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General synthetic methods for the preparation of pinwheel receptors

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Abstract—The synthesis of bis-trityl diynes, used as cooperative fluorescent chemosensors, is described. The most convenient sequence for the preparation of the sensor framework was found to be intolerant of most functionality. Therefore, an unfunctionalized framework is constructed and recognition elements are selectively installed via electrophilic substitution on an electronically differentiated key intermediate. A divergent synthesis of a general class of chemical sensors emerges. This synthetic method is highlighted by its simplicity and modularity allowing for the introduction of various recognition elements and fluorophores. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Fluorescent chemosensors have become an increasingly valuable tool for real time detection of analytes in their native environment.[1] Generally speaking, a chemosensor is a receptor with a fluorescent tag that modulates its fluorescent properties upon binding of an analyte to the receptor. Many schemes have been developed for converting a binding event into a fluorescent signal.[2] We have recently reported a novel chemical sensor framework in which cooperativity is used to enhance the affinity of the sensor for its analyte.[3] In this sensor, the fluorescent groups are part of the recognition element and fluorescence quenching correlates with metal ion binding. With a view toward generating a general sensor platform, we have developed a second-generation cooperative chemical sensor (compound **1**, Fig. 1) in which the recognition elements are separate from the fluorescent read-out.[4] In this sensor design, binding of the analyte (A) between the pairs of recognition elements (R) causes an interaction between a pair of fluorophores (Fluor) which is read spectroscopically. It is anticipated that this framework will serve as a convenient platform for sensing various analytes, as any binding event should register a fluorescent response regardless of the recognition element employed or the analyte targeted. In order for such a sensor platform to be truly general, a divergent synthetic procedure is required. Ideally, a common synthetic intermediate would be used to append any recognition element and any fluorophore. Herein is described our approach to such a divergent synthetic strategy.

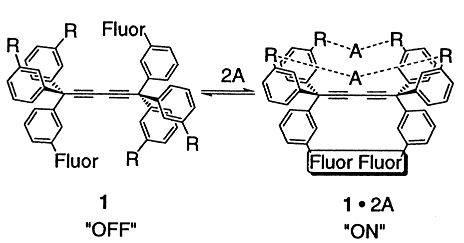
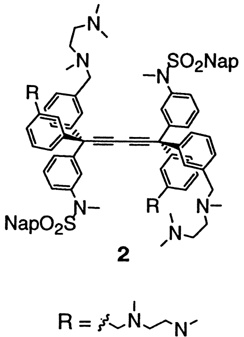


Figure 1. Two site cooperative chemosensor, with an integrated fluorescent reporter. R=Recogntion element, Fluor=fluorescent Group, A=analyte.

2. Results and discussion

Compound **1** is a bis-trityl butadiyne in which each trityl group is substituted with two recognition elements (R) and one fluorophore (Fluor). Prior to this work, only the parent unsubstituted bistritylbutadiyne was known.[5] Initially, this class of compounds appeared to be readily accessible via Glaser coupling[6] of the corresponding monotritylacetylene. However, the most convenient preparation of trityl acetylene compounds entails both strong acid and strong base conditions, limiting the functionality that can be incorporated into the recognition elements or fluorophores.[7] This



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Keywords: molecular recognition; fluorescent chemosensors; receptors; trityl; triphenylmethyl.

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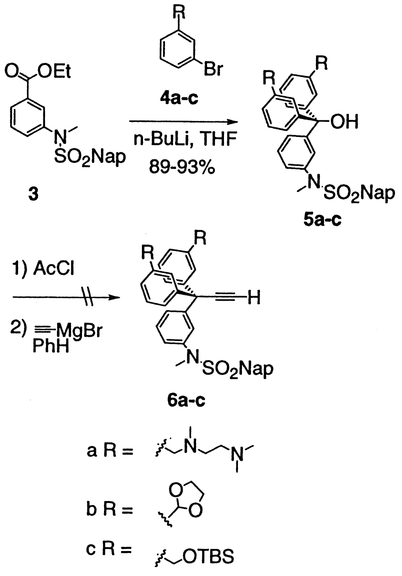
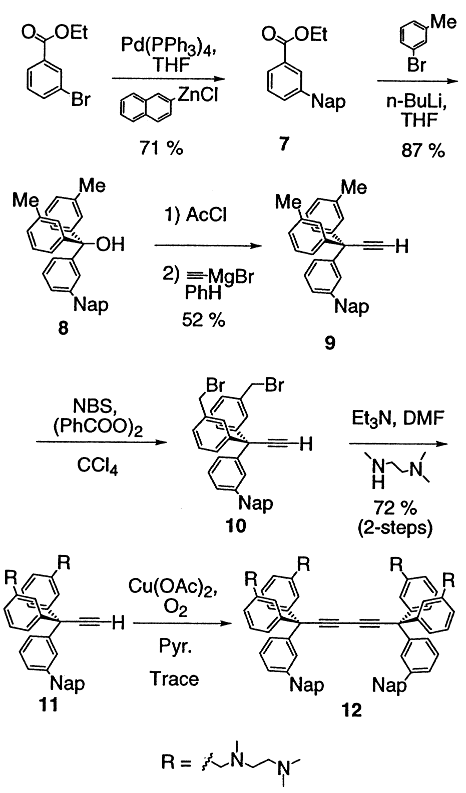


Scheme 1.



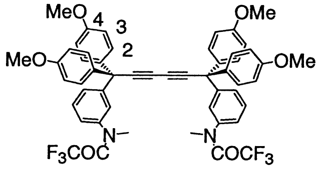
Scheme 2.

limitation is particularly constraining in light of the sensitivity of many common fluorophores. The synthetic procedure for compound **1** must address these limitations with a view toward incorporating various recognition elements as well as fluorophores.

As a proof of concept, compound **2** was chosen as the initial synthetic target. Ethylene diamine groups were designed as recognition elements for metal ions[2a] and naphthyl sulfonanilides were designed as fluorescent groups. The naphthyl sulfonanilide was chosen because aryl sulfonanilides are stable to strong acid and strong base conditions. Moreover, aryl sulfonanilides can be deprotected under reductive conditions and the aniline nitrogen which results can then be used as a handle to attach different fluorophores.

The trityl acetylene from which compound **2** would be derived, could be easily obtained from the corresponding trityl alcohol, however, the conditions are typically harsh: chlorination under acidic conditions followed by addition of acetylene Grignard at elevated temperature.[8] Unfortunately, variously substituted trityl alcohols **5a–c** (Scheme 1) prepared en route to compound **2** failed to provide the corresponding trityl acetylenes **6a–c** due to the instability of the functional groups to the reaction conditions. Neither amines, dioxolanes, nor protected benzylic alcohols provided clean products despite attempts at using more mild conditions.

Recognizing that benzylic functionality was not tolerated in this system, simple methyl substituents were then used, anticipating that free radical halogenation followed by alkylation would produce the desired recognition elements. We reasoned that the methyl group of the *N*-methyl sulfonanilide might participate in a radical substitution reaction, therefore, the fluorophore was changed to a simple naphthyl (Scheme 2). Thus, ethyl-3-bromobenzoate was coupled to the zincate of 2-bromonaphthalene to form naphthyl ester **7**,[9] which was converted to trityl alcohol **8**. Now, the relatively unfunctionalized alcohol **8** was converted to trityl acetylene **9** in moderate yield. Free radical bromination of compound **9** gave dibromide **10**. Displacement of the bromides of **10** with *N*,*N*,*N′*-trimethyl ethylene diamine yielded the binding group appended trityl acetylene **11** in good overall yield. We were disappointed to find that Glaser coupling of **11** yielded only trace amounts of compound **12**, though a variety of conditions were tested.[10,11] The low yield of the Glaser coupling was attributed to oxidation of the amine recognition elements.



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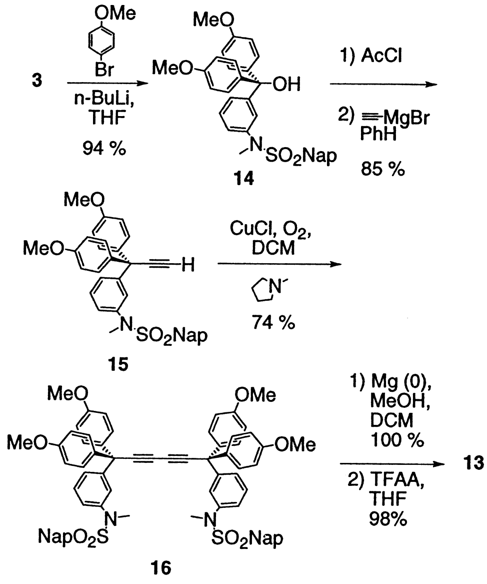
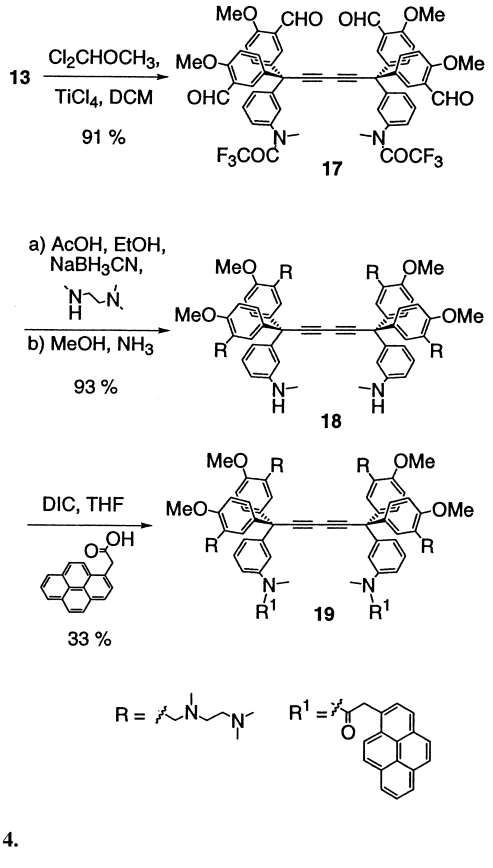
Recognizing the low functional group tolerance of the synthetic procedure, we explored alternative methods of introducing the required functionality at a later stage. We designed intermediate **13** with four anisole groups and a pair of protected aniline groups. The advantage of this compound is that the recognition elements could be installed via electrophilic chemistry on the anisole rings, and the fluorophores attached at the aniline nitrogens. The C3 position of the anisole groups is most reactive toward electrophiles since the trifluoroacetanilide deactivates the remaining aromatic groups. Furthermore, the butadiyne spacer should be unreactive toward electrophiles, as it is sufficiently sterically encumbered. Importantly, the anisole groups should be compatible with conditions for formation of the trityl acetylene. This methodology was particularly attractive because the wide range of electrophilic aromatic



Scheme 3.

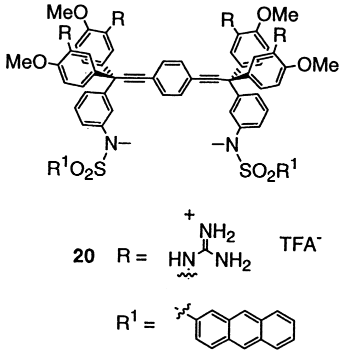
substitution chemistry would lend itself to a general strategy for incorporation of recognition elements.

Thus, intermediate **13** was synthesized as shown in Scheme 3. Trityl alcohol **14** was prepared from ester **3**[12] and was smoothly converted to trityl acetylene **15**. The ability of the methoxy groups to stabilize the carbocation intermediate greatly facilitated the chlorination/Grignard addition sequence resulting in higher overall yield. Glaser coupling of compound **15** gave the tetraanisole intermediate **16** in good yield. Compound **16** was deprotected under mild reductive conditions.[13] The resulting anilines were reprotected as the trifluoroacetanilides to produce compound **13** in good overall yield (Scheme 4).



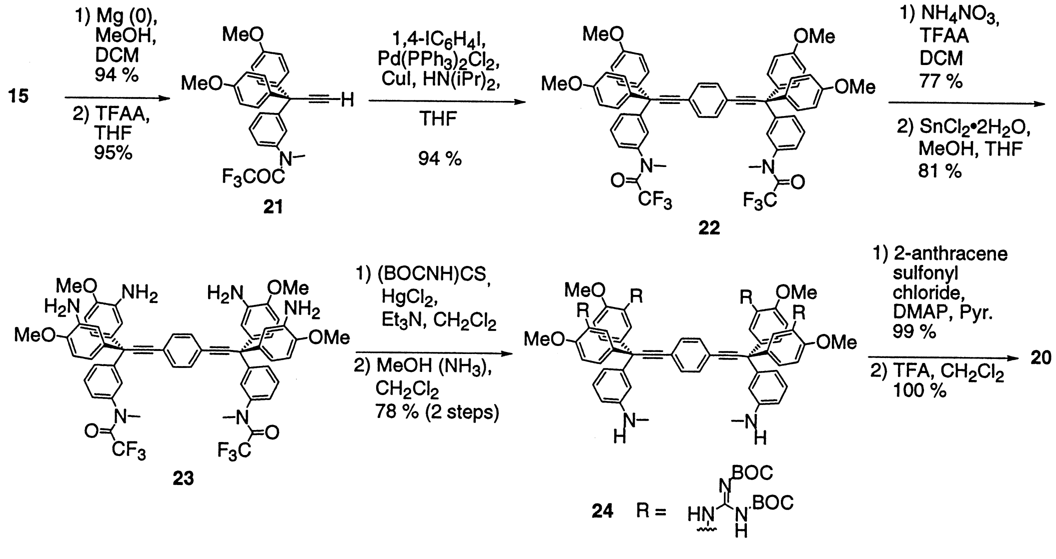
Scheme 4.

With the key intermediate **13** in hand, electrophilic formylation produced the tetraaldehyde **17** with no sign of any other regiochemical isomers. These results validated our supposition that the methoxy substituents would be amenable to the trityl acetylene preparation procedure and would serve as a handle to install the necessary functional groups after construction of the framework. Reductive amination yielded compound **18** following deprotection of the trifluoroacetanilides. Any number of amine reactive fluorescent groups could be appended at this stage.[14] For example, pyrene acetic acid was coupled to compound **18** in order to yield compound **19** which acts as a sensor for metal ions. Thus, compound **13** represents a key intermediate in the synthesis of bis-tritylbutadiynes as the anisole groups allow for the selective installation of binding groups via electrophilic aromatic substitution, and the suitably protected aniline groups can be unmasked, and condensed with a variety of fluorescent groups.



Having successfully prepared a metal ion sensor, we wanted to show that this strategy would be generally applicable to other sensors with different recognition elements and fluorophores. For example, compound **20** was designed to bind dicarboxylates in a cooperative fashion similar to sensor **19**. This compound differs from **19** in that it has a larger phenyldiyne spacer, guanidinium recognition elements and anthracene fluorophores. Yet, this sensor could be constructed from an electronically differentiated intermediate using the same synthetic strategy as described earlier.

The synthesis of compound **20** is shown in Scheme 5. In this case, the naphthalene sulfonanilide of compound **15** was exchanged with a trifluoroacetanilide to give compound **21**. This trityl acetylene was coupled to 1,4-diiodobenzene under Sonogashira conditions[15] to give the complete skeleton **22** in excellent yield. Nitration of **22** with ammonium nitrate and trifluoroacetic anhydride gave the desired tetranitro compound with no trace of undesired regioisomers. Reduction of the nitro groups with Sn(II) gave tetraamine **23**. The guanidine recognition elements were then installed by reaction with bis-BOC thiourea in the presence of mercury (II) chloride.[16] Removal of the trifluoroacetanilides gave the protected tetra guanidine **24**. Addition of the anthracenesulfonyl chloride appended the fluorophores



Scheme 5.

and deprotection of the BOC groups gave the final sensor **20**.[17] Thus, the generality of this strategy was demonstrated.

3. Conclusions

In conclusion, we have developed the synthesis of a novel class of fluorescent, cooperative chemical sensors based on two differing bis-trityl diyne core structures. The frameworks are prepared by oxidative or palladium catalyzed coupling of a trityl acetylene, which is derived from the corresponding trityl alcohol. Although the sequence to bis-trityl diynes is efficient, it is intolerant of virtually any functionality. Therefore, we developed two key intermediates, **13** and **22**, which are differentiated electronically such that recognition elements could be installed via electrophilic substitution chemistry and fluorophores could be appended to an amine functionality. This synthetic method is divergent in that different types of sensors can in principle be derived from a common intermediate. The preparation of various sensors based on this methodology is currently underway in our laboratory.

4. Experimental

4.1. General

All reactions were carried out in dried glassware under argon atmosphere unless otherwise noted. Tetrahydrofuran (THF) and benzene were distilled from sodium benzophenone ketyl under argon immediately before use. Methylene chloride (CH_2Cl_2) and triethyl amine (Et_3N) were distilled from CaH_2 under argon immediately before use. Flash chromatography[18] was performed with 32–63 μm silica gel. All melting points are uncorrected. NMR spectra were recorded on a Bruker WP-200, AC-200, DPX-300, AMX-360, DRX-400, or AMX-500 in $CDCl_3$ using TMS as a reference unless otherwise noted.

4.1.1. Compound 4a. A solution of 3-bromobenzaldehyde (1.0 mL, 8.5 mmol), trimethylethylene diamine (2.2 mL, 17.1 mmol), acetic acid (10 mL), and abs. ethanol (90 mL) was stirred at room temperature, over 4 Å mol sieves for 6.5 h. The reaction was cooled to 0°C, and $NaBH_4$ (1.61 g, 42.7 mmol) was added slowly. The reaction was allowed to stir at room temperature for 10 h. The reaction was poured slowly over ice water, and then made basic with 10 M NaOH. The aqueous layer was extracted with 3×25 mL $CHCl_3$, and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting residue was purified via flash chromatography (ammoniated MeOH/$CHCl_3$, 10:90). The title compound **4a** was afforded as a yellow oil (2.25 g, 8.3 mmol, 97% yield); ^{1}H NMR (360 MHz) δ 2.21 (s, 6H), 2.22 (s, 3H), 2.40–2.50 (m, 4H), 3.47 (s, 2H), 7.16 (t, J=7.7 Hz, 1H), 7.24 (d, J=7.7 Hz, 1H), 7.36 (d, J=7.8 Hz, 1H), 7.49 (s, 1H); ^{13}C NMR (75 MHz) δ 42.9, 46.2, 55.6, 57.8, 62.7, 122.8, 127.9, 130.1, 130.4, 132.2, 141.9; IR (neat) 3058, 2941, 2766, 1594, 1569, 1464, 1360, 1263, 1125, 1068, 1030, 690, 670 cm^{-1}; HRMS calcd for $C_{12}H_{20}NBr$ (M+H$^+$): 271.0810, found: 271.0812.

4.1.2. Compound 5a. *n*-BuLi (890 μL, 2.22 mmol, 2.5 M in hexanes) was added to a stirred solution of THF (25 mL) and compound **4a** (617 mg, 2.27 mmol) at −78°C. The reaction mixture was allowed to stir for 20 min, followed by addition of compound **3** (210 mg, 0.57 mmol) at −78°C. The reaction mixture was allowed to warm to 0°C, and quenched with $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. Flash chromatography (ammoniated MeOH/$CHCl_3$, 10:90) afforded the title compound **5a** as a yellow oil (360 mg, 0.51 mmol, 89% yield); ^{1}H NMR (360 MHz) δ 2.14 (s, 12H), 2.16 (s, 6H), 2.36–2.42 (m, 8H), 3.14 (s, 3H), 3.44 (s, 4H), 6.88 (d, J=7.7 Hz, 2H), 7.00 (s, 1H), 7.08–7.27 (m, 9H), 7.37 (dd, J=8.6, 1.8 Hz, 1H), 7.55–7.65 (m, 2H), 7.72 (d, J=8.7 Hz, 1H), 7.84–7.87 (m, 2H), 8.14 (s, 1H); ^{13}C NMR (90 MHz) δ 38.6, 42.9, 46.2, 55.4, 57.7, 63.1, 81.9, 123.6, 126.1, 126.3, 127.0, 127.5, 127.8, 128.0, 128.3, 128.5, 128.7, 128.8, 129.1, 129.2, 129.4, 129.7, 132.4, 134.0, 135.2, 139.1, 141.5, 146.9; IR (neat) 3056, 2945, 2777, 1600, 1463, 1349, 1266, 1165, 1029, 909, 787, 733, 653 cm^{-1}; HRMS calcd for $C_{42}H_{54}N_5O_3S$ $(M+Na^+)$: 708.3947, found: 708.3962.

4.1.3. Compound 5b. *n*-BuLi (510 μL, 1.28 mmol, 2.5 M in hexanes) was added to a stirred solution of THF (15 mL) and 2-(3-bromophenyl)-1,3-dioxolane (0.20 mL, 1.35 mmol) at −78°C. The reaction mixture was allowed to stir for 20 min, followed by addition of compound **3** (200 mg, 0.54 mmol) at −78°C. The reaction mixture was allowed to warm to 0°C, and quenched with NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. Flash chromatography (EtOAc/hex, 50:50) afforded the title compound **5b** as a white amorphous solid (314 mg, 0.50 mmol, 93% yield); ^1H NMR (300 MHz) δ 2.92 (s, 1H), 3.11 (s, 3H), 3.90–4.06 (m, 8H), 5.68 (s, 2H), 36.92 (s, 1H), 7.01 (d, $J=7.9$ Hz, 2H), 7.13–7.25 (m, 5H), 7.33–7.38 (m, 5H), 7.53–7.64 (m, 2H), 7.71 (d, $J=8.7$ Hz, 1H), 7.84 (t, $J=7.2$ Hz, 2H), 8.14 (s, 1H); ^{13}C NMR (90 MHz) δ 38.6, 65.7, 81.9, 104.0, 123.6, 125.9, 126.0, 126.3, 126.8, 127.4, 127.8, 128.3, 128.4, 128.9, 129.1, 129.3, 129.5, 129.7, 134.0, 135.2, 138.2, 141.7, 146.8, 147.9; IR (neat) 3475, 3058, 3017, 2974, 2889, 2251, 1589, 1503, 1483, 1438, 1348, 1166. 1074, 966, 908, 798, 652 cm^{-1}; HRMS calcd for $C_{36}H_{32}NO_6S$ $(M-OH)$: 606.1950, found: 606.1954.

4.1.4. Compound 5c. *n*-BuLi (460 μL, 1.15 mmol, 2.5 M in hexanes) was added to a stirred solution of THF (10 mL) and 3-(*t*-butyldiphenylsiloxymethyl)-bromobenzene[19] (506 mg, 1.19 mmol) at −78°C. The reaction mixture was allowed to stir for 20 min, followed by addition of compound **3** (177 mg, 0.48 mmol) at −78°C. The reaction mixture was allowed to warm to 0°C, and quenched with NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. Flash chromatography (EtOAc/hex, 30:70) afforded the title compound **5c** as a white amorphous solid (445 mg, 0.44 mmol, 91% yield); ^1H NMR (200 MHz) δ 1.01 (s, 18H), 2.54 (s, 1H), 3.11 (s, 3H), 4.69 (s, 4H), 6.99–7.02 (m, 3H), 7.12–7.24 (m, 7H), 7.26–7.40 (m, 15H), 7.49 (td, $J=7.3$, 1.6 Hz, 1H), 7.55 (td, $J=6.8$, 1.3 Hz, 1H), 7.60–7.63 (m, 9H), 7.76 (d, $J=3.7$ Hz, 1H), 7.78 (d, $J=3.3$ Hz, 1H), 8.10 (s, 1H); ^{13}C NMR δ 19.7, 27.3, 38.6, 65.9, 82.1, 123.6, 125.5, 125.7, 126.6, 126.8, 127.5, 127.8, 128.1, 128.3, 128.4, 128.7, 129.1, 129.2, 129.5, 129.6, 130.1, 132.3, 133.8, 133.8, 133.9, 135.2, 136.0, 141.3, 141.7, 146.8, 148.3; IR (neat) 3499, 3070, 2930, 2857, 1600, 1484, 1427, 1349, 1165, 1112, 1074, 909, 823, 703 cm^{-1}; HRMS calcd for $C_{64}H_{65}NO_5SSi_2Na$ $(M+Na^+)$: 1038.4020, found: 1038.4046.

4.1.5. Compound 7. *n*-BuLi (8.8 mL, 22.0 mmol, 2.5 M in hex) was added to a stirred solution of 2-bromonaphthalene (4.33 g, 20.9 mmol) and THF (225 mL) at −78°C. The reaction was allowed to stir at −78°C for 15 min $ZnCl_2$ (25.1 mL, 25.1 mmol, 1.0 M in diethyl ether) was added, and the reaction was warmed to rt. To this solution, $Pd(PPh_3)_4$ (2.43 g, 2.1 mmol) and ethyl-3-bromobenzoate (1.67 mL, 10.5 mmol) was added, and the reaction was stirred at 65°C for 48 h. The reaction was quenched with NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting residue was purified via flash chromatography (EtOAc/hex, 1:99) to afford the title compound **7** as a white crystalline solid (2.06 g, 7.42 mmol, 71% yield), mp 101–103°C; ^1H NMR (200 MHz) δ 1.44 (t, $J=7.1$ Hz, 3H), 4.44 (q, $J=7.2$ Hz, 2H), 7.49–7.60 (m, 3H), 7.77 (dd, $J=1.9$, 8.6 Hz, 1H), 7.86–7.97 (m, 4H), 8.06 (dt, $J=1.4$, 7.7 Hz, 2H), 8.09 (d, $J=1.0$ Hz, 1H), 8.41 (t, $J=1.8$ Hz, 1H); ^{13}C NMR δ 14.8, 61.5, 125.7, 126.4, 126.6, 126.9, 128.1, 128.7, 128.8, 128.9, 129.0, 129.3, 131.5, 132.1, 133.2, 134.0, 137.9, 141.7, 167.0; IR (neat) 3047, 2979, 1716, 1584, 1366, 1302, 1250, 1224, 1108, 813, 756 cm^{-1}; HRMS calcd for $C_{19}H_{17}O_2$ $(M+H^+)$: 277.1228, found: 277.1215.

4.1.6. Compound 8. *n*-BuLi (6.4 mL, 15.9 mmol, 2.5 M in hexanes) was added to a stirred solution of THF (175 mL) and 3-bromotoluene (2.15 mL, 17.7 mmol) at −78°C. The reaction mixture was allowed to stir for 20 min, followed by addition of compound **7** (979 mg, 3.54 mmol) at −78°C. The reaction mixture was allowed to warm to 0°C, and quenched with NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. Flash chromatography (EtOAc/hex, 5:95) afforded the title compound **8** as a white amorphous solid (1.28 g, 3.08 mmol, 87% yield); ^1H NMR (360 MHz) δ 2.33 (s, 6H), 2.86 (s, 1H), 7.05–7.12 (m, 4H), 7.18–7.25 (m, 5H), 7.41 (t, $J=7.6$ Hz, 1H), 7.46 (d, $J=4.3$ Hz, 1H), 7.49 (t, $J=1.2$ Hz, 1H), 7.62–7.70 (m, 2H), 7.75 (t, $J=1.8$ Hz, 1H), 7.82–7.90 (m, 3H), 7.98 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (100 MHz) δ 21.6, 82.1, 125.2, 125.6, 125.8, 125.9, 126.2, 126.21, 126.8, 127.1, 127.6, 127.8, 128.1, 128.14, 128.3, 128.31, 128.4, 132.5, 133.6, 137.6, 138.4, 140.6, 146.8, 147.6; IR (neat) 3456, 3055, 2920, 1601, 1486, 1443, 1320, 1140, 1017, 908, 792, 730, 707 cm^{-1}; HRMS calcd for $C_{31}H_{26}ONa$ $(M+Na^+)$: 437.1881, found: 437.1897.

4.1.7. Compound 9. A solution of compound **8** (931 mg, 2.24 mmol) and acetyl chloride (20 mL) was stirred at room temperature for 3 h. The solvent was removed in vacuo, and the resulting solid was dried under high vacuum for 1 h. The solid was redissolved in benzene (25 mL) and ethynylmagnesium bromide (22.4 mL, 11.22 mmol, 0.5 M in THF) was added. The reaction mixture was stirred at rt for 48 h. The reaction was quenched with NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. Flash chromatography (ether/hex, 1:99) afforded the title compound **9** (489 mg, 1.16 mmol, 52%), as a viscous oil; ^1H NMR (200 MHz) δ 2.31 (s, 6H), 2.75 (s, 1H), 7.03–7.23 (m, 9H), 7.39 (t, $J=7.8$ Hz, 1H), 7.44–7.49 (m, 2H), 7.59–7.68 (m, 2H), 7.84 (t, $J=1.7$ Hz, 1H), 7.8–7.88 (m, 3H), 8.02 (d, $J=0.86$ Hz, 1H); ^{13}C NMR (100 MHz) δ 22.06, 55.9, 74.0, 90.4, 126.0, 126.2, 126.3, 126.7, 128.0, 128.2, 128.2, 128.6, 128.7, 128.7, 128.8, 130.2, 133.0, 134.0, 138.1, 141.1, 145.1, 146.0; IR (neat) 3288, 3054, 2919, 1600, 1485, 907, 857, 820, 786, 774, 725, 702, 650, 473 cm^{-1}; HRMS calcd for $C_{33}H_{26}$ $(M+Na^+)$: 437.1881, found: 437.1897.

4.1.8. Compound 10. Benzoyl peroxide (18 mg, 0.072 mmol) was added to a solution of *N*-bromosuccinimide (710 mg, 3.99 mmol), compound **9** (766 mg, 1.81 mmol), and CCl_4 (20 mL) in a sealed tube. The reaction was stirred at 90°C for 24 h. *N*-bromosuccinimide (162 mg, 0.91 mmol) and benzoyl peroxide (18 mg, 0.072 mmol) were added, and the reaction was stirred at 90°C for 8 h. The reaction was cooled to rt, and filtered. The solvent was removed in vacuo and the resulting residue was purified via flash chromatography (EtOAc/hex, 2:98). The title compound **10** was obtained as an impure solid and carried on without further purification.

4.1.9. Compound 11. A solution of trimethylethylene diamine (0.50 mL, 3.96 mmol), compound **10** (115 mg, 0.20 mmol), Et_3N (0.2 mL), and DMF (1.8 mL) was stirred at 90°C for 3 h. The reaction was cooled to rt and the solvent was removed in vacuo. The resulting residue was purified via flash chromatography (Et_3N/EtOAc, 50:50). The title compound **11** was obtained as a yellow oil (66 mg, 0.11 mmol, 72% yield (2-steps); ^{1}H NMR (300 MHz) δ 2.15 (s, 12H), 2.18 (s, 6H), 2.36–2.43 (m, 8H), 2.74 (s, 1H), 3.49 (s, 4H), 7.11–7.14 (m, 2H), 7.18–7.27 (m, 5H), 7.34 (s, 2H), 7.38 (t, *J*=7.8 Hz, 1H), 7.44–7.48 (m, 2H), 7.60–7.64 (m, 2H), 7.71 (t, *J*=1.7 Hz, 1H), 7.81–7.86 (m, 3H), 7.92 (s, 1H); ^{13}C NMR (75 MHz) δ 42.8, 46.0, 55.2, 55.9, 57.5, 63.1, 74.1, 90.2, 125.9, 126.2, 126.3, 126.4, 126.7, 128.0, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6, 128.7, 128.8, 130.3, 133.0, 134.0, 138.4, 139.0, 141.1, 145.0, 145.9; IR (neat) 3297, 3054, 2942, 2813, 2769, 1810, 1599, 1484, 1464, 1029, 791, 729, 705 cm^{-1}; HRMS calcd for $C_{43}H_{51}N_4$ (M+H$^+$): 623.4114, found: 623.4125.

4.1.10. Compound 21. Compound **15** (12.5 g, 22.8 mmol) and Mg turnings (55.4 g, 2.28 mol) were added to a stirred solution of CH_2Cl_2 (1 L) and MeOH (1 L). The reaction was cooled to 0°C. After 10 min, the reaction began to reflux, and continued until most of the Mg had dissolved. The solution was stirred at 0°C for 5 h. The solvent was removed in vacuo, and the residue was brought up in 50% AcOH (aq.), and extracted with CH_2Cl_2 (3×300 mL). The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (500 mL) and washed with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×100 mL), and the combined organics were dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified via flash chromatography (EtOAc/hex, 1:4), and the free aniline was isolated as a white solid (7.7 g, 21.5 mmol, 94% yield). Mp 121–122°C; ^{1}H NMR (300 MHz) δ 2.65 (s, 1H), 2.75 (s, 3H), 3.62 (s, 1H), 3.78 (s, 6H), 6.46–6.56 (m, 3H), 6.80 (dt, *J*=2.7, 9.0 Hz, 4H), 7.10 (t, *J*=8.3 Hz, 1H), 7.19 (dt, *J*=2.7, 9.0 Hz, 4H); ^{13}C NMR (75 MHz) δ 30.7, 54.1, 55.2, 72.7, 90.3, 110.3, 113.1, 113.9, 118.3, 128.7, 130.1, 137.4, 146.2, 149.0, 158.2; IR (neat) 3416, 3285, 3000, 2953, 2835, 1606, 1504, 1298, 1248, 1178, 1034, 910, 830 cm^{-1}; HRMS calcd for $C_{24}H_{24}NO_2$ (M+H$^+$): 358.1807, found: 358.1800.

Trifluoroacetic anhydride (15.2 mL, 107.5 mmol) was added to a stirred solution of THF (200 mL) and the above aniline (7.7 g, 21.5 mmol) at 0°C. The solution was warmed to ambient temperature and quenched with saturated $NaHCO_3$ (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3×100 mL), and the collected organic layers were dried over $MgSO_4$. Removal of the solvent in vacuo afforded the title compound **21** as a white amorphous solid (9.2 g, 20.4 mmol, 95% yield); ^{1}H NMR (360 MHz) δ 2.71 (s, 1H), 3.29 (s, 3H), 3.77 (s, 6H), 6.82 (dt, *J*=2.7, 8.9 Hz, 4H), 7.13–7.15 (m, 6H), 7.33–7.35 (m, 2H); ^{13}C NMR (75 MHz) δ 40.0, 54.4, 55.6, 74.0, 89.8, 113.9, 116.8 (q, *J*=288 Hz), 126.1, 128.5, 129.5, 130.0, 130.4, 136.8, 140.7, 148.0, 157.2 (q, *J*=35.7 Hz), 159.0; IR (neat) 3291, 3062, 2935, 2837, 1698, 1605, 1506, 1300, 1116, 1035, 910, 704 cms^{-1}; HRMS calcd for $C_{26}H_{23}NO_3F_3$ (M+H$^+$): 454.1630, found: 454.1630.

4.1.11. Compound 22. $Pd(PPh_3)_2Cl_2$ (526 mg, 0.750 mmol) was added to a solution of compound **21** (6.80 g, 15.0 mmol), copper (I) iodide (286 mg, 1.50 mmol), and diiodobenzene (2.47 g, 7.50 mmol) in THF (30 mL) and diisopropylamine (30 mL, deoxygenated by sparging with argon prior to use). The reaction was stirred at 60°C for 14 h. After cooling to room temperature, the solvent was removed in vacuo. The resulting residue was dissolved in CH_2Cl_2 (50 mL), and washed with saturated NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), and the collected organic layers were dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified via flash chromatography (CH_2Cl_2), and the title compound **22** was isolated as light brown solid (6.95 g, 14.3 mmol, 94% yield). Mp 234–236°C (decomp.); ^{1}H NMR (400 MHz) δ 3.30 (s, 6H), 3.80 (s, 12H), 6.80 (d, *J*=8.9 Hz, 8H), 7.15–7.20 (m, 12H), 7.35–7.38 (m, 4H), 7.43 (s, 4H); ^{13}C NMR (100 MHz) δ 39.6, 54.6, 55.2, 84.8, 96.7, 113.5, 116.3 (q, *J*=288 Hz), 123.0, 125.6, 128.1, 129.1, 129.5, 129.9, 131.4, 136.7, 140.3, 147.9, 156.8 (q, *J*=35.8 Hz), 158.5; IR (neat) 3037, 3002, 3000, 2934, 2837, 2254, 1694, 1603, 1505, 1300, 1199, 1115, 1035, 910, 833 cm^{-1}; HRMS calcd for $C_{58}H_{47}F_6N_2O_6$ (M+H$^+$): 981.3338, found: 981.3342.

4.1.12. Compound 23. Ammonium nitrate (2.26 g, 28.2 mmol) was added to a stirred solution of CH_2Cl_2 (75 mL) and compound **22** (6.93 g, 7.06 mmol) at ambient temperature. Trifluoroacetic anhydride (13.9 mL, 98.8 mmol) was added to the reaction. The reaction was stirred at ambient temperature for 2 h. The mixture was slowly poured over saturated $NaHCO_3$ (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. The resulting residue was purified via flash chromatography (Et_2O/CH_2Cl_2, 1:19) and the tetranitro compound was isolated as a yellow amorphous solid (6.33 g, 5.43 mmol, 77%); ^{1}H NMR (400 MHz) δ 3.35 (s, 6H), 4.00 (s, 12H), 7.15 (d, *J*=9.0 Hz, 4H), 7.23 (s, 2H), 7.29 (d, *J*=7.9 Hz, 2H), 7.37 (d, *J*=8.1 Hz, 2H), 7.47–7.53 (m, 10H), 7.84 (d, *J*=2.3 Hz, 4H); ^{13}C NMR (75 MHz) δ 39.5, 54.0, 56.6, 86.6, 94.2, 113.6, 120.2 (q, *J*=288.4 Hz), 122.4, 125.6, 126.7, 127.7, 129.0, 129.9, 131.6, 134.2, 135.6, 139.0, 140.8, 145.1, 152.2, 156.4 (q, *J*=35.7 Hz). IR (neat) 3062, 2979, 2945, 2845, 1700, 1619, 1533, 1498, 1353, 1283, 1204, 1153, 1089, 1018, 898, 756, 706 cm^{-1}. HRMS for M+H$^+$ calcd for $C_{58}H_{43}F_6N_6O_{14}$: 1161.2741, found: 1161.2739.

Tin chloride dihydrate (3.25 g, 12.7 mmol) was added to a stirred solution of MeOH (6 mL), THF (6 mL), and the above tetranitro compound (738 mg, 0.636 mmol). The reaction was stirred at 70°C for 3.5 h. The reaction was cooled, and the solvent removed in vacuo. The resulting residue was dissolved THF (10 mL), and poured over a saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was made basic (pH>10) with 10 M NaOH and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. The resulting residue was purified via flash chromatography (THF/CH_2Cl_2, 1:19) and the title compound **23** was isolated as a yellow amorphous solid (533 mg, 0.515 mmol, 81%); ^1H NMR (300 MHz) δ 3.30 (s, 6H), 3.73 (s, 8H), 3.84 (s, 12H), 6.55 (dd, J=2.3, 6.2 Hz, 4H), 6.67 (d, J=2.2 Hz, 4H), 6.69 (d, J=8.5 Hz, 4H), 7.11 (d, J=7.5 Hz, 2H), 7.20 (s, 2H), 7.31–7.38 (m, 4H), 7.41 (s, 4H); ^{13}C NMR (75 MHz) δ 39.6, 54.8, 55.4, 84.4, 97.2, 109.5, 115.9, 116.4 (q, J=288. Hz), 119.0, 123.1, 125.4, 128.2, 128.8, 129.7, 131.4, 135.6, 137.3, 140.0, 146.3, 148.2, 156.8 (q, J=35.6 Hz). IR (neat) 3472, 3376, 3002, 2956, 2933, 2837, 2242, 1695, 1616, 1512, 1433, 1283, 1231, 1154, 1031, 910, 733 cm^{-1}. HRMS for $M+H^+$ calcd for $C_{58}H_{51}F_6N_6O_6$: 1041.3774, found: 1041.3773.

4.1.13. Compound 24. To a stirred solution of *N*,*N*′-bis-(*t*-butoxycarbonyl)thiourea (684 mg, 2.52 mmol), compound **23** (262 mg, 0.252 mmol), Et_3N (0.5 mL), and CH_2Cl_2 (4.5 mL) at 0°C, was added $HgCl_2$ (684 mg, 2.52 mmol). The reaction was allowed to warm over a period of 1 h, then filtered through a pad of celite. The solvent was removed in vacuo, and the resulting residue was dissolved in CH_2Cl_2 (5 mL) and added to a sealed tube with ammoniated MeOH (5 mL). The reaction was allowed to stir at ambient temperature for 16 h. The reaction was then filtered, and the solvent removed in vacuo. The resulting residue was purified via flash chromatography (Et_2O/CH_2Cl_2, 1:49) to yield the title compound **24** as a white amorphous solid (358 mg, 0.197 mmol, 78%); ^1H NMR (300 MHz) δ 1.36 (s, 36H), 1.51 (s, 36H), 2.76 (s, 6H), 3.86 (s, 12H), 6.46 (dd, J=1.3, 7.2 Hz, 2H), 6.79 (d, J=8.8 Hz, 8H), 7.14 (t, J=8.2 Hz, 2H), 7.21 (dd, J=2.4, 8.6 Hz, 4H), 7.44 (s, 4H), 8.16 (d, J=2.4 Hz, 4H); ^{13}C NMR (75 MHz) δ 28.1, 30.7, 55.3, 56.0, 78.8, 83.0, 85.6, 97.2, 109.8, 110.0, 114.2, 118.6, 123.4, 125.0, 125.3, 125.9, 128.7, 131.5, 138.0, 146.0, 148.8, 149.1, 152.9, 153.2, 163.3. IR (neat) 3406, 3376, 3260, 2978, 1724, 1639, 1494, 1408, 1341, 1136, 1058, 733 cm^{-1}. HRMS for $M+H^+$ calcd for $C_{98}H_{125}N_{14}O_{20}$: 1817.9194, found: 1817.9195.

4.1.14. Compound 20. 2-anthracenesulfonyl chloride (6 mg, 0.0212 mmol) was added to a flask containing 4-*N*,*N*-dimethylaminopyridine (0.6 mg, 0.00530 mmol), compound **24** (9.6 mg, 0.00530 mmol), and pyridine (1 mL). The reaction was stirred at ambient temperature for 22 h. After removal of the solvent in vacuo, the resulting residue was purified via flash chromatography (EtOAc/hex, 2:3) to afford the sulfonanilide as a white amorphous solid (12.1 mg, 0.00520 mmol, 99%); ^1H NMR (400 MHz) δ 1.33 (s, 36H), 1.51 (s, 36H), 3.18 (s, 6H), 3.71 (s, 12H), 6.48 (d, J=8.7 Hz, 4H), 6.88 (dd, J=1.8, 8.5 Hz, 4H), 6.96 (s, 2H), 7.03 (s, 4H), 7.24 (d, J=9.0 Hz, 2H), 7.36–7.47 (m, 10H), 7.73 (d, J=9.0 Hz, 2H), 7.93 (d, J=7.8 Hz, 4H), 8.13–8.14 (m, 4H), 8.27 (s, 2H), 8.30 (s, 2H), 8.38 (s, 2H); ^{13}C NMR (75 MHz) δ 28.1, 28.1, 38.2, 55.1, 55.8, 78.9, 82.0, 83.2, 85.8, 96.2, 109.5, 122.0, 122.8, 124.4, 125.3, 125.4, 125.5, 126.2, 126.5, 126.5, 126.8, 128.1, 128.3, 128.4, 128.6, 128.6, 129.1, 129.4, 130.1, 131.1, 131.7, 132.1, 132.8, 133.0, 137.1, 141.0, 146.0, 148.9, 152.9, 153.1, 163.6. IR (neat) 3258, 2979, 1798, 1724, 1639, 1407, 1340, 1232, 1135, 1058, 1028, 732 cm^{-1}. HRMS for $M+H^+$ calcd for $C_{126}H_{140}N_{14}O_{24}S_2$: 2297.9685, found: 2297.9665.

Trifluoroacetic acid (1 mL) and CH_2Cl_2 (1 mL) were added to a flask containing the above sulfonanilide (9.6 mg, 0.00420 mmol). The reaction was stirred at ambient temperature for 2.5 h. Removal of the solvent in vacuo afforded the title compound **20** as a yellow amorphous solid (8.2 mg, 0.00420 mmol, 100%); ^1H NMR (500 MHz, CD_3OD) δ 3.26 (s, 6H), 3.85 (s, 12H), 6.97 (d, J=9.5 Hz, 4H), 7.03 (s, 4H), 7.17–7.20 (m, 10H), 7.27–7.32 (m, 6H), 7.33 (t, J=7.9 Hz, 2H), 7.46–7.49 (m, 4H), 7.96 (d, J=8.8 Hz, 2H), 7.99–8.01 (m, 4H), 8.36 (s, 2H), 8.42 (s, 2H), 8.51 (s, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 38.8, 56.0, 56.7, 87.3, 97.0, 113.4, 122.9, 123.9, 124.0, 126.7, 127.8, 127.9, 128.1, 128.4, 129.2, 129.5, 129.6, 129.8, 130.0, 130.2, 130.8, 130.9, 131.4, 131.7, 132.5, 133.3, 134.0, 134.3, 134.9, 138.8, 143.2, 146.9, 155.5, 158.6, 162.3 (q, J=36 Hz). IR (KBr pellet) 3368, 3154, 1676, 1631, 1596, 1560, 1508, 1282, 1203, 1140, 832, 722 cm^{-1}. HRMS for $M-3H^+-4CF_3CO_2^-$ calcd for $C_{86}H_{77}N_{14}O_8S_2$: 1497.5490, found: 1497.5420.

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