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A Novel Anthracenyl Tagged Protecting Group for "Phase-Switching" Applications in Parallel Synthesis

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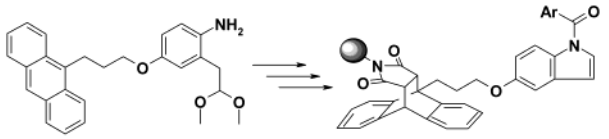
A new "phase-switching" protecting group **1** that facilitates the parallel synthesis of carboxylic acids, esters, and carboxamides is described. Its use permits chemistries to be performed in solution, which may be conveniently monitored with conventional analytical techniques, followed by subsequent immobilization onto a solid-phase support to aid compound purification. Carboxylic acids, esters, and carboxamides are then cleaved from the solid support following activation of the "safety-catch" and treatment with the desired nucleophile.

Introduction

In recent years, solid-phase organic synthesis (SPOS) has emerged as a powerful method for the preparation of compound libraries for use in high throughput screening campaigns.[1,2] However, SPOS often suffers from the disadvantage of requiring tedious reaction optimization prior to library synthesis and this is compounded by the inability to use many conventional solution phase analytical techniques. In contrast, solution phase synthesis may suffer from difficulties associated with compound purification, although the application of polymer supported reagents and scavenger resins is proving beneficial in this respect.[3] An attractive alternative would be to combine the attributes of both solid and solution phase methodologies in a single synthetic strategy whereby the substrate may be moved between different phases to aid both synthesis and final purification. Such a strategy may be realized in practice by "tagging" the substrate with a protecting group that enables "phase-switching".[4] For example, Parlow has reported the use of an anthracenyl tag that may be readily attached to the solid phase following a Diels−Alder reaction with a resin-bound maleimide to facilitate the synthesis of esters.[5] In addition, the anthracenyl moiety has been shown to be a useful analytical "tag" that allows the convenient monitoring of chemistries on solid phase following initial cleavage into solution.[6] The anthracenyl substituent was found to be comparatively unreactive and, importantly, absorbs in a remote region of the UV spectrum (380−390 nm), which is typically free from absorptions associated with other chromophores that may be present thereby facilitating quantitative reaction monitoring by HPLC.



1 **2**

Herein, we describe a new solution phase protecting group **1** that extends the scope of the anthracenyl "phase-switch" concept. The protecting group **1** incorporates an anthracenyl "tag" in combination with Fukuyama's anilino protecting group for carboxylic acids.[7] When immobilized on resin, this latter protecting group has also been used as a "safety-catch" linker for solid-phase synthesis.[8] Amides derived from acylation of **1** are stable toward basic or nucleophilic reagents. However, upon ring closure to the corresponding more electrophilic indolylamides **2**, compound release can be effected by nucleophilic cleavage under mild conditions. The utility of **1** is demonstrated by the preparation of carboxylic acids, esters, and carboxamides, using a "phase-switching" approach.

Results and Discussion

Synthesis of the Anthracenyl-Tagged Linker 1. The anthracenyl-tagged linker **1** may be conveniently prepared as outlined in Scheme 1. Alkylation of com-

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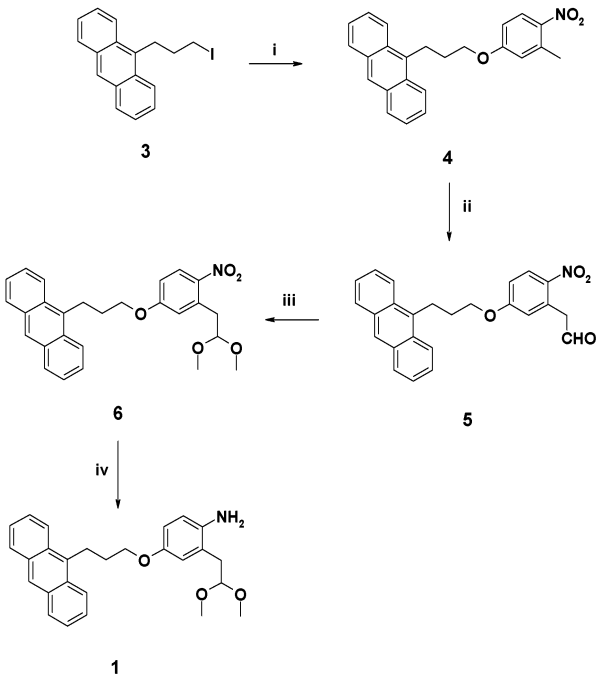
SCHEME 1 [a]



[a] Reagents and conditions: (i) 3-methyl-4-nitrophenol, K_2CO_3, DMF, 90 °C, 99%; (ii) (a) dimethylformamide dimethyl acetal, DMF, reflux, (b) 10% HCl aqueous solution, diethyl ether, reflux, 73%; (iii) trimethyl orthoformate, *p*-TsOH, MeOH, reflux, 100%; (iv) $NaBH_4$, $Cu(acac)_2$, CH_2Cl_2/MeOH/*i*-PrOH, reflux, 74%.

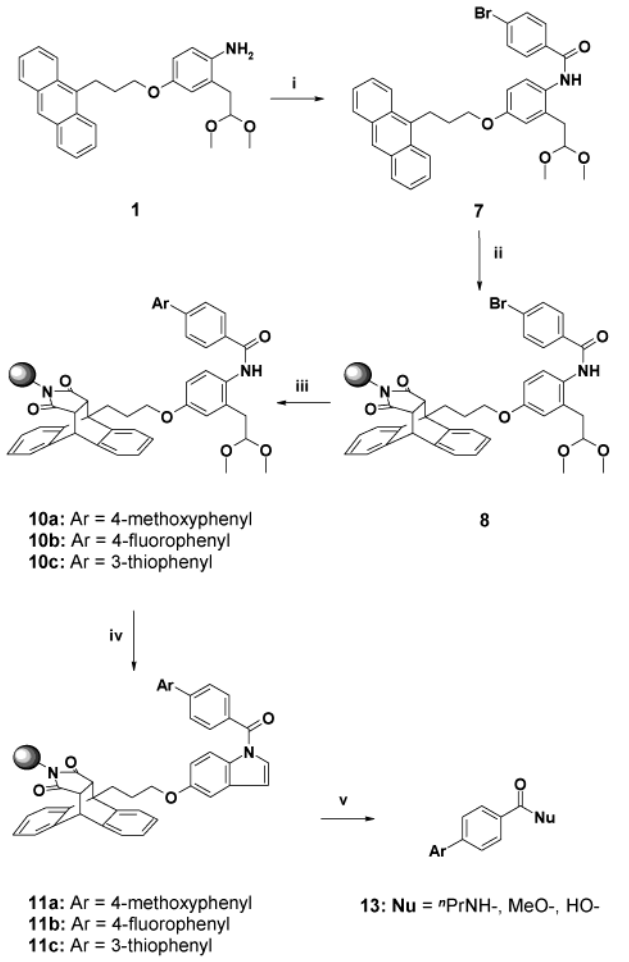
mercially available 3-methyl-4-nitrophenol with 9-(3-iodopropyl)anthracene **3** gave the desired ether **4** in high yield.

The ether **4** was heated with dimethylformamide dimethyl acetal to afford the intermediate unstable vinyl dimethylamine, which was hydrolyzed in the presence of 10% HCl to give the phenyl acetaldehyde **5**. Upon exposure to trimethyl orthoformate the aldehyde **5** was protected as the dimethyl acetal **6**. To avoid the risk of concomitant reduction of the anthracenyl moiety, the nitro substituent in **6** was reduced with sodium borohydride in the presence of copper(II) acetonylacetonate[9] at 40 °C to provide the desired aniline **1** in 53% overall yield.

Construction of a Nine-Member Library with 1. To demonstrate the utility of the new protecting group **1** in synthesis, a small library containing 9 compounds was constructed by using a "phase-switching" strategy (Scheme 2).

Thus, acylation of **1** with 4-bromobenzoyl chloride was performed in solution in the presence of diisopropylethylamine on polystyrene (PS-DIPEA). The use of the polymer supported base reduced the workup to a simple filtration. Reaction progress was monitored by HPLC with UV detection at 386 nm under which conditions only anthracenyl tagged material was visible (Figure 1a). The time-course data indicated that, under the experimental conditions employed, amidation of **1** was complete after 5 h (Figure 1b). Extending the reaction time or the use of a large excess of the acylating reagent led to diacylation of the aniline. Any residual acid chloride could be readily removed by filtration of the reaction mixture

SCHEME 2 [a]



[a] Reagents and conditions: (i) 4-bromobenzoyl chloride, CH_2Cl_2, PS-DIPEA, 99%; (ii) maleimide resin, toluene, 100 °C; (iii) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, DME, 80 °C; (iv) PPTS, THF, 50 °C; (v) NuH, solvent.

through an Isolute-NH_2 cartridge to afford the anthracenyl tagged amide **7** in almost quantitative yield.

Next, we addressed the homologation of the carboxamide **7** using a palladium-mediated Suzuki coupling reaction. We observed that competing reduction of the aryl bromide to the corresponding phenyl derivative was sometimes a problem under solution phase Suzuki conditions and we therefore decided to effect a "phase-switch" at this stage and conduct the Suzuki reaction on solid-phase. This also greatly simplified reaction workup since residual palladium contaminants and excess reagents could be readily washed away. Therefore, according to Parlow's procedure[5,10] maleimide functionalized polystyrene resin was prepared and heated with the amide **7** in toluene to promote the Diels−Alder reaction, affording the resin-bound bromide **8**. The progress of the reaction was again monitored by the disappearance of the anthracenyl UV absorption at 386 nm and the kinetic plot is shown in Figure 2. Whereas the "phase-switch" takes approximately 7 h at 90 °C, the process is complete in only 4 h at 100 °C. In addition, although the resin-bound

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(10) The maleimide resin was prepared on 1−2% cross-linked polystyrene and determined to have a loading of ~1.2 mmol/g according to *N* combustion analysis.

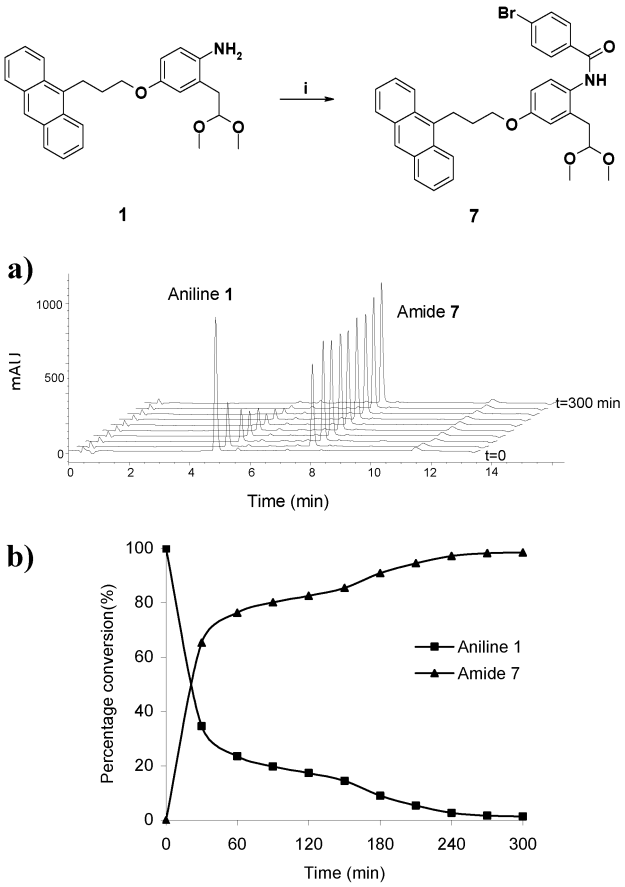
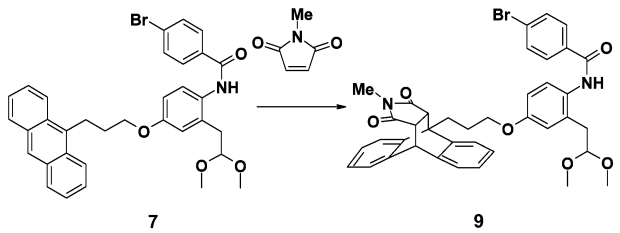


FIGURE 1. Acylation of aniline **1** with 4-bromobenzoyl chloride to afford carboxamide **7**. (a) Time course to show the disappearance of **1** and the appearance of **7** at room temperature monitored by HPLC at 386 nm. (b) Normalized kinetic plot for the conversion of **1** into **7** obtained by HPLC monitoring at 386 nm.

maleimide was used in excess, the gel-phase FT-IR spectrum obtained after the Diels−Alder reaction showed a significant decrease in intensity of the *cis*-(HC═CH) vinylic wagging band at 828 cm^{-1} and the appearance of a new carboxamide N−H stretching band was observed at 3346 cm^{-1}.

Further evidence for the formation of the resin-bound Diels−Alder adduct **8** was obtained from examination of the gel-phase ^{1}H HRMAS NMR spectrum. First, to provide a model compound for comparison, the adduct **9** was prepared by subjecting the carboxamide **7** to a Diels−Alder reaction with *N*-Me maleimide in solution. Distinctive signals for the amidic proton and the dimethoxy groups were observed at 9.44 and 3.46 ppm, respectively, in the solution phase ^{1}H NMR spectrum of **9** and corresponding signals were observed at 9.54 and 3.51 ppm in the ^{1}H HRMAS NMR spectrum of resin **8**.



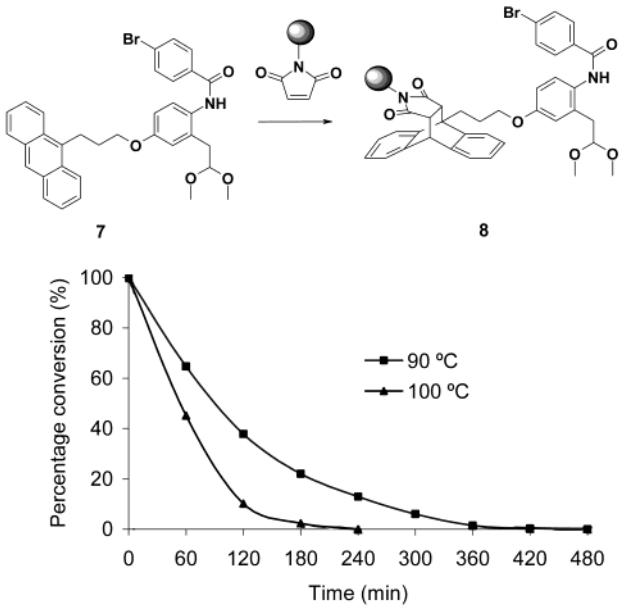
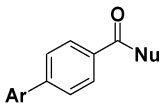


FIGURE 2. Time-course plot to show the temperature dependence for the Diels−Alder "phase-switch" reaction of **7** with PS-maleimide resin to afford **8**. Monitored by HPLC analysis of the supernatant solution at 386 nm.

TABLE 1. Purities and Yields of Benzoic Acid Derivatives 13 Prepared by Nucleophilic Cleavage from Resins 11a−c



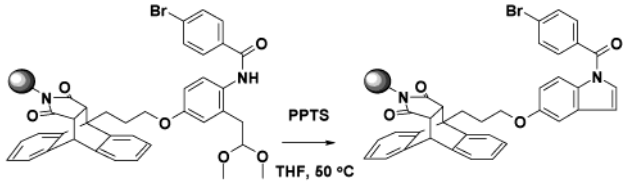
product	boronic acid ($ArB(OH)_2$)	nucleophile (NuH)	purity, %[a]	yield, %[b]
13a[c]	4-methoxophenyl-	^{n}PrNH$_2$	98	75
13b[c]	4-fluorophenyl-	^{n}PrNH$_2$	95	74
13c[c]	3-thiophenyl-	^{n}PrNH$_2$	92	80
13d[d]	4-methoxyphenyl-	MeOH	97	70
13e[d]	4-fluorophenyl-	MeOH	95	65
13f[d]	3-thiophenyl-	MeOH	98	66
13g[e]	4-methoxyphenyl-	H_2O	94	77
13h[e]	4-fluorophenyl-	H_2O	98	70
13i[e]	3-thiophenyl-	H_2O	97	77

[a] HPLC purity with UV detection at 254 nm. [b] ^{1}H NMR yield obtained by integration vs residual protio-DMSO peaks in d_6-DMSO calibrated with 4-nitrophenol as an external standard.[12] [c] 20% propylamine in THF, rt, 16 h. [d] $NaNH_2$, MeOH/THF (1:4), rt, 16 h. [e] $CsOH·H_2O$, H_2O/THF (1:10), rt, 16 h.

The Suzuki coupling reaction of resin **8** was carried out with three different boronic acids (cf. Scheme 2) in degassed DME at 80 °C, using $Pd(PPh_3)_4$ as the catalyst and cesium carbonate as the base to afford the resins **10a−c**. Under these conditions competing reduction of the aryl bromide did not occur to any significant extent—as was evident from the high purities of the final compounds obtained following cleavage from the resin (Table 1). Similarly, consistent with the observations of Abell et al.,[8] the high cleavage yields obtained demonstrate that the "safety-catch" linker is resistant to premature nucleophilic cleavage, even in the presence of aqueous cesium carbonate at 80 °C for up to 2 days. It is unlikely that a simple ester linkage would have remained intact under these conditions. Excess reagents and the

palladium residues that often prove to be problematic contaminants in solution phase were readily removed from the solid phase by thorough washing of the resin.

Finally, activation of the "safety-catch" prior to nucleophilic cleavage of the desired substrates from resin was performed by heating the resins **10a**−**c** with PPTS in THF at 50 °C for 16 h to give the resin-bound indolylamides **11a**−**c**. These conditions were determined for a model study in which the resin-bound carboxamide **8** was converted to the corresponding bromide **12.** The disappearance of both the band at 3346 cm^{-1} in the gel-phase FT-IR and the amidic and dimethoxyl signals at 9.60 and 3.56 ppm, respectively, in the gel-phase ^1H HRMAS NMR spectra for **12** indicated that conversion to the resin-bound indolylamide went to completion under these conditions. In addition the signals at 106.5, 54.1, and 36.8 ppm in the gel-phase ^{13}C NMR for **8** disappeared and were replaced by signals at 108.5 and 104.0 ppm which correspond to the sp^2 centers at the C-2 and C-3 positions of the newly formed indole ring in **12**.



8 12

Each of the resins **11a**−**c** was then subjected to cleavage under these standard conditions in the presence of three different nucleophiles to afford the desired cleavage products **13a**−**i** (Table 1).

Thus, the *n*-propylamides, **13a**−**c** were obtained in high yield and good purity following exposure of the resins **11a**−**c** to 20% v/v *n*-propylamine in THF at room temperature for 16 h. The excess amine was removed by evaporation under high vacuum. When nonvolatile amines (1^y, 2^y, and cyclic) were used (not reported), the excess amine could be conveniently removed by elution through an acidic Isolute SCX-2 cartridge.

Alternatively, treatment of the resins **11a**−**c** with sodium amide in MeOH/THF (1:4) at room temperature for 16 h followed by an aqueous quench of the resin with NH_4Cl solution gave the methyl esters **13d**−**f** again in good yield and high purity after extraction into dichloromethane.

Similarly, exposure of the resins **11a**−**c** to aqueous cesium hydroxide gave the corresponding carboxylic acids **13g**−**i** in high yield and excellent purities.

Conclusion

In summary, we have described the preparation of a new anthracenyl-tagged protecting group **1** and demonstrated that it may be used to conveniently prepare carboxylic acids, esters, and amides in good yields and high purities by invoking a "phase-switching" strategy in combination with PS-maleimide resin. In addition, the monitoring of solution phase transformations of **1** is greatly facilitated by the presence of the sensitive anthracenyl UV chromophore, which has absorptions in a remote region of the UV spectrum. The development of other tagged protected groups for "phase-switching" transformations is currently underway in our laboratory and these results will be reported in due course.

Experimental Section

9-[3-(3-Methyl-4-nitrophenoxy)propyl]anthracene (4). A suspension of 9-(3-iodopropyl)anthracene (**3**, 18.3 g, 52.9 mmol), 3-methyl-4-nitrophenol (9.9 g, 64.6 mmol), and K_2CO_3 (21.1 g, 64.8 mmol) in DMF (180 mL) was heated at 90 °C under nitrogen for 3 h. The reaction mixture was concentrated in vacuo and the residue was partitioned between 2 M Na_2CO_3 aqueous solution (200 mL) and ethyl acetate (200 mL). The organic layer was separated, washed with 2 M Na_2CO_3 aqueous solution and saturated brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo to afford **4** as a yellow solid (19.6 g, 99%). Mp 132−133 °C. HPLC (254 nm): $t_R = 7.95$ min (100%). IR: υ_{max} 1587, 1330 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (2H, tt, $J = 5.8$ and 7.6 Hz), 2.62 (3H, s), 3.84 (2H, t, $J = 7.6$ Hz), 4.10 (2H, t, $J = 5.8$ Hz), 6.80 (2H, m), 7.45 (4H, m), 8.01 (2H, m), 8.08 (1H, d, $J = 8.4$ Hz), 8.27 (2H, m), 8.37 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 141.5, 136.4, 132.6, 131.0, 129.1, 128.6, 126.9, 125.5, 125.1, 124.2, 123.4, 117.3, 111.7, 67.1, 29.7, 23.3, 21.0. HRMS (ESI): *m*/*z* calcd ($C_{24}H_{21}NO_3Na$) 394.1419, found 394.1412 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.67; H, 5.61; N, 3.69.

[5-(3-Anthracen-9-ylpropoxy)-2-nitrophenyl]acetaldehyde (5). To a solution of anthracene **4** (19.6 g, 52.8 mmol) in DMF (200 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (10.9 mL, 82.3 mmol). The resulting solution was refluxed under nitrogen for 16 h and the solvent was evaporated in vacuo to leave the intermediate vinyl dimethylamine as a dark red oil. The oil was dissolved in diethyl ether (100 mL) and treated with 10% HCl aqueous solution (25 mL), and the resulting mixture was refluxed for 2 h. The organic layer was separated, washed with saturated brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo to leave a semisolid that was purified by column chromatography eluting with a mixture of ethyl acetate and hexane (1:4) to give **5** as a yellow solid (15.5 g, 73%). Mp 139−140 °C. HPLC (254 nm): $t_R = 7.10$ min (100%). IR: υ_{max} 1720, 1589, 1332 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (2H, tt, $J = 6.0$ and 7.6 Hz), 3.84 (2H, t, $J = 7.6$ Hz), 4.06 (2H, s), 4.10 (2H, t, $J = 6.0$ Hz), 6.73 (1H, d, $J = 2.8$ Hz), 6.91 (1H, dd, $J = 2.8$ and 9.2 Hz), 7.46 (4H, m), 8.01 (2H, m), 8.19 (1H, d, $J = 9.2$ Hz), 8.26 (2H, m), 8.36 (1H, s), 9.83 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 162.4, 141.0, 132.5, 130.9, 129.1, 128.7, 127.5, 125.6, 125.1, 124.3, 123.3, 118.5, 113.0, 67.4, 48.4, 29.6, 23.2. LC-MS (ESI): $t_R = 4.98$ min (*m*/*z* 400.2 $[M + H]^+$). HRMS (ESI): *m*/*z* calcd ($C_{25}H_{21}NO_4Na$) 422.1368, found 422.1372 $[M + Na]^+$. Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 74.83; H, 5.33; N, 3.35.

9-{3-[3-(2,2-Dimethoxyethyl)-4-nitrophenoxy]propyl}anthracene (6). To a solution of aldehyde **5** (8.50 g, 21.3 mmol) in CH_2Cl_2 (150 mL) was added *p*-toluenesulfonic acid (400 mg, 2.2 mmol) and trimethyl orthoformate (50 mL). The resulting mixture was refluxed for 30 min. The reaction mixture was concentrated in vacuo and the residue was partitioned between saturated $NaHCO_3$ aqueous solution and ethyl acetate. The organic layer was separated, washed with saturated brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo to afford **6** as yellow oil (9.50 g, 100%). HPLC (386 nm): $t_R = 7.59$ min (100%). IR: υ_{max} 1578, 1334 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (2H, m), 3.25 (2H, d, $J = 5.2$ Hz), 3.35 (6H, s), 3.84 (2H, t, $J = 7.7$ Hz), 4.11 (2H, t, $J = 5.9$ Hz), 4.59 (1H, t, $J = 5.2$ Hz), 6.82 (1H, dd, $J = 2.6$ and 9.2 Hz), 6.88 (1H, d, $J = 2.6$ Hz), 7.45 (4H, m), 8.00 (3H, m), 8.27 (2H, m), 8.36 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 141.9, 134.4, 132.6, 130.9, 129.1, 128.6, 126.7, 125.5, 125.1, 124.2, 123.4, 118.4, 112.4, 103.9, 67.2, 53.7, 37.4, 29.6, 23.3. LC-MS (ESI): $t_R = 5.22$ min (*m*/*z* 414.2 $[M - MeO]^-$). HRMS (ESI): *m*/*z* calcd ($C_{27}H_{27}NO_5Na$) 468.1787, found 468.1795 $[M + Na]^+$.

4-(3-Anthracen-9-ylpropoxy)-2-(2,2-dimethoxyethyl)-phenylamine (1). To a solution of **6** (9.50 g, 21.3 mmol) in a mixture of CH_2Cl_2 (150 mL) and 2-propanol (30 mL) was added copper acetylacetonate (1.12 g, 4.30 mmol) and sodium borohydride (2.43 g, 64.2 mmol) with ice−water bath cooling. The resulting mixture was stirred at room temperature for 5 min and then MeOH (30 mL) was slowly added. The mixture was heated under reflux for 30 min and allowed to cool to room temperature. The reaction was quenched by slowly adding water (30 mL). After gas evolution ceased, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo and the residue was partitioned between ethyl acetate (200 mL) and saturated brine (200 mL). The separated organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by column chromatography eluting with a mixture of ethyl acetate, hexane, and triethylamine (10: 30: 3) to give **1** as a light brown oil (6.58 g, 74%). HPLC (254 nm): $t_R = 4.87$ min (94%). IR: υ_{max} 3421, 3350, 1622 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (2H, dd, $J = 5.8$ and 7.8 Hz), 2.86 (2H, d, $J = 5.4$ Hz), 3.37 (6H, s), 3.82 (2H, t, $J = 7.8$ Hz), 4.03 (2H, t, $J = 5.8$ Hz), 4.51 (1H, t, $J = 5.4$ Hz), 6.69 (3H, m), 7.45 (4H, m), 8.00 (2H, m), 8.32 (2H, m), 8.34 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 138.8, 133.6, 131.0, 129.1, 128.5, 125.2, 124.9, 124.2, 123.8, 123.4, 117.3, 116.7, 113.3, 105.9, 67.3, 53.3, 36.0, 30.2, 23.7. LC-MS (ESI): $t_R = 4.72$ min (*m*/*z* 384.3 [M − MeO] $^-$). HRMS (ESI): *m*/*z* calcd ($C_{27}H_{29}NO_3Na$) 438.2045, found 438.2038 [M + Na]$^+$.

***N*-[4-(3-Anthracen-9-ylpropoxy)-2-(2,2-dimethoxyethyl)phenyl]-4-bromobenzamide (7).** To a suspension of 4-bromobenzoyl chloride (135.6 mg, 0.62 mmol) and PS-DIPEA (1.0 g, ∼2.2 mmol/g, ∼2.2 mmol) in CH_2Cl_2 (4 mL) was added a solution of amine **1** (214 mg, 0.52 mmol) in CH_2Cl_2 (4 mL). The resulting suspension was stirred at room temperature for 5 h and filtered. The resin was washed with CH_2Cl_2 (3 × 5 mL) and the combined filtrates were loaded onto an Isolute-NH_2 cartridge (1 g). The cartridge was eluted with CH_2Cl_2 (3 × 5 mL) and MeOH (3 × 5 mL) and the eluant was evaporated in vacuo to give **7** as a pale yellow oil (310 mg, 99%). HPLC (254 nm): $t_R = 7.93$ min (100%). IR: υ_{max} 3333, 1669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (2H, tt, $J = 5.8$ and 7.8 Hz), 2.95 (2H, d, $J = 5.2$ Hz), 3.45 (6H, s), 3.83 (2H, t, $J = 7.8$ Hz), 4.09 (2H, t, $J = 5.8$ Hz), 4.52 (1H, t, $J = 5.2$ Hz), 6.81 (1H, d, $J = 2.8$ Hz), 6.92 (1H, dd, $J = 2.8$ and 8.8 Hz), 7.47 (4H, m), 7.63 (2H, d, $J = 8.4$ Hz), 7.82 (2H, d, $J = 8.4$ Hz), 7.91(1H, d, $J = 8.8$ Hz), 8.00 (2H, d, $J = 8.4$ Hz), 8.31 (2H, d, $J = 8.4$ Hz), 8.35 (1H, s), 9.42 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 155.5, 133.34, 133.28, 131.2, 131.0, 129.3, 129.1, 129.0, 128.6, 128.0, 125.5, 125.3, 125.0, 124.7, 124.2, 123.6, 116.8, 112.6, 106.5, 66.9, 54.0, 36.7, 30.1, 23.6. LC-MS (ESI): $t_R = 5.35$ min (*m*/*z* 598.4 [M − H] $^-$ and 568.3 [M − MeO]$^-$). HRMS (ESI): *m*/*z* calcd ($C_{34}H_{32}BrNO_4Na$) 620.1412, found 620.1440 [M + Na]$^+$.

Preparation of Resin (8) by Diels−Alder Cycloaddition. A solution of anthracene **7** (285 mg, 0.46 mmol) in toluene (2 mL) was added to pre-swollen PS-maleimide resin[10] (0.70 g, ∼1.2 mmol/g, ∼0.84 mmol) in toluene (8 mL). The reaction tube was sealed and stirred at 100 °C for 4 h. The resin was thoroughly washed with CH_2Cl_2, and dried under high vacuum to give brown beads of **8** (0.99 g). IR: υ_{max} 3346, 1710, 828 (ω *cis*-CH=CH) cm^{-1}. ^1H HRMAS NMR (400 MHz, $CDCl_3$): δ (selected signals) 3.56 (s), 7.69, 7.90, and 9.60 (s).[11] ^{13}C NMR (100 MHz, $CDCl_3$): δ (selected signals) 106.5, 54.1, and 36.8.

General Procedure for Solid-Phase Suzuki Coupling Reaction (10a−c). To a suspension of resin **8** (200 mg, ∼92 μmol) in DME (2 mL), was added $Pd(PPh_3)_4$ (26 mg, 23 μmol), 2 M Cs_2CO_3 aqueous solution (880 μL), and the boronic acid (**10**, 5 equiv) under nitrogen. The reaction vessel was sealed and shaken at 80 °C for 48 h. The resin was thoroughly washed (2 × THF, 2 × DMF/H_2O, 3 × DMF, and 3 × CH_2Cl_2) and dried under high vacuum to give brown beads of **10a−c** (∼200 mg).

General Procedure for Activation of the "Safety-Catch": Preparation of Resin-Bound Indolylamides (11a−c). To a suspension of each of the biaryl resins **10a−c** (50 mg) in anhydrous THF (2 mL) under nitrogen was added PPTS (5 mg). The reaction vessels were sealed and shaken at 50 °C for 16 h. The resins were thoroughly washed with anhydrous CH_2Cl_2 and dried under high vacuum to afford indolylamide resins **11a−c**. These were used directly in the following cleavage studies, a separate batch of resins **11a−c** being prepared prior to treatment with each nucleophile. In all cases, yields were determined by NMR integration relative to residual protio signals in d_6-DMSO precalibrated with *p*-nitrophenol.[12]

Preparation of the Indolylamide Resin (12). According to the general procedure, resin **8** (300 mg) was suspended in THF (5 mL) containing PPTS (150 mg) and gently stirred at 50 °C for 16 h to afford the resin **12** (∼300 mg). ^{13}C NMR (100 MHz, $CDCl_3$): δ (selected signals) 108.5, 104.0.

General Procedure for Cleavage with Propylamine: Preparation of Amides 13a−c. The resins **11a−c** (50 mg each) were treated with 20% v/v propylamine in anhydrous THF (2 mL) at room temperature for 16 h. The suspensions were filtered, and resins were washed with CH_2Cl_2 (3 × 2 mL). The combined filtrates were evaporated in vacuo and the residues obtained were further dried under high vacuum to afford amides **13a−c** free of residual propylamine.

4′-Methoxybiphenyl-4-carboxylic Acid Propylamide (13a). HPLC (254 nm): $t_R = 5.17$ min (92%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.4$ Hz), 1.52 (2H, tq, $J = 7.2$ and 7.4 Hz), 3.20 (2H, dt, $J = 5.6$ and 7.2 Hz), 3.78 (3H, s), 7.01 (2H, d, $J = 9.0$ Hz), 7.65 (2H, d, $J = 9.0$ Hz), 7.68 (2H, d, $J = 8.0$ Hz), 7.87 (2H, d, $J = 8.0$ Hz), 8.42 (1H, t, $J = 5.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 159.1, 142.0, 132.6, 131.3, 127.8, 127.6, 125.6, 114.2, 55.0, 40.8, 22.2, and 11.3. LC-MS (ESI): $t_R = 4.11$ min (*m*/*z* 270.2 [M + H]$^+$). HRMS (ESI): *m*/*z* calcd ($C_{17}H_{20}NO_2$) 270.1494, found 270.1498 [M + H]$^+$.

4′-Fluorobiphenyl-4-carboxylic Acid Propylamide (13b). HPLC (254 nm): $t_R = 5.26$ min (95%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.4$ Hz), 1.51 (2H, tq, $J = 7.1$ and 7.4 Hz), 3.21 (2H, dt, $J = 5.6$ and 7.1 Hz), 7.29 (2H, dd, $J = 8.6$ and 8.6 Hz), 7.71 (2H, d, $J = 8.4$ Hz), 7.75 (2H, dd, $J = 5.4$ and 8.6 Hz), 7.90 (2H, d, $J = 8.4$ Hz), 8.46 (1H, t, $J = 5.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 141.2, 135.5, 133.3, 128.7, 128.7, 127.6, 126.2, 115.7, 115.5, 40.8, 22.2, and 11.3. LC-MS (ESI): $t_R = 4.16$ min (*m*/*z* 258.2 [M + H]$^+$). HRMS (ESI): *m*/*z* calcd ($C_{16}H_{17}NOF$) 258.1294, found 258.1302 [M + H]$^+$.

***N*-Propyl-4-(thiophen-3-yl)benzamide (13c).** HPLC (254 nm): $t_R = 4.96$ min (98%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.4$ Hz), 1.51 (2H, tq, $J = 7.2$ and 7.4 Hz), 3.20 (2H, dt, $J = 5.6$ and 7.2 Hz), 7.61 (1H, dd, $J = 1.4$ and 5.2 Hz), 7.64 (1H, dd, $J = 2.8$ and 5.2 Hz), 7.78 (2H, d, $J = 8.4$ Hz), 7.86 (2H, d, $J = 8.4$) Hz, 7.97 (1H, dd, $J = 1.4$ and 2.8 Hz), 8.42 (1H, t, $J = 5.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 140.4, 137.2, 132.8, 127.6, 127.1, 126.0, 125.5, 122.0, 40.8, 22.2, and 11.3. LC-MS (ESI): $t_R = 4.03$ min (*m*/*z* 246.1 [M + H]$^+$). HRMS (ESI): *m*/*z* calcd ($C_{14}H_{16}NOS$) 246.0952, found 246.0946 [M + H]$^+$.

General Procedure for Cleavage with Sodium Amide: Preparation of Methyl Esters (13d−f). To a suspension of each of the indolylamide resins **11a−c** (50 mg each) in a mixture of anhydrous MeOH and THF (1:4; 2 mL) was added $NaNH_2$ (2 mg). The suspensions were shaken at room temperature for 16 h and the reactions were quenched by carefully adding saturated NH_4Cl aqueous solution (2 mL). The resulting suspensions were filtered and the resins were washed with

(11) In the ^1H HRMAS NMR spectra of 1−2% polystyrenes, all signals suffered from varying degrees of line broadening but the signals at 9.60 and 3.56 ppm were particularly well resolved.

(12) Basso, A.; Evans, B.; Pegg, N.; Bradley, M. *Tetrahedron Lett.* **2000**, *41*, 3763−3767.

saturated NH_4Cl aqueous solution (3 × 2 mL) and CH_2Cl_2 (3 × 2 mL). The separated CH_2Cl_2 layers were evaporated in vacuo, and the residues obtained were further dried under high vacuum to afford the methyl esters **13d**−**f**.

4′-Methoxybiphenyl-4-carboxylic Acid Methyl Ester (13d). HPLC (254 nm): t_R = 6.05 min (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s), 3.84 (3H, s), 7.03 (2H, d, J = 8.8 Hz), 7.68 (2H, d, J = 8.8 Hz), 7.76 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 159.4, 144.1, 130.8, 129.6, 128.0, 127.4, 126.1, 114.3, 55.0, and 51.9. LC-MS (ESI): t_R = 4.53 min (m/z 243.3 $[M + H]^+$). HRMS (ESI): m/z calcd ($C_{15}H_{14}O_3Na$) 265.0841, found 265.0844 $[M + Na]^+$.

4′-Fluorobiphenyl-4-carboxylic Acid Methyl Ester (13e). HPLC (254 nm): t_R = 6.01 min (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (3H, s), 7.31 (2H, t, J = 9.0 Hz), 7.79 (4H, m), 8.0 (2H, d, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 163.4, 143.4, 135.1, 129.6, 129.0, 128.9, 128.2, 126.7, 115.9, 115.6, and 52.0. LC-MS (ESI): t_R = 4.53 min (m/z 231.2 $[M + H]^+$). HRMS (ESI): m/z calcd ($C_{14}H_{11}O_2FNa$) 253.0641, found 253.0632 $[M + Na]^+$.

4-Thiophen-3-ylbenzoic Acid Methyl Ester (13f). HPLC (254 nm): t_R = 5.77 min (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (3H, s), 7.62 (1H, dd, J = 1.4 and 5.0 Hz), 7.67 (1H, dd, J = 2.8 and 5.0 Hz), 7.87 (2H, d, J = 8.4 Hz), 7.97 (2H, d, J = 8.4 Hz), 8.06 (1H, dd, J = 1.4 and 2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 139.9, 139.3, 129.6, 127.7, 127.4, 126.0, 123.0, and 51.9. LC-MS (ESI): t_R = 4.43 min (m/z 219.2 $[M + H]^+$). HRMS (ESI): m/z calcd ($C_{12}H_{10}O_2SNa$) 241.0299, found 241.0296 $[M + Na]^+$.

General Procedure for Cleavage with Cesium Hydroxide: Preparation of Carboxylic Acids 13 g−i. To a suspension of each of the indolylamide resins **11a**−**c** (50 mg each) in a mixture of THF and water (10:1; 2 mL) was added $CsOH·2H_2O$ (2 mg) The suspensions were shaken at room temperature for 16 h and then filtered. The resins were washed with 10% HCl aqueous solution (3 × 2 mL) and CH_2Cl_2 (3 × 2 mL). The separated organic layers were evaporated in vacuo to leave oils which were further dried under high vacuum to afford carboxylic acids **13g**−**i**.

4′-Methoxybiphenyl-4-carboxylic Acid (13g). HPLC (254 nm): t_R = 6.07 min (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (3H, s), 7.03 (2H, d, J = 8.8 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.72 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.8 Hz), 12.87 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 159.3, 143.7, 131.1, 129.7, 128.8, 127.9, 125.9, 114.3, and 55.0. LC-MS (ESI): t_R = 4.68 min (m/z 227.3 $[M - H]^-$). HRMS (ESI): m/z calcd ($C_{14}H_{13}O_3$) 229.0864, found 229.0856 $[M + H]^+$.

4′-Fluorobiphenyl-4-carboxylic Acid (13h). HPLC (254 nm): t_R = 5.94 min (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (2H, t, J = 9.0 Hz), 7.76 (4H, m), 7.99 (2H, d, J = 8.8 Hz), 12.94 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 143.0, 135.3, 129.7, 129.5, 128.9, 128.8, 126.5, 115.8, and 115.6. LC-MS (ESI): t_R = 4.78 min (m/z 215.4 $[M - H]^-$). HRMS (ESI): m/z calcd ($C_{13}H_9FO_2$) 216.05865, found 216.05970 $[M]^+$.

4-Thiophen-3-ylbenzoic Acid (13i). HPLC (254 nm): t_R = 5.56 min (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (1H, dd, J = 1.4 and 5.2 Hz), 7.66 (1H, dd, J = 2.8 and 5.2 Hz), 7.82 (2H, d, J = 8.4 Hz), 7.94 (2H, d, J = 8.4 Hz), 8.02 (1H, dd, J = 1.4 and 2.8 Hz), 12.90 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 140.2, 138.8, 129.8, 129.2, 127.3, 126.0, 125.8, and 122.6. LC-MS (ESI): t_R = 4.50 min (m/z 203.4 $[M - H]^-$). HRMS (ESI): m/z calcd ($C_{11}H_8O_2S$) 204.02450, found 204.02355 $[M]^+$.

Preparation of Adduct 9: Diels−Alder Cycloddition between Anthracene 7 and *N*-Methylmaleimide. To a solution of anthracene **7** (285 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) was added *N*-methylmaleimide (81.5 mg, 0.73 mmol). The resulting mixture was stirred at room temperature for 48 h. Amino-silica gel (Isolute-NH_2; 4 g) was added to the reaction mixture, and the resulting suspension was stirred at 50 °C for 2 h. The mixture was filtered and the silica gel was thoroughly washed with CH_2Cl_2 (5 × 5 mL). The combined filtrates were evaporated in vacuo, and the residue was further dried under high vacuum to give **9** as an oil (276 mg, 85%). HPLC (254 nm): t_R = 6.80 min (100%). IR: υ_{max} 3344, and 1698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (5H, m), 2.86 (1H, m), 3.03 (3H, m), 3.18 (1H, d, J = 8.8 Hz), 3.30 (1H, dd, J = 3.2 and 8.4 Hz), 3.46 (6H, s), 4.35 (2H, m), 4.56 (1H, t, J = 5.2 Hz), 4.73 (1H, d, J = 3.2 Hz), 6.90 (1H, d, J = 2.8 Hz), 7.00 (1H, dd, J = 2.8 and 8.8 Hz), 7.07−7.30 (6H, m), 7.38 (1H, dd, J = 1.6 and 6.8 Hz), 7.53 (1H, d, J = 7.0 Hz), 7.63 (2H, d, J = 8.0 Hz), 7.82 (2H, d, J = 8.0 Hz), 7.95 (1H, d, J = 8.8 Hz), and 9.44 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 175.3, 163.6, 155.5, 142.1, 142.0, 140.8, 138.4, 133.3, 131.2, 129.4, 129.1, 128.0, 126.2, 126.0, 125.8, 125.7, 125.5, 124.8, 124.2, 123.6, 122.7, 121.6, 116.8, 112.5, 106.5, 67.8, 54.0, 47.2, 47.0, 45.5, 44.9, 36.7, 24.5, 23.7, and 23.6. LC-MS (ESI): t_R = 4.84 min (m/z 709.5 $[M - H]^-$ and 679.3 $[M - MeO]^-$). HRMS (ESI): m/z calcd ($C_{39}H_{37}BrN_2O_6Na$) 731.1733, found 731.1759 $[M + Na]^+$.

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Supporting Information Available: General experimental methods and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **4**, **5**, **6**, **7**, **9**, and **13a**−**i**, and ^{1}H HRMAS and gel-phase ^{13}C NMR spectra of **8** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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