a multicomponent reaction comprising one C−N and two Stille couplings.

RESULTS AND DISCUSSION

We started our investigations using a stoichiometric mixture of 2,7-dibromofluorene and *N*-methylaniline. This amine was chosen as an acyclic aliphatic-aromatic substrate. Different catalytic conditions were examined, and their corresponding selectivities of mono versus diaminated products were outlined in Figure 1. Monodentate triarylphosphines, such as PPh_3 and P(*o*-Tol)$_3$ were tested with low success (entries 1−2). PPh_3 exhibited a poor conversion (5%), whereas P(*o*-Tol)$_3$ favored diamination (25%) with dehalogenation side reactions. Reductive dehalogenation was also observed with first generation ligand PCy_3 (entry 3). Almost all the other ligands afforded the aminated products (**2a** and **3a**) in complete mass balance relative to the amine starting materials (entries 3−10). The monodentate ligands (**L4**−**8**) mainly led to the diaminofluorene (**3a**) (entries 3−8). The chelating bidentate ligands (XantPhos and BINAP) resulted in the monoaminated fluorene (**2a**) as the major product in line with previous studies conducted on dibromobenzene (entries 9−10).[4i,j,12]

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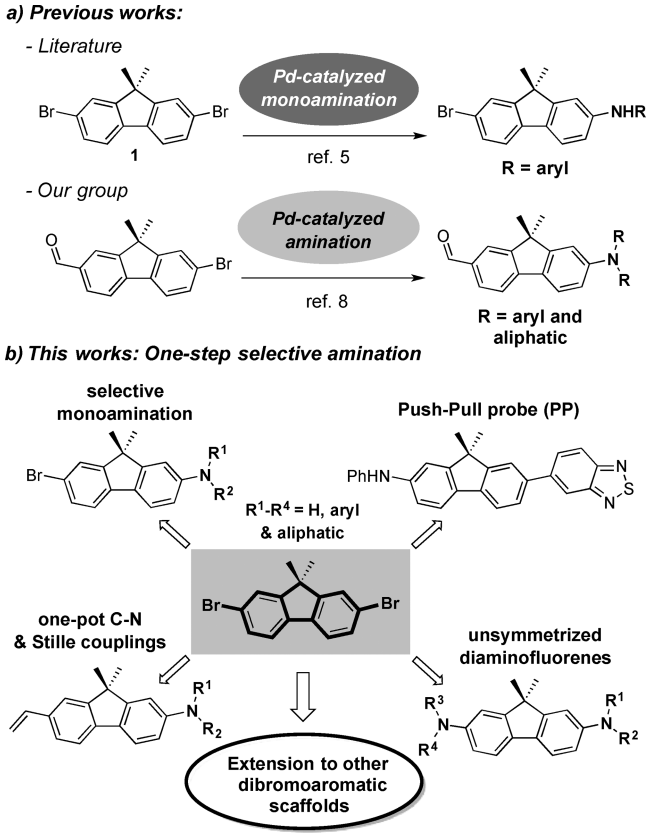
Scheme 1. State-of-the-Art Selective Functionalization of Bromofluorenes



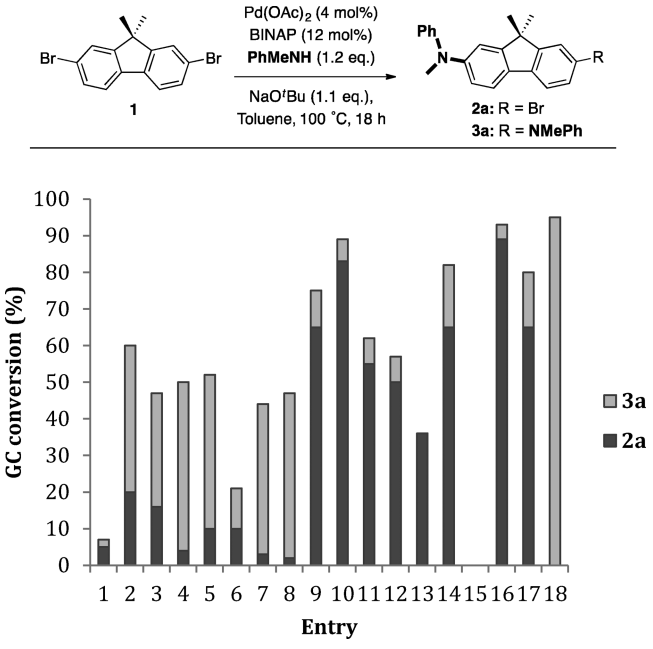
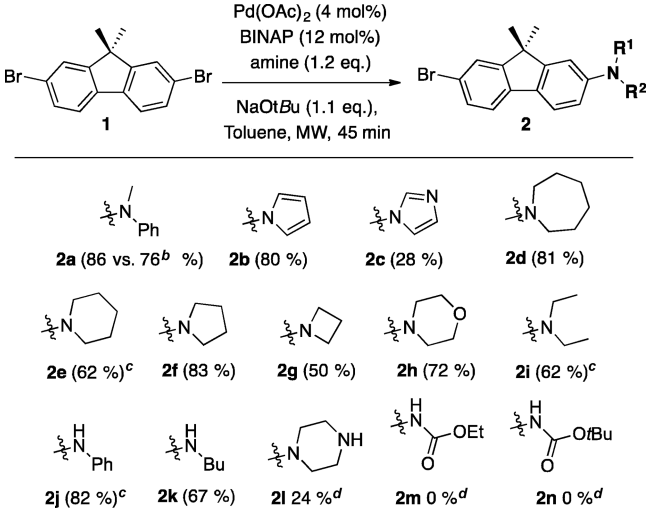


Figure 1. Optimization of the reaction conditions. Results were depicted as bar graphs displaying the GCMS conversion and the selectivity of mono/di aminated products (**2a**/**3a**). The corresponding entries were summarized in table by displaying the changed parameter.

Cs_2CO_3 as a representative of carbonate base demonstrated a moderate conversion (entry 11). *t*-BuOK and *t*-BuONa almost gave the same efficient results (entries 10 vs 12). $Pd(dba)_2$ was monoselective; however, the reaction did not reach to completion after 18 h (entry 13). The observed slower kinetics is consistent with the more sterically hindered $Pd(dba)L_2$ species.[13] The cross-coupling did not work at room temperature (rt) (entry 15). Dioxane (entry 14) mostly afforded the monoproduct, nonetheless the reaction was cleaner in toluene. MW activation gave the shortest reaction time (entries 10 vs 16). The best molar ratio of the [Pd]:ligand was optimized as 1:3 with a loading of 4 mol % (entries 10 vs 17). A lowering to 1 mol % inevitably slowed down the reaction rate. Premixing the catalytic system significantly accelerated the kinetics presuming an efficient activation of Pd(0) complex. It is noteworthy that premixing becomes a prerequisite in the case of BINAP.[14] The monoamination conditions were established as follows: $Pd(OAc)_2$ (4 mol %), BINAP (12 mol %), NaO*t*Bu (1.1 equiv), amine (1.2 equiv), toluene MW irradiations for 45 min (entry 16). Doubling the catalytic loading along with excess of amine (entry 18) led to complete diamination.

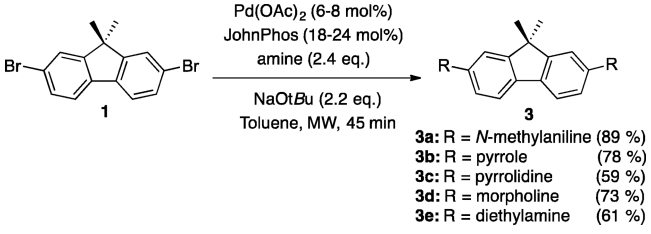
The scope and limitations of this methodology were investigated (Schemes 2 and 3). The chosen monoamination conditions were applied to introduce a variety of amines (Scheme 2). The selective mono cross-coupling was efficient on pyrrole (**2b**, 80%), cyclic secondary amines (**2d**–**h**, 50–81%), and primary amines (**2j**–**k**, 67–82%). To our delight, the diethylamine was also coupled efficiently (**2i**, 62%). Most reactions proceeded to completion in 45 min under MW irradiation. Piperidine **2e** and azetidine **2g** were irradiated twice for 45 min, their yields remained moderate (50–62%). The reaction was efficiently scaled-up to 1 g (**2e**, **2i**–**j**). Considering

Scheme 2. Scope and Limitation Pattern of the Selective Monoamination of 1[a]



[a]Yields in parentheses. [b]Under thermal heating conditions. [c]Reaction performed at 1 g scale. [d]GCMS conversion to the product.

Scheme 3. Diamination Reaction of 1



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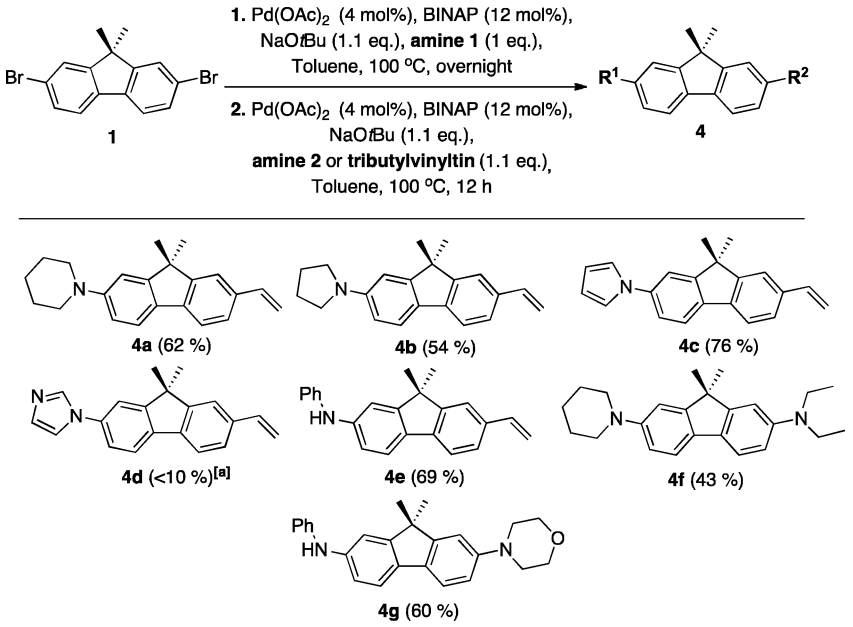
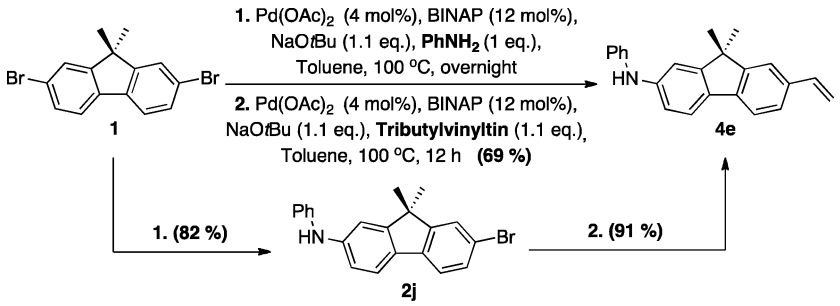
Scheme 4. Sequential Couplings of 1[a]



[a]GCMS conversion.

Scheme 5. Sequential One-Pot versus Classical Two-Step Synthesis of 4e



the unprotected piperazine **2l**, low conversion of starting material was obtained. Surprisingly, no dimerization was observed. This might open up new prospects for conjugation avoiding the additional steps of protection−deprotection of piperazine. The reaction conditions were limited on imidazole **2c**. Regarding carbamate coupling (**2m−n**), it required higher palladium catalytic loadings, which yielded the debrominated monocoupled derivative as the major product. Since carbamates present a different reactivity: *t*-BuOH, NMP, and THF were likewise screened without success.[15]

Minor modification of the catalytic system allows for the preparation of diaminofluorenes (Scheme 3).[16] A control reaction by using a large excess of amine (5 equiv) evidenced no inhibition of the process. A range of diaminofluorenes (**3a−e**) was prepared in good to excellent yields (61−89%). The employed conditions revealed to be effective and tolerant toward various model aliphatic and aromatic amines.

Next, we examined the synthesis of unsymmetrical fluorenes using a one-pot two-step protocol (Scheme 4). In this case, MW conditions were too demanding and generated inseparable mixtures. On the other side, thermal heating proved to be promising. Products **4a−e** (46−76%) were obtained by the sequential C−N/Stille couplings using the optimized conditions of entry **8**. Specifically, once the monoaminated product was formed, tributylvinyl tin and a subsequent catalytic loading were concomitantly added. The synthesis of products bearing two distinct amines (**4f−g**) was also achieved (43−60%) by sequential one-pot C−N/C−N couplings. The limitations of this type of desymmetrization are reflective of those of selective monoamination (compare **4d** and **2c**). The choice of amines[17] that worked efficiently for monoamination (Scheme 1) would lead to an efficient sequential one-pot coupling. Regarding the second catalytic loading, the reaction showed poor yields when it was not followed by a subsequent addition of the catalytic system. The addition of a second stoichiometric base is mandatory. We chose to focus on the double catalytic addition in this work to obtain good yields, as many factors can directly deactivate the palladium catalyst outside the glovebox, and this challenging reaction aims to synthesize useful materials. The highest yield of this series was observed for the pyrryl **4c** (76%).

Scheme 5 compares the one-pot approach (69%) to the classical two-step synthesis (76%) of compound **4e**. The good yield demonstrates that the developed procedure is cost- and time-efficient in synthesizing interesting products.

To further scope this method, different dibromo coupling partners with electronic diversity were tested. The results were illustrated in Chart 1. Regarding the electron-neutral naphthalene moiety, all the optimized catalytic systems worked as adequately as on fluorenes. Aromatic and aliphatic amines

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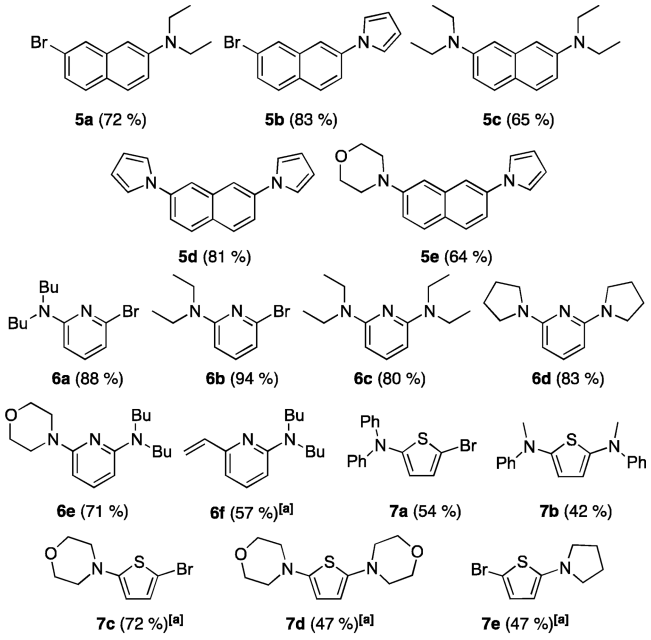
Chart 1. Scope and Limitations of Different Dibromoaromatic Scaffolds[a]

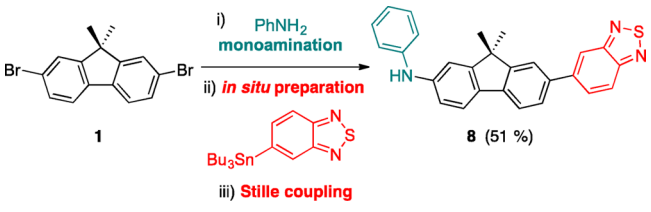


[a]GCMS conversion to the product.

were introduced with mono or diselectivity as desired furnishing **5a–d** (65–83%). The sequential synthesis of naphthalenes bearing varied combinations of amines was fruitful and generated compound **5e** in appreciable yields (64%). The electron-deficient pyridine reacted in higher yields (**6a–f**, 71–94%). **6e** was prepared as an example of the sequential addition in significant yield (71%). It is worth noting that 2,5-dibromopyridine underwent monoamination with 0.5 mol % $Pd(OAc)_2$ catalytic system or even with excess amine (5 equiv) in the absence of palladium catalyst. Nevertheless, di- or sequential amination of this heteroaryl compound undoubtedly requested the developed catalytic conditions. Arylaminothiophenes were obtained successfully and were stable to isolate (**7a–b**, 42–54%). Amination was still selective on such electron-rich aromatic scaffold. Considering saturated cyclic amines (**7c–e**), the mono/di conditions were selective with acceptable conversions (47–72%). However, these electron-rich products proved to be unstable upon isolation and appeared as a scope limitation.

The strength of this method permitted to access the near-IR probe **8** (λ_{Abs} = 395 nm and λ_{Em} = 640 nm in chloroform, Figure S1) in a three-step simple protocol (Scheme 6). This multicomponent reaction clearly asserts the versatility of our synthetic approach. The synthesis was concise and good yielding. It resulted in synthesis of an advanced dye without the tedious isolation of two intermediates.

Scheme 6. Construction of Push–Pull Sensor 8



CONCLUSION

In summary, an appendage DOS was realized starting from simple dibromoaromatic compounds and based on a platform of versatile palladium cross-couplings. The atom- and step-efficient methodology has allowed the synthesis of 35 examples including most challenging unsymmetrical substrates. We believe this catalytic route constitutes a more viable alternative to other long synthetic routes. The obtained vinylamino products are valuable intermediates that could be further employed to deliver a variety of light harvesting-materials and polymers. Using the same conditions, synthesis of near-IR probe was achieved via a versatile three-step reaction involving a C–N and two Stille couplings.

EXPERIMENTAL SECTION

All reactions involving water- or air-sensitive material were performed in oven-dried glassware under an argon or nitrogen atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and dry solvents. The reactions were monitored simultaneously by gas chromatography (GC/MS) and by thin-layer chromatography and visualized both by UV radiation (254 and 365 nm) and by spraying with relevant staining agent ($KMnO_4$ or Ninhydrin). Chemical shifts (δ) are given in ppm to the nearest 0.01 (^{1}H) or 0.1 ppm ($^{13}C\{^1H\}$NMR) (recorded with complete proton decoupling and written as ^{13}C in the experimental part for simplicity). The coupling constants (J) are given in Hertz (Hz). The signals are reported as follows: (s = singlet, d = doublet, t = triplet, quint = quintet, sext = sextet, m = multiplet, br = broad). GCMS mass spectra were recorded using an ion trap mass spectrometer with EI source (70 eV). LCMS mass spectra were recorded using an ion trap mass spectrometer equipped with an ESI source. HRMS was recorded on a hybrid ion trap–Orbitrap mass spectrometer using ESI. Microwave reactions were conducted using a monowave focused heating model with an internal probe.

9,9-Dimethyl-9*H*-fluorene. To a stirred solution of 9*H*-fluorene (3.00 g, 18.1 mmol, 1 equiv) in DMSO (35 mL) at 60 °C were sequentially added potassium iodide (300 mg, 1.8 mmol, 0.1 equiv), iodomethane (5.76 g, 40.6 mmol, 2.25 equiv), and very cautiously powdered potassium hydroxide (8.30 g, 146.8 mmol, 4 equiv). The resulting reaction mixture was stirred at rt overnight before being poured into 200 mL of water. A light-yellow precipitate was formed, then filtered out, washed with cold water, and dried under vacuum. The light-yellow solid was purified by crystallization from methanol to provide the 9,9-dimethylated fluorene (2.94 g, 84%) as white crystals. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.77–7.73 (m, 2H), 7.48–7.42 (m, 2H), 7.41–7.33 (m, 4H), 1.51 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 153.7 (2C), 139.3 (2C), 127.4 (2C), 126.9 (2C), 122.7 (2C), 120.1 (2C), 47.4, 27.3 (2C). GC-MS (m/z): 194.2 $[M]^{+\cdot}$. Mp: 96–98 °C.

2,7-Dibromo-9,9-dimethyl-9*H*-fluorene (1). To a solution of 9,9-dimethyl-9*H*-fluorene (2.18 g, 11.2 mmol, 1 equiv) in $CHCl_3$ (25 mL) in a reaction vessel suspended in ice bath, liquid bromine (1.40 mL, 25.8 mmol, 2.3 equiv) was carefully added dropwise. The reaction mixture was stirred for 4 h, quenched with sat. aq. $Na_2S_2O_3$ (15 mL), and extracted with $CHCl_3$ (3 × 15 mL). The separated organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by crystallization from DCM/MeOH to give **1** (2.85 g, 76%) as white crystals. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.55 (d, ^3J = 8.0 Hz, 2H, H4,5), 7.54 (d, ^4J = 1.5 Hz, 2H, H1,8), 7.45 (dd, ^4J = 1.5 Hz, ^3J = 8.0 Hz, 2H, H3,6), 1.46 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.4 (2C), 137.3 (2C), 130.5 (2C), 126.3 (2C), 121.6 (4C), 47.5, 27.0 (2C). MS (m/z): 352.0 $[M]^{+\cdot}$. Mp: 179–181 °C.

Synthesis of 2a–l: General Procedure for the Buchwald–Hartwig Selective Monoamination (GP-A). $Pd(OAc)_2$ (4 mol %), *t*-BuONa (1.1 equiv), and BINAP (12 mol %) were added to a previously dried reaction tube containing a magnetic bar. The tube was purged with argon for three cycles using Schlenk technique. The

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mixture was dissolved in toluene (0.1 M) and stirred for 15 min under argon at rt. Then, the dibromo aryl reagent (1 equiv) was added, followed by 15 min of further stirring (at rt or 100 °C for better). Finally, the amine (liquid or dissolved in toluene) (1.1 equiv) was added, and the reaction mixture was irradiated in the microwave oven at 300 W/180 °C for 45 min (or classically heated at 100 °C in an oil bath overnight for thermal activation). The reaction was concomitantly monitored by TLC and GCMS until complete conversion. The resulting mixture was cooled down to rt, diluted by CH_2Cl_2, and filtered over a pad of Celite. The volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography using a slow gradient to give the desired product. **2a–k** series of products was prepared on 100 mg scale (0.28 mmol) except when otherwise indicated.

*7-Bromo-N,9,9-trimethyl-N-phenyl-9H-fluoren-2-amine (**2a**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.45) providing **2a** as a yellow solid (89 mg, 0.24 mmol, 86%). Thermal heating: (80 mg, 0.21 mmol, 76%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.49–7.16 (m, 6H), 7.02–6.86 (m, 5H), 3.29 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.5, 154.9, 149.1 (2C), 138.4, 131.5, 130.1, 129.4 (2C), 126.1, 121.6, 120.8 (3C), 120.6, 119.8, 119.4, 114.4, 47.2, 40.7, 27.7 (2C). HRMS (ESI$^+$): m/z calcd for $C_{22}H_{21}NBr$: 378.0852 $[M + H]^+$; found 378.0855.

*1-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)-1H-pyrrole (**2b**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.45) providing **2b** as a yellow solid (74 mg, 0.22 mmol, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.72 (d, ^3J = 8.0 Hz, 1H), 7.60–7.36 (m, 5H), 7.16 (t, J = 2.0 Hz, 2H), 6.40 (t, J = 2.0 Hz, 2H), 1.52 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.7, 155.0, 140.6, 137.6, 135.9, 130.4, 126.3, 121.4, 121.1, 121.1, 120.0, 119.7 (2C), 115.4, 110.6 (2C), 47.7, 27.1 (2C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{17}NBr$: 338.0539 $[M + H]^+$; found 338.0540.

*1-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)-1H-imidazole (**2c**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98:2) providing **2c** as a yellow solid (24 mg, 0.07 mmol, 28%) ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.90 (s, 1H), 7.75 (d, ^3J = 8.0 Hz, 1H), 7.59 (d, ^3J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.47 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H), 7.40–7.32 (m, 3H), 7.23 (s, 1H), 1.51 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.7, 155.3, 137.7, 137.0, 136.9, 135.8, 130.6 (2C), 126.4, 121.8, 121.7, 121.3, 121.0, 118.6, 116.4, 47.5, 27.1 (2C). HRMS (ESI$^+$): m/z calcd for $C_{18}H_{16}N_2Br$: 339.0491 $[M + H]^+$; found 339.0494. Mp: 172–174 °C.

*1-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)azepane (**2d**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.5) providing **2d** as a yellow solid (83 mg, 0.23 mmol, 81%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.51 (br d, ^3J = 8.0 Hz, 1H, H4′), 7.46 (br s, 1H, H8′), 7.43–7.34 (m, 2H, H5′,6′), 6.70 (br s, 1H, H1′), 6.68 (br d, ^3J = 8.0 Hz, 1H, H3′), 3.53 (t, ^3J = 6.0 Hz, 4H, $CH_2$2,7), 1.84 (br m, 4H, $CH_2$3,6), 1.59 (br m, 4H, $CH_2$4,5), 1.45 (s, 6H, 2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.3, 154.9, 149.4, 139.2, 129.9, 129.4, 125.8, 121.1, 119.7, 118.4, 110.5, 105.1, 49.6 (2C), 47.0, 27.9 (2C), 27.5 (2C), 27.3 (2C). HRMS (ESI$^+$): m/z calcd for $C_{21}H_{25}NBr$: 370.1165 $[M + H]^+$; found 370.1166. Mp: 140–142 °C.

*1-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)piperidine (**2e**): Reaction Performed on 1 g Scale (2.84 mmol).* Eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.6) providing **2e** as a yellow solid (625 mg, 1.76 mmol, 62%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.55 (d, ^3J = 8.0 Hz, 1H, H4′), 7.49 (d, ^4J = 2.0 Hz, 1H, H8′), 7.42 (d, ^3J = 8.0 Hz, 1H, H5′), 7.39 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, H6′), 7.00 (br s, 1H, H1′), 6.94 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, H3′), 3.23 (t, ^3J = 6.0 Hz, 4H, $CH_2$2,6), 1.77 (br m, 4H, $CH_2$3,5), 1.62 (br m, 2H, $CH_2$4), 1.45 (s, 6H, 2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.3, 154.7, 152.6, 138.7, 130.0, 129.6, 125.9, 120.7, 120.4, 119.3, 115.5, 110.8, 51.1 (2C), 47.1, 27.3 (2C), 26.0 (2C), 24.4. HRMS (ESI$^+$): m/z calcd for $C_{20}H_{23}NBr$: 356.1008 $[M + H]^+$; found 356.1008. Mp: 133–135 °C.

*1-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)pyrrolidine (**2f**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 97:3, R_f = 0.32) providing **2f** as a yellow solid (79 mg, 0.23 mmol, 83%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.41 (d, ^3J = 8.0 Hz, 1H, H4′), 7.36 (br d, ^4J = 2.0 Hz, 1H, H8′), 7.27 (m, 2H, H5′,6′), 6.45 (br s, 1H, H1′), 6.42 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, H3′), 3.24 (t, ^3J = 7.0 Hz, 4H, $CH_2$2,5), 1.91 (m, 4H, $CH_2$3,4), 1.34 (s, 6H, 2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.2, 154.9, 148.2, 139.3, 129.9 (2C), 125.8, 121.1, 119.7, 118.3, 110.9, 105.5, 48.0 (2C), 47.0, 27.5 (2C), 25.6 (2C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{21}NBr$: 342.0852 $[M + H]^+$; found 342.0852.

*1-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)azetidine (**2g**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98/2, R_f = 0.18) providing **2g** as a yellow solid (45 mg, 0.14 mmol, 50%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.43 (d, ^3J = 8.0 Hz, 1H, H4′), 7.39 (br s, 1H, H8′), 7.33–7.27 (m, 2H, H5′,6′), 6.37 (br d, ^4J = 2.0 Hz, 1H, H1′), 6.33 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, H3′), 3.87 (t, ^3J = 7.0 Hz, 4H, $CH_2$2,4), 2.32 (q, ^3J = 7.0 Hz, 2H, $CH_2$3), 1.35 (s, 6H, 2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.0 (2C), 152.4, 139.1, 130.0 (2C), 125.9, 120.8, 120.0, 118.9, 110.4, 105.3, 52.7 (2C), 47.0, 27.4 (2C), 17.0. HRMS (ESI$^+$): m/z calcd for $C_{18}H_{19}NBr$: 328.0695 $[M + H]^+$; found 328.0696.

*4-(7-Bromo-9,9-dimethyl-9H-fluoren-2-yl)morpholine (**2h**).* Eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.15) providing **2h** as a yellow solid (71 mg, 0.20 mmol, 72%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.40–7.31 (m, 3H), 7.21 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H), 6.77 (d, ^4J = 2.0 Hz, 1H), 6.69 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H), 3.71 (t, ^3J = 5.0 Hz, 4H), 3.05 (t, ^3J = 5.0 Hz, 4H), 1.26 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.4, 154.9, 151.6, 138.4, 130.6, 130.1, 126.0, 120.9, 120.6, 119.7, 114.8, 110.1, 67.0 (2C), 49.8 (2C), 47.2, 27.4 (2C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{21}NOBr$: 358.0801 $[M + H]^+$; found 358.0804. Mp: 165–167 °C.

*7-Bromo-N,N-diethyl-9,9-dimethyl-9H-fluoren-2-amine (**2i**):[6d] Reaction Performed on 1 g Scale (2.84 mmol).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98/2, R_f = 0.35) providing **2i** as a yellow solid (606 mg, 1.76 mmol, 62%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.54–7.40 (m, 4H), 6.69–6.65 (m, 2H), 3.43 (q, ^3J = 7.0 Hz, 4H), 1.45 (s, 6H), 1.22 (t, ^3J = 7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.3, 154.9, 148.1, 139.1, 129.9, 125.8, 121.2, 119.8, 118.4, 111.0, 105.7, 47.0, 44.9 (2C), 27.5 (2C), 12.7 (2C). GC-MS (m/z): 343.1 $[M]^+$. Mp: 142–144 °C.

*7-Bromo-9,9-dimethyl-N-phenyl-9H-fluoren-2-amine (**2j**): Reaction Performed on 1 g Scale (2.84 mmol).* Eluent for flash chromatography (PE/DCM = gradient up to 9/1, R_f = 0.13) providing **2j** as a yellow solid (848 mg, 2.33 mmol, 82%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.62–7.41 (m, 4H), 7.37–7.22 (m, 2H), 7.16–6.95 (m, 5H), 1.47 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.3, 155.1, 143.1 (2C), 138.4, 131.4, 130.1, 129.5 (2C), 126.0, 121.3, 121.1, 120.5, 119.7, 118.0 (2C), 116.9, 112.0, 47.1, 27.2 (2C). HRMS (ESI$^+$): m/z calcd for $C_{21}H_{19}NBr$: 364.0695 $[M + H]^+$; found 364.0698.

*7-Bromo-N-butyl-9,9-dimethyl-9H-fluoren-2-amine (**2k**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 99/1, R_f = 0.11) providing 2k as an amorphous yellow solid (64 mg, 0.18 mol, 67%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.56–7.27 (m, 4H), 6.71–6.56 (m, 2H), 3.18 (t, ^3J = 7.0 Hz, 2H), 1.66 (q, ^3J = 7.0 Hz, 2H), 1.52–1.26 (m, 2H), 1.43 (s, 6H), 0.98 (t, ^3J = 7.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.3, 154.9, 148.7, 140.0, 139.1, 130.0, 125.9, 121.2, 119.9, 118.8, 112.0, 106.9, 47.0, 44.2, 31.8, 27.4 (2C), 20.5, 14.1. GC-MS (m/z): 343.1 $[M]^+$.

Synthesis of 3a–e: General Procedure for the Buchwald–Hartwig Diamination (GP-B). $Pd(OAc)_2$ (8 mol %), *t*-BuONa (2.2 equiv), and JohnPhos (24 mol %) were added to a previously dried reaction tube containing a magnetic bar. The tube was purged with argon for three cycles using Schlenk technique. The mixture was dissolved in toluene (0.1 M) and stirred for 15 min at rt under argon. Then, the dibromo aryl reagent (1 equiv) was added and followed by 15 min further stirred for 15 min (at rt or 100 °C for better activation). Finally, the amine (liquid or dissolved in toluene) (2.2 equiv) was added, and the reaction mixture was irradiated in the microwave oven at 300 W/180 °C for 1 h (or classically heated at 100 °C in an oil bath overnight for thermal activation). The reaction was monitored by TLC and GCMS until complete conversion. The resulting mixture was cooled down to rt, diluted by CH_2Cl_2, and filtered over a pad of Celite. The volatiles were removed under

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reduced pressure, and the residue was purified by silica gel column chromatography to give the desired product. **3a–e** series of products was prepared on 100 mg scale (0.28 mmol).

*N^2,N^7,9,9-Tetramethyl-N^2,N^7-diphenyl-9H-fluorene-2,7-diamine (**3a**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.25) providing **3a** as a yellow solid (101 mg, 0.25 mmol, 89%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.49 (d, ^3J = 8.0 Hz, 2H), 7.22 (t, ^3J = 8.0 Hz, 4H), 7.08 (br s, 2H), 6.99–6.95 (m, 6H), 6.90–6.83 (m, 2H), 3.32 (s, 6H), 1.37 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.0 (2C), 149.4 (2C), 147.8 (2C), 133.5 (2C), 129.3 (4C), 120.8 (2C), 120.4 (2C), 120.1 (2C), 119.1 (4C), 116.2 (2C), 47.0, 40.8 (2C), 27.4 (2C). HRMS (ESI$^+$): m/z calcd for $C_{29}H_{29}N_2$: 405.2325 $[M + H]^+$; found 405.2321. Mp: 143–145 °C.

*1,1′-(9,9-Dimethyl-9H-fluorene-2,7-diyl)di-1H-pyrrole (**3b**).* Eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.26) providing **3b** as a yellow solid (70 mg, 0.22 mmol, 78%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.73 (d, ^3J = 8.0 Hz, 2H, H4,5), 7.45 (d, ^4J = 2.0 Hz, 2H, H1,8), 7.39 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 2H, H3,6), 7.16 (t, ^3J = 2.0 Hz, 4H, NCHpyr), 6.39 (t, ^3J = 2.0 Hz, 4H, CHpyr), 1.55 (s, 6H, $2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.3 (2C, Ca,b), 140.3 (2C, C2,7), 136.3 (2C, *Cc*,d), 120.9 (2C, C4,5), 120.1 (2C, C3,6), 119.8 (4C, N(CHpyr)), 115.5 (2C, C1,8), 110.5 (4C, CHpyr), 47.4 (C9), 27.3 ($2CH_3$). HRMS (ESI$^+$): m/z calcd for $C_{23}H_{21}N_2$: 325.1699 $[M + H]^+$; found 325.1700. Mp: 265–267 °C.

*1,1′-(9,9-Dimethyl-9H-fluorene-2,7-diyl)dipyrrolidine (**3c**).* Eluent for flash chromatography (PE/EA = gradient up to 98:2, R_f = 0.38) providing **3c** as a yellow solid (55 mg, 0.16 mmol, 59%). ^{1}H NMR (200 MHz, TFA-d^1, δ): 8.02 (d, ^3J = 8.5 Hz, 2H, H4,5), 7.88 (d, ^4J = 2.0 Hz, 2H, H1,8), 7.58 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 2H, H3,6), 4.26 (br t, ^3J = 5.0 Hz, 4H, $N(CH_2)_2$), 3.79 (br t, ^3J = 5.0 Hz, 4H, $N(CH_2)_2$), 2.51 (m, 8H, $2N(CH_2CH_2)_2$), 1.58 (s, 6H, $2CH_3$). ^{13}C NMR (50 MHz, TFA-d^1, δ): 159.5 (2C, Ca,b), 142.3 (2C, *Cc*,d), 141.8 (2C, C2,7), 124.9 (2C, C4,5), 122.2 (2C, C3,6), 117.5 (2C, C1,8), 62.6 (4C, $N(CH_2)$), 50.5 (C9), 27.4 ($2CH_3$), 25.7 (4C, $N(CH_2\underline{C}H_2)$). HRMS (ESI$^+$): m/z calcd for $C_{23}H_{29}N_2$: 333.2321 $[M + H]^+$; found 333.2325. Mp: 162–164 °C.

*4,4′-(9,9-Dimethyl-9H-fluorene-2,7-diyl)dimorpholine (**3d**).* Eluent for flash chromatography (PE/EA = gradient up to 9:1, R_f = 0.16) providing **3d** as a yellow solid (74 mg, 0.20 mmol, 73%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.52 (d, ^3J = 8.0 Hz, 2H, H4,5), 6.97 (d, ^4J = 2.0 Hz, 2H, H1,8), 6.87 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 2H, H3,6), 3.90 (t, ^3J = 5.0 Hz, 8H, $2O(CH_2)_2$), 3.21 (t, ^3J = 5.0 Hz, 8H, $2N(CH_2)_2$), 1.45 (s, 6H, $2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 154.7 (2C), 150.5 (2C), 132.2 (2C), 119.8 (2C), 114.8 (2C), 110.7 (2C), 67.2 (4C), 50.3 (4C), 47.0, 27.8 (2C). HRMS (ESI$^+$): m/z calcd for $C_{23}H_{29}O_2N_2$: 365.2224 $[M + H]^+$; found 365.2226. Mp: 232–234 °C.

*N^2,N^2,N^7,N^7-Tetraethyl-9,9-dimethyl-9H-fluorene-2,7-diamine (**3e**).* Eluent for flash chromatography (PE/EA = gradient up to 98:2, R_f = 0.34) providing **3e** as a yellow solid (57 mg, 0.61 mmol, 61%). ^{1}H NMR (500 MHz, TFA-d^1, δ): 8.14 (d, ^3J = 8.0 Hz, 2H, H4,5), 7.70 (s, 2H, H1,8), 7.58 (br d, ^3J = 8.0 Hz, 2H, H3,6), 3.92 (m, 4H, $2CH_2$), 3.81 (m, 4H, $2CH_2$), 1.66 (s, 6H, $2CH_3$), 1.34 (t, 12H, ^3J = 8.0 Hz, $(CH_2CH_3)_4$). ^{13}C NMR (125 MHz, TFA-d^1, δ): 159.9 (2C), 142.6 (2C), 138.5 (2C), 125.6 (2C), 123.5 (2C), 118.6 (2C), 58.2 (2C), 50.6, 27.9 (2C), 11.4 (2C). GC-MS (m/z): 336.3 $[M]^{+\cdot}$. HRMS (ESI$^+$): m/z calcd for $C_{23}H_{33}N_2$: 337.2638 $[M + H]^+$; found 337.2639. Mp: 130–132 °C.

Synthesis of 4a–h: General Procedure for the Sequential C–N/C–N and C–N/Stille Unsymmetrical Couplings. General procedure GP-A was carried out, and the monoaminated bromoaromatic product was isolated. The pure product was subjected to GP-A using another nucleophile (amine for a second Buchwald–Hartwig coupling or tributylvinyl tin for subsequent Stille coupling).

Procedure for Sequential One-Pot (GP-C). $Pd(OAc)_2$ (4 mol %), *t*-BuONa (1.1 equiv), and BINAP (12 mol %) were added to a previously dried reaction tube containing a magnetic bar. The tube was purged with argon for three cycles using Schlenk technique. The mixture was dissolved in toluene (0.1 M) and stirred for 15 min at rt under argon. Then, the dibromo aryl reagent (1 equiv) was added, followed by 15 min further stirring (at rt or 100 °C for better activation). Finally, the amine (liquid or dissolved in toluene) (1.1 equiv) was added, and the reaction mixture was heated at 100 °C in an oil bath. The reaction was monitored by TLC and GCMS until diaminated product started to appear (between 12 and 16 h). Then, another loading of the catalytic system (4 mol % [Pd]/ 12 mol % L/ 1.1 equiv *t*-BuONa) was re-added followed by excess of second nucleophile (2 equiv). The final mixture was stirred at 100 °C overnight and monitored by TLC and GCMS until complete conversion. The reaction was cooled down to rt, diluted by CH_2Cl_2, and filtered over a pad of Celite. The volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the desired product.

*1-(9,9-Dimethyl-7-vinyl-9H-fluoren-2-yl)piperidine (**4a**).* Eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.71) providing **4a** as a yellow solid (52 mg, 0.17 mmol, 62%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.59 (d, ^3J = 8.0 Hz, 1H), 7.57 (d, ^3J = 8.0 Hz, 1H), 7.47 (br s, 1H), 7.36 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H), 7.04 (d, ^4J = 2.0 Hz, 1H), 6.94 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H), 6.82 (dd, $^3J_{trans}$ = 17.5 Hz, $^3J_{cis}$ = 11.0 Hz, 1H), 5.80 (d, $^3J_{trans}$ = 17.5 Hz, 1H), 5.24 (d, $^3J_{cis}$ = 11.0 Hz, 1H), 3.25 (t, ^3J = 5.5 Hz, 4H), 1.78 (br m, 4H), 1.65 (br m, 2H), 1.50 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.4, 153.6, 152.4, 139.6, 137.5, 135.3, 130.6, 125.7, 120.7, 120.1, 119.1, 115.5, 112.4, 111.1, 51.3 (2C), 46.8, 27.6 (2C), 26.1 (2C), 24.4. HRMS (ESI$^+$): m/z calcd for $C_{22}H_{26}N$: 304.2061 $[M + H]^+$; found 304.2060.

*1-(9,9-Dimethyl-7-vinyl-9H-fluoren-2-yl)pyrrolidine (**4b**).* Eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.7) providing **4b** as a yellow solid (43 mg, 0.15 mmol, 54%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.54 (m, 2H), 7.43 (br s, 1H), 7.33 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H), 6.78 (dd, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 11.0 Hz, 1H), 6.60 (d, ^4J = 2.0 Hz, 1H), 6.56 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H), 5.75 (d, $^3J_{trans}$ = 17.0 Hz, 1H), 5.20 (d, $^3J_{cis}$ = 11.0 Hz, 1H), 3.38 (t, ^3J = 6.5 Hz, 4H), 2.04 (m, 4H), 1.48 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 156.0, 153.1, 148.1, 140.3, 137.8, 134.5, 126.9, 125.7, 121.1, 119.9, 118.4, 112.0, 110.8, 105.6, 48.1 (2C), 46.7, 27.7 (2C), 25.7 (2C). HRMS (ESI$^+$): m/z calcd for $C_{21}H_{24}N$: 290.1903 $[M + H]^+$; found 290.1903.

*1-(9,9-Dimethyl-7-vinyl-9H-fluoren-2-yl)-1H-pyrrole (**4c**).* Yellow solid (60 mg, 0.21 mmol, 76%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.74 (d, ^3J = 8.0 Hz, 1H), 7.68 (d, ^3J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.45–7.36 (m, 3H), 7.17 (t, J = 2.0 Hz, 2H), 6.83 (dd, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 11.0 Hz, 1H), 6.40 (t, J = 2.0 Hz, 2H), 5.84 (d, $^3J_{trans}$ = 17.0 Hz, 1H), 5.30 (d, $^3J_{cis}$ = 11.0 Hz, 1H), 1.54 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.6, 154.1, 140.3, 138.4, 137.2, 136.9, 136.8, 125.9, 121.0, 120.4, 120.1, 119.9, 119.8 (2C), 115.5, 113.5, 110.5 (2C), 47.0, 27.5 (2C). HRMS (ESI$^+$): m/z calcd for $C_{21}H_{20}N$: 286.1591 $[M + H]^+$; found 286.1590. Mp: 175–177 °C.

*9,9-Dimethyl-N-phenyl-7-vinyl-9H-fluoren-2-amine (**4e**).* Eluent for flash chromatography (PE/DCM = gradient up to 9/1, R_f = 0.28) providing **4e** as a yellow solid (60 mg, 0.19 mmol, 69%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.48 (d, ^3J = 8.0 Hz, 2H), 7.36 (s, 1H), 7.29–7.13 (m, 3H), 7.06–6.92 (m, 4H), 6.90–6.62 (m, 2H), 5.73 (br s, 1H, NH), 5.69 (d, $^3J_{trans}$ = 17.0 Hz, 1H), 5.15 (d, $^3J_{cis}$ = 11.0 Hz, 1H), 1.38 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.8, 153.6, 143.4, 142.7, 139.3, 137.4, 135.7, 132.4, 129.6 (2C), 125.8, 121.1, 121.0, 120.2, 119.2, 117.8 (2C), 117.0, 112.8, 112.4, 46.8, 27.4 (2C). HRMS (ESI$^+$): m/z calcd for $C_{23}H_{22}N$: 312.1747 $[M + H]^+$; found 312.1747.

*N,N-Diethyl-9,9-dimethyl-7-(piperidin-1-yl)-9H-fluoren-2-amine (**4f**).* Eluent for flash chromatography (PE/Et_2O = 99:1, R_f = 0.12) providing **4f** as a yellow solid (41 mg, 0.12 mmol, 43%). ^{1}H NMR (200 MHz, TFA-*d*, δ): 8.05–7.98 (m, 2H), 7.68–7.46 (m, 4H), 3.99–3.77 (m, 4H), 3.75–3.61 (m, 4H), 2.25–2.04 (m, 4H), 1.55 (s, 6H), 1.28–1.25 (m, 8H). ^{13}C NMR (125 MHz, TFA-*d*, δ): 159.9, 159.4, 143.7, 142.6, 142.2, 138.3, 125.4, 125.2, 123.3, 122.1, 118.4, 117.2, 61.2 (2C), 57.7 (2C), 50.4, 27.3 (2C), 25.9 (2C), 22.9, 11.4 (2C). HRMS (ESI$^+$): m/z calcd for $C_{24}H_{33}N_2$: 349.2638 $[M + H]^+$; found 349.2638.

*9,9-Dimethyl-7-morpholino-N-phenyl-9H-fluoren-2-amine (**4g**).* Eluent for flash chromatography (PE/EA = gradient up to 9:1, R_f = 0.22) providing **4g** as a yellow solid (62 mg, 0.18 mmol, 60%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.49 (d, ^3J = 8.0 Hz, 1H), 7.47 (d, ^3J =

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8.0 Hz, 1H), 7.28−6.82 (m, 9H), 3.87 (t, ^3J = 5.0 Hz, 4H), 3.18 (t, ^3J = 5.0 Hz, 4H), 1.41 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.0, 154.7, 150.6, 143.9, 141.5, 133.2, 132.1, 129.5 (2C), 120.6, 120.0, 119.9, 117.6, 117.3 (2C), 114.8, 113.1, 110.7, 67.2 (2C), 50.2 (2C), 47.0, 27.6 (2C). HRMS (ESI$^+$): m/z calcd for $C_{25}H_{27}ON_2$: 371.2118 [M + H]$^+$; found 371.2120. Mp: 160−162 °C.

Desymmetrization of Dibromoaromatics. All the series of products (**5a−f**, **6a−f**, and **7a−b**) were prepared on 100 mg scale.

*7-Bromo-N,N-diethylnaphthalen-2-amine (**5a**).* Following general procedure GP-A, eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.49) provided **5a** as a yellow solid (70 mg, 0.25 mmol, 72%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.76 (br s, 1H), 7.64 (d, ^3J = 9.0 Hz, 1H), 7.50 (d, ^3J = 8.5 Hz, 1H), 7.19 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H), 7.08 (dd, ^3J = 9.0 ^4J = 2.5 Hz, 1H), 6.73 (d, ^4J = 2.0 Hz, 1H), 3.45 (q, ^3J = 7.0 Hz, 4H), 1.22 (t, ^3J = 7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 146.5, 136.8, 129.2, 129.0, 127.8, 124.7, 124.6, 120.4, 116.1, 104.2, 44.7 (2C), 12.8 (2C). HRMS (ESI$^+$): m/z calcd for $C_{14}H_{17}NBr$: 278.0539 [M + H]$^+$; found 278.0542.

*1-(7-Bromonaphthalen-2-yl)-1H-pyrrole (**5b**).* Following general procedure GP-A, eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.54) provided **5b** as a yellow solid (79 mg, 0.29 mmol, 83%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.87 (br s, 1H), 7.74 (d, ^3J = 9.0 Hz, 1H), 7.58 (d, ^3J = 9.0 Hz, 1H), 7.56 (s, 1H), 7.47 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H), 7.42 (dd, ^3J = 8.5 ^4J = 2. Hz, 1H), 7.10 (t, J = 2.0 Hz, 2H), 6.32 (t, J = 2.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 139.1, 135.1, 129.8, 129.7 (2C), 129.5, 129.0, 121.3, 120.5, 119.5 (2C), 116.3, 111.1 (2C). HRMS (ESI$^+$): m/z calcd for $C_{14}H_{11}NBr$: 272.0069 [M + H]$^+$; found 272.0070.

*N^2,N^2,N^7,N^7-Tetraethylnaphthalene-2,7-diamine (**5c**).* Following general procedure GP-B, eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.29) provided **5c** as a yellow solid (62 mg, 0.23 mmol, 65%). ^{1}H NMR (200 MHz, TFA-d^1, δ): 8.30 (d, ^3J = 9.0 Hz, 2H, H4,5), 8.20 (s, 2H, H1,8), 7.73 (d, ^3J = 9.0 Hz, 2H, H3,6), 3.85 (q, ^3J = 6.5 Hz, 8H, $4CH_2$), 1.23 (t, ^3J = 6.5 Hz, 12H, $4CH_3$). ^{13}C NMR (50 MHz, TFA- d^1, δ): 137.8 (2C), 136.5, 134.9 (2C), 134.8, 125.3 (2C), 121.5 (2C), 57.4 (4C), 11.3 (4C). HRMS (ESI$^+$): m/z calcd for $C_{18}H_{27}N_2$: 271.2169 [M + H]$^+$; found 271.2170. Mp: 120−122 °C.

*(Naphthalene-2,7-diyl)di-1H-pyrrole (**5d**).* Following general procedure GP-B, eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.5) provided **5d** as a yellow solid (73 mg, 0.28 mmol, 81%).^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.81 (d, ^3J = 9.0 Hz, 2H, H4,5), 7.68 (br s, 2H, H1,8), 7.47 (dd, ^3J = 9.0 Hz, ^4J = 2.0 Hz, 2H, H3,6), 7.15 (t, J = 2.0 Hz, 4H, NCHpyr), 6.33 (t, J = 2.0 Hz, 4H, CHpyr). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 139.3 (2C), 134.6, 129.6 (2C), 129.4, 119.9 (2C), 119.6 (4C), 117.0 (2C), 111.0 (4C). GC-MS (m/z): 258.1 [M]$^+$. Mp: 205−207 °C.

*4-(7-(1H-Pyrrol-1-yl)naphthalen-2-yl)morpholine (**5e**).* Following general procedure GP-C, eluent for flash chromatography (PE/EA = gradient up to 95:5, R_f = 0.13) provided **5e** as a yellow solid (62 mg, 0.22 mmol, 64%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.79 (d, ^3J = 8.5 Hz, 1H), 7.76 (d, ^3J = 8.5 Hz, 1H), 7.66 (d, ^4J = 2.0 Hz, 1H), 7.41 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H), 7.26 (m, 1H), 7.23 (t, ^3J = 2.0 Hz, 2H), 7.13 (br s, 1H), 6.41 (t, ^3J = 2.0 Hz, 2H), 3.94 (t, ^3J = 5.0 Hz, 4H), 3.30 (t, ^3J = 5.0 Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 150.1, 138.9, 135.2, 129.2, 128.8, 126.6, 119.7 (2C), 118.5, 117.8, 116.5, 110.6 (2C), 109.7, 67.0 (2C), 49.6 (2C). HRMS (ESI$^+$): m/z calcd for $C_{18}H_{19}ON_2$: 279.1492 [M + H]$^+$; found 279.1494. Mp: 182−184 °C.

*6-Bromo-N,N-dibutylpyridin-2-amine (**6a**).*[18] Following general procedure GP-A, eluent for flash chromatography (CyHex, R_f = 0.21) provided **6a** as an amorphous yellow solid (98 mg, 0.34 mmol, 88%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.18 (t, ^3J = 8.0 Hz, 1H, H4), 6.58 (d, ^3J = 8.0 Hz, 1H, H5), 6.29 (d, ^3J = 8.0 Hz, 1H, H3), 3.39 (t, ^3J = 7.5 Hz, 4H, $N(CH_2)_2$), 1.55 (quint, ^3J = 7.5 Hz, 4H, $N(CH_2CH_2)_2$), 1.43−1.25 (m, 4H, $(CH_3CH_2)_2$), 0.95 (t, ^3J = 7.0 Hz, 6H, $2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 156.8, 140.4, 139.0, 113.5, 103.7, 48.4 (2C), 29.7 (2C), 20.3 (2C), 14.1 (2C). GC-MS (m/z): 286.1 [M+2]$^{+\cdot}$.

*6-Bromo-N,N-diethylpyridin-2-amine (**6b**).*[19] Following general procedure GP-A, eluent for flash chromatography (PE/DCM = gradient up to 9:1, R_f = 0.5) provided **6b** as an amorphous yellow solid (84 mg, 0.36 mmol, 94%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.10 (t, ^3J = 8.0 Hz, 1H, H4), 6.50 (d, ^3J = 8.0 Hz, H5), 6.23 (d, ^3J = 8.0 Hz, 1H, H3), 3.36 (q, ^3J = 7.0 Hz, 4H, $2CH_2$), 1.06 (t, ^3J = 7.0 Hz, 6H, $2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 157.5, 140.4, 139.1, 113.6, 103.6, 42.5 (2C), 12.8 (2C). GC-MS (m/z): 230.1 [M+2]$^{+\cdot}$.

*N^2,N^2,N^6,N^6-Tetraethylpyridine-2,6-diamine (**6c**).*[20] Following general procedure GP-B, eluent for flash chromatography (PE/Et_2O = gradient up to 98:2, R_f = 0.67) provided **6c** as an amorphous yellow solid (69 mg, 0.31 mmol, 80%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.23 (t, ^3J = 8.0 Hz, 1H, H4), 5.72 (d, ^3J = 8.0 Hz, 2H, H3,5), 3.47 (q, ^3J = 7.0 Hz, 8H, $4CH_2$), 1.16 (t, ^3J = 7.0 Hz, 12H, $4CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 156.8 (2C, C2,6), 138.4 (C4), 91.9 (2C, C3,5), 42.5 (4C, NCH_2), 13.4 (4C, $4CH_3$). GC-MS (m/z): 222.2 [M]$^{+\cdot}$.

*2,6-Di(pyrrolidin-1-yl)pyridine (**6d**).*[7c] Following general procedure GP-B, eluent for flash chromatography (PE/Et_2O = gradient up to 95/5, R_f = 0.47) provided **6d** as an amorphous yellow solid (70 mg, 0.32 mmol, 83%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.25 (t, ^3J = 8.0 Hz, 1H, H4), 5.64 (d, ^3J = 8.0 Hz, 2H, H3,5), 3.43 (t, ^3J = 6.5 Hz, 8H, $2N(CH_2)_2$), 1.95 (q, ^3J = 6.5 Hz, 8H, $2N(CH_2CH_2)_2$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 157.0 (2C, C2,6), 138.1 (C4), 93.1 (2C, C3,5), 46.5 (4C, NCH_2), 25.7 (4C, CH_2). GC-MS (m/z): 217.2 [M]$^{+\cdot}$.

*N,N-Dibutyl-6-morpholinopyridin-2-amine (**6e**).* Following general procedure GP-C, eluent for flash chromatography (PE/Et_2O = gradient up to 9:1, R_f = 0.48) provided **6e** as an amorphous yellow solid (108 mg, 0.27 mmol, 71%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.28 (t, ^3J = 8.0 Hz, 1H, H4), 5.86 (d, ^3J = 8.0 Hz, 2H, H3), 5.84 (d, ^3J = 8.0 Hz, 2H, H5), 3.81 (t, ^3J = 5.0 Hz, 4H, $(CH_2)_2O$), 3.44 (t, ^3J = 5.0 Hz, 4H, $(CH_2)_2N_{morph}$), 3.38 (t, ^3J = 7.5 Hz, 4H, $N(CH_2)_2$), 1.57 (quint, ^3J = 7.5 Hz, 4H, $N(CH_2CH_2)_2$), 1.33 (m, 4H, $(CH_3CH_2)_2$), 0.94 (t, ^3J = 7.5 Hz, 6H, $2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 158.7, 156.9, 138.7, 95.4, 92.9, 67.0 (2C), 48.7 (2C), 45.8 (2C), 30.1 (2C), 20.5 (2C), 14.2 (2C). HRMS (ESI$^+$): m/z calcd for $C_{17}H_{30}ON_3$: 292.2383 [M + H]$^+$; found 292.2384.

*5-Bromo-N,N-diphenylthiophen-2-amine (**7a**).* Following general procedure GP-A, eluent for flash chromatography (PE/Et_2O = gradient up to 99/1, R_f = 0.55) provided **7a** as an amorphous yellow solid (72 mg, 0.22 mmol, 54%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.40−7.33 (m, 5H), 7.23−7.01 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 146.5, 129.4, 129.3, 123.6, 123.0, 121.9, 108.8. GC-MS (m/z): 330.2 [M + 2]$^{+\cdot}$.

*N^2,N^5-Dimethyl-N^2,N^5-diphenylthiophene-2,5-diamine (**7b**).* Following general procedure GP-B provided **7b** as an amorphous yellow solid (50 mg, 0.17 mmol, 42%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.20 (dd, ^3J = 7.5 Hz, ^4J = 2.0 Hz, 2H, Hphenyl), 6.95−6.82 (m, 8H, Hphenyl), 6.62 and 6.61 (d each, ^4J = 1.5 Hz, 2H, Hthiophene), 3.31 (s, 6H, $2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 153.7 (C2, C5), 149.4 (2C-*i*-Ph), 129.1 (4C-*m*-Ph), 125.9, 120.0 (C-*p*-Ph), 119.6 (C-*p*-Ph), 118.8, 116.4, 42.1 ($2CH_3$). GC-MS (m/z): 294.1 [M+2]$^{+\cdot}$.

7-(Benzo[*c*][1,2,5]thiadiazol-5-yl)-9,9-dimethyl-*N*-phenyl-9*H*-fluoren-2-amine (8) Requires the Preparation of Two Reactions in Two Previously Dried Tubes. *First Tube.* $Pd(OAc)_2$ (3 mg, 0.011 mmol, 4 mol %), *t*-BuONa (30 mg, 0,32 mmol, 1.1 equiv), and BINAP (21 mg, 0,034 mmol, 12 mol %) were added to a previously dried reaction tube containing a magnetic bar. The tube was purged with argon for three cycles using Schlenk technique. The mixture was dissolved in 3 mL of toluene (0.1 M) and stirred for 15 min at rt under argon. Then, dibromofluorene **1** (100 mg, 0,287 mmol, 1.0 equiv) was added followed by 15 min further stirring at 100 °C. Finally, aniline (30 mg, 0,32 mmol, 1.1 equiv) was added, and the reaction mixture was heated at 100 °C in an oil bath. The reaction was monitored by TLC and GCMS until bis-aminated product started to appear (14 h).

Second Tube. $Pd(OAc)_2$ (4 mg, 0,017 mmol, 4 mol % relative to 1.5 equiv of 5-bromo-2,1,3-benzothiadiazole), *t*-BuONa (45 mg, 0,47 mmol, 1.1 equiv), and BINAP (32 mg, 0,051 mmol, 12 mol %) were added to a previously dried reaction tube containing a magnetic bar. The tube was purged with argon for three cycles using Schlenk technique. The mixture was dissolved in 4 mL of toluene (0.1 M) and stirred for 15 min at rt under argon. Then, 5-bromo-2,1,3-benzothiadiazole (92 mg, 0,43 mmol, 1.5 equiv) was added followed

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by 15 min further stirring at 100 °C. Finally, bis(tributyltin) (249 mg, 0,43 mmol, 1.5 equiv) was added, and the reaction mixture was heated at 100 °C in an oil bath for 4 h. Note: this second reaction tube was prepared around 10 h after the beginning of the first reaction. Then, another loading of the catalytic system (4 mol % [Pd]/12 mol % L/1.1 equiv *t*-BuONa) was re-added to the first reaction tube followed by the content of the second tube (2 equiv). The final mixture was stirred at 100 °C overnight. The reaction was cooled down to rt, quenched with NaOH (1 N), and stirred for additional 30 min. The organic layer was extracted with DCM (2×), and the combined extracts were washed with water (3×), dried over magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluted with CyHex/EA (4/1, v/v) to provide compound **8** (61 mg, 51%) as a bright-yellow solid. Purification by RP-HPLC provided an analytical sample for photophysical characterization; (apparatus: WatersTM 600 Controller with WatersTM 996 Photodiode Array Detector and Jasco LC-Net II/ADC, semipreparative column: Clarity 5 μ Oligo-RP column 250 × 10 mm Phenomenex, flow rate 2.5 mL/min, using the following gradient system: 25% A − (5 min)→ 5% A/95% B − (25 min)→ 100% B − (10 min) with A = 0.25 CH_3CN:0.75 Milli-Q water and B = CH_3CN. ^{1}H NMR (500 MHz, CD_2Cl_2, δ): 8.24 (d, ^4J = 1.0 Hz, 1H), 8.07 (d, ^3J = 8.0 Hz, 1H), 8.01 (dd, ^3J = 8.0 Hz, ^4J = 1.0 Hz, 1H), 7.78 (d, ^4J = 1.0 Hz, 1H), 7.76 (d, ^3J = 8.0 Hz, 1H), 7.31 (t, ^3J = 7.5 Hz, 2H), 7.22 (d, ^4J = 1.5 Hz, 1H), 7.15 (dd, ^3J = 7.5 Hz, ^4J = 1.0 Hz, 2H), 7.08 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H), 6.96 (t, ^3J = 7.5 Hz, 1H), 1.54 (s, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2, δ): 156.3, 156.1, 154.7, 154.6, 143.7, 143.5, 143.3, 140.2, 137.6, 131.9, 130.7, 129.8, 127.0, 122.0, 121.7, 121.6, 121.5, 119.9, 118.3, 118.3, 117.0, 112.2, 47.4, 27.5. HRMS (ESI$^+$): *m*/*z* calcd for $C_{27}H_{22}N_3S$: 420.1529 $[M + H]^+$; found 420.1530.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01248.

General methods and characterization (mass and NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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