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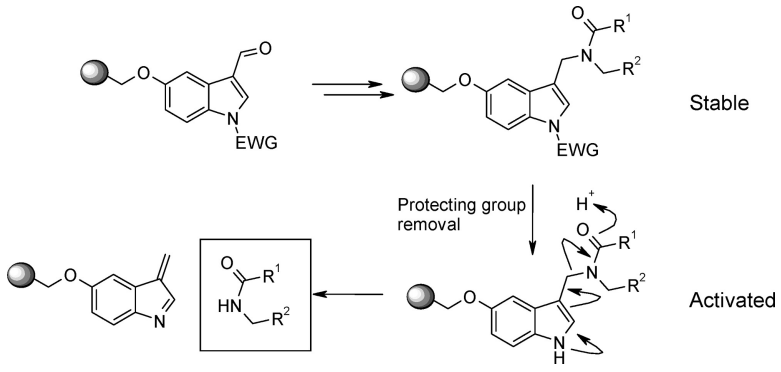

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Development of an Indole Safety-Catch Linker Using Analytical Constructs

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The development, evaluation, and application of a novel safety-catch linker for solid-phase synthesis based on an *N*-tosylindole is reported. The development of this linker using analytical constructs to aid analysis is discussed.

Solid-phase organic synthesis has become widely accepted for the preparation of combinatorial libraries and compound arrays to accelerate hit discovery and lead optimization processes.[1−4] The use of the solid phase allows simple separation of resin-bound products from solution-phase reagents; the ability to drive reactions to completion by using excesses of reagents in high concentration; and the generation of synthetic protocols that are unhindered by the physical characteristics of each individual library member, thus facilitating the automation of the process. The growing complexity of chemistry being performed on the solid phase requires the continuous development of suitable linker molecules with the desired properties.[5−8]

The safety-catch principle, as applied to linkers,[5,6] involves the conversion of a relatively stable, "inactivated" form of the linker into a labile, isolable, and cleavable entity.[9] An advantage of safety-catch linkers is their ability to tolerate harsh or otherwise incompatible reaction conditions through an entire reaction sequence and then, after removal of the safety catch, to release the desired product into solution under mild conditions or in such a way as not to require further purification. The latter aspect could be particularly important for lawn-format screening processes where the compound is released from the resin in situ.[10]

Observations on the acid lability of indole-based systems during combinatorial library production and the subsequent publication of the indole-derived linker **1** by Estep and co-workers at Pfizer[11] suggested an indole-based safety-catch linker (ISC) **2** that could be exploited for the release of secondary amides, sulfonamides, and carbamates. (See Figure 1.)

The modified linker **2** would be predicted to exhibit enhanced stability over **1** to a range of reaction conditions, especially strong acid, but would have the advantage of being cleaved under mild conditions once the safety catch was removed. It was envisaged that protection of the indole nitrogen with various electron-withdrawing groups would prevent the acid-mediated cleavage of the 3-substituent (Scheme 1). Removal of the protecting group would then activate the linker to acid-mediated cleavage. With a variety of protecting groups on the indole nitrogen, the safety catch could be removed under a range of conditions and the linker could then cleaved by acidolysis. In this way, the *mechanism* of the final cleavage step would be the same regardless of the type of safety catch used, ensuring that the releases of material from different linkers would be comparable. This approach would be particularly advantageous in differential release combinatorial library screening,[12] which relies on sequential cleavage of equimolar quantities of library product from single resin beads.

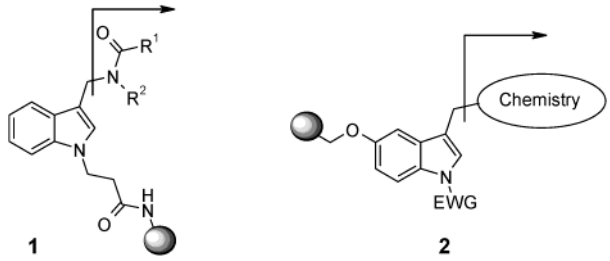

Figure 1. Indole linkers.

This linker family could be exploited for the release of secondary amides, sulfonamides, and carbamates. Herein, we describe proof-of-concept studies, both in solution and on analytical construct resin, for the development of an indole safety-catch linker for the release of secondary amides.

We chose to exploit analytical constructs[13] to explore loading, reaction monitoring, and cleavage of the linker on the solid phase. The key steps in the development of a new linker system are the establishment of good general conditions for loading the resin-bound linker with substrate and for the subsequent cleavage reaction to release target product into solution. Although approaches using FTIR[14] and gel-phase NMR[15] spectroscopies have been developed, these crucial steps are often notoriously difficult to quantify. Immobilizing the linker onto an analytical construct (outlined

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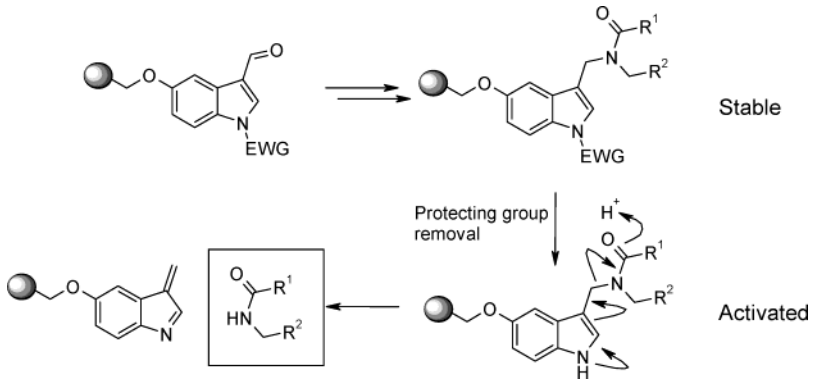
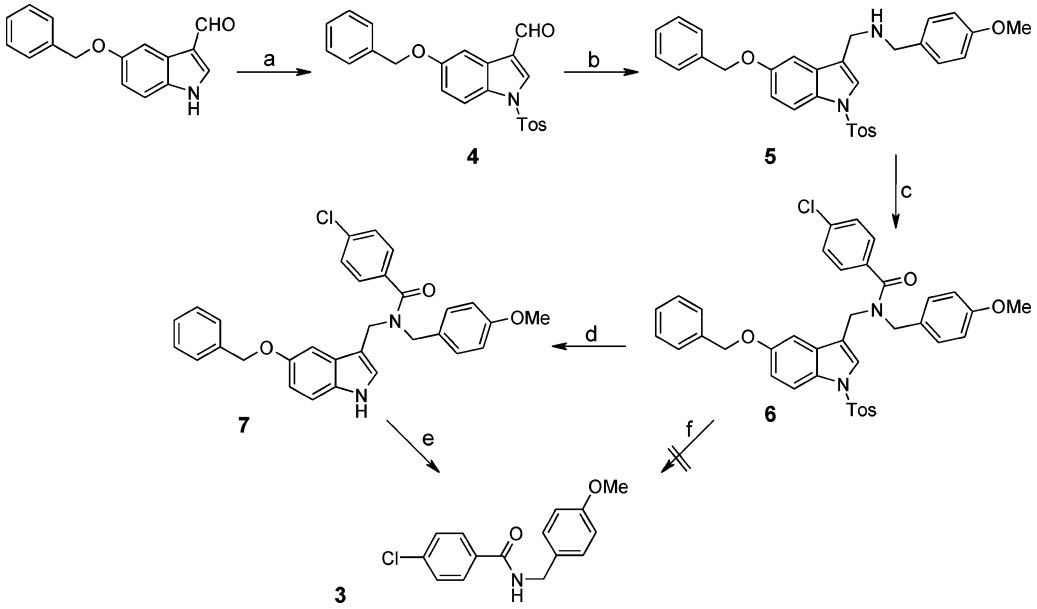
Scheme 1. Indole-Based Safety-Catch Linker Family: Safety-Catch Concept



Scheme 2[a]



[a] Reagents and Conditions: (a) NaH, 4-toluenesulfonyl chloride, DMF, 0°C, 1.5 h, 80%; (b) PS−$CNBH_3$, 4-methoxybenzylamine, MeOH, room temperature (RT), 5 days, 32%; (c) 4-chlorobenzoyl chloride, PS−NMM, PS-DMAP, CH_2Cl_2, RT, 72 h, 80%; (d) KOH, 1,4-dioxane, 90°C, 1 h, 56%; (e) 1% TFA, $CDCl_3$, RT, <1 h, 65%; (f) 50% TFA, $CDCl_3$, RT.

below) and subsequent "analytical cleavage" releases the linker tagged with an embedded UV chromophore and MS signature for rapid high-throughput analysis. This process enables facile monitoring of all reaction steps, including loading and cleavage.

Results and Discussion

(A) Solution-Phase Proof-of-Concept Study for Amide Release. Prior to any solid-phase synthesis being undertaken, it was necessary to carry out a proof-of-concept study in solution. It was important to demonstrate, first, that the activated indole linker did indeed undergo fragmentation under very mild acidic conditions and, second, that the safety-catch-protected linker was reasonably stable to strongly acidic conditions. Amide **3** was chosen for the model study for ease of analysis by NMR spectroscopy (Scheme 2).

Tosylation of 5-benzyloxyindole-3-carboxaldehyde in the presence of sodium hydride proceeded in 80% yield on a small scale to give the protected indole **4**. Reductive amination of **4** with 4-methoxybenzylamine utilizing polymer-supported cyanoborohydride[16] gave the required secondary amine **5** in acceptable yield. Acylation of **5** with 4-chlorobenzoyl chloride in the presence of polymer-supported base gave the amide **6** in 80% yield. Basic hydrolysis at elevated temperature cleaved the tosyl group to give the model activated linker **7**.

Although indole **7** was found to yield the target amide **3** slowly on standing, treatment with 1% TFA in deuteriochloroform resulted in complete release of product **3** in under 1 h. The amide **3** was separated from the indole byproducts by flash chromatography in 85% yield. The stability of the protected indole **6** was investigated by dilution of the NMR sample with an equal volume of TFA. After 2 h, TLC and HPLC analysis indicated no change in the integrity of compound **6**; however, after incubation for 2 days, amide **3** was the only identifiable product.

These results indicated that the release of secondary amides from an indole linker related to model compound **7** should be feasible and that, with an electron-withdrawing protecting group in place, the system would to be sufficiently stable to acidic conditions to enable it to function as a safety-catch linker.

(B) Solid-Phase Proof-of-Concept Study Using Analytical Constructs. Having established the linker concept in

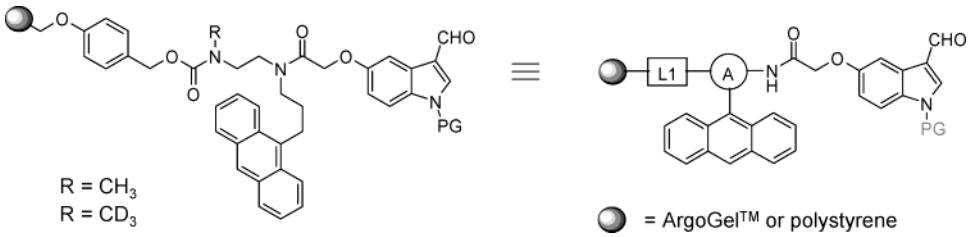
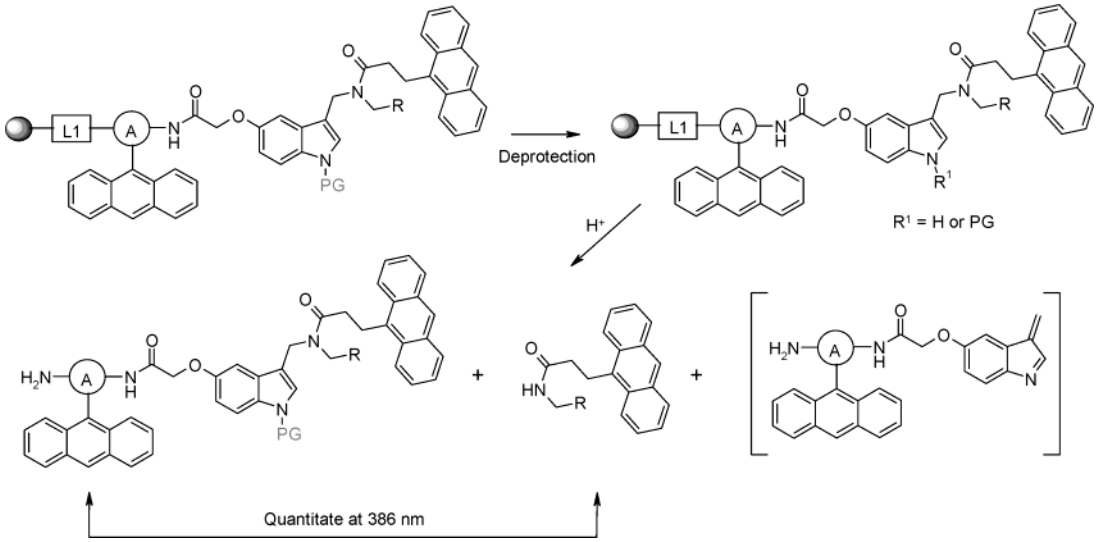


Figure 2. Analytical construct design and schematic representation. L1 = Wang carbamate linker, A = analysis enhancing group for LCMS detection containing,up on cleavage, an amine to ensure consistent MS ionization and a 1:1 isotopic mixture of substrates for rapid peak identification.[13] The use of the anthryl group enables HPLC analysis at 386 nm.[24]

Scheme 3. Schematic Representation of the Exploitation of an Analytical Construct to Monitor the Safety-Catch Cleavage and Substrate Release Steps[a]



[a] Incorporation of an anthryl group in the product secondary amide facilitates the monitoring of the safety-catch cleavage step.

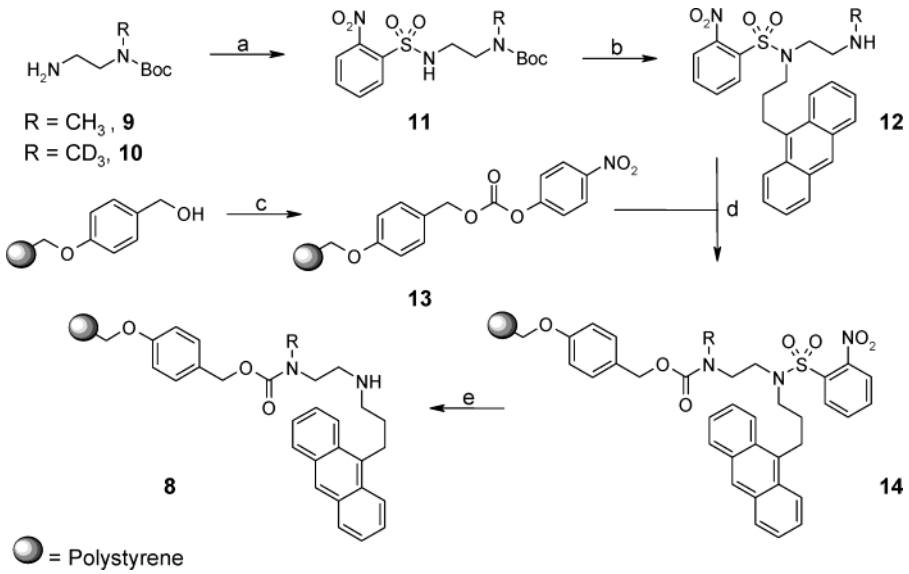
solution, it was considered essential that further work on linker development should take place on the solid phase to avoid any discrepancies between solution- and solid-phase chemistry. In developing new linker systems, the investigation of the loading and release steps is of paramount importance; however, qualitative and quantitative monitoring of these crucial stages is often difficult.[17] Both dual-linker systems[18,19] and analytical constructs[13,20] have been shown to be useful for studying these key steps as part of the process of developing new linkers. In particular, analytical constructs have been exploited for the investigation of linker stability[21,22] and for the automated study of linker loading and cleavage.[23] The solid-phase proof-of-concept studies were therefore carried out with the safety-catch indole linker immobilized on an analytical construct to facilitate the studies of substrate immobilization, safety-catch release, and cleavage of the linker.

By incorporation of the Wang carbamate linker[25] into an analytical construct as an analytical linker (L1, Figure 2), the reductive amination and acylation of substrates bound to the ISC linker could be monitored (Scheme 3). However, removal of the safety catch cannot be easily followed, as analytical cleavage of the construct would result in fragmentation of the activated indole linker, releasing the amide product into solution. This limitation was overcome by incorporating an anthryl group into the secondary amide synthesized on the linker. TFA treatment of the activated linker would therefore release the anthryl-tagged secondary amide into solution, enabling relative quantification by HPLC of this material against any residual construct-linked substrate, also containing the anthryl group, at a chromophore-specific wavelength (386 nm).[24]

The required analytical construct precursor **8** was prepared from a 1:1 mixture of commercially available, labeled mono-Boc-protected diaminoethanes **9** and **10**[26] (Scheme 4). Sulfonation of this mixture with *o*-nitrobenzenesulfonyl chloride gave the doubly protected diamine mixture **11** in high yield. The anthryl chromophore was introduced by Fukuyama−Mitsunobu alkylation of **11** with 3-anthracen-9-yl-propan-1-ol[27] in the presence of polymer-supported triphenylphosphine and di-*tert*-butyl azodicarboxylate.[28] After the reaction was complete, treatment of the reaction mixture with TFA decomposed any residual azodicarboxylate together with the corresponding byproduct. Concomitant Boc deprotection gave the mono-protected diamine **12**. The use of supported triphenylphosphine and the acid removal of byproducts greatly simplified the subsequent purification. Secondary amine **12** was immobilized onto a Wang carbamate linker via the corresponding Wang *p*-nitrophenyl carbonate[29] **13** using polystyrene as the base resin to give resin **14**. Cleavage of the sulfonamide group was achieved by treatment with a solution of sodium thiophenolate in DMF buffered with thiophenol,[23] giving smooth, quantitative conversion to the required resin-bound secondary amine **8**.

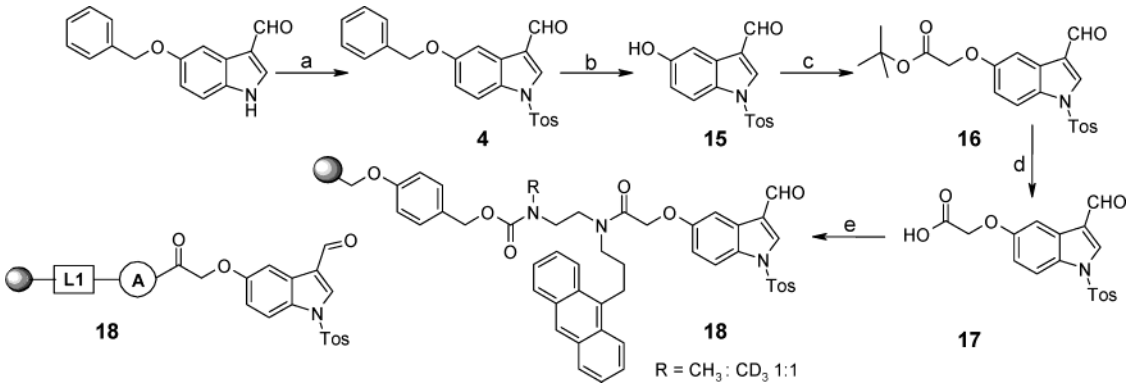
The tosyl group was chosen for the initial study to allow direct comparison with the solution-phase work described

Scheme 4[a]



[a] Reagents and Conditions: (a) *o*-nitrobenzenesulfonyl chloride, DIEA, CH_2Cl_2, room temperature (RT), 20 h, 84%; (b) (i) 3-anthracene-9-ylpropan-1-ol, PS−PPh_2, di-*tert*-butyl azodicarboxylate, CH_2Cl_2, 0°C to RT, 16 h, (ii) TFA, RT, 16 h, 66%; (c) *p*-nitrophenylchloroformate, *N*-methylmorpholine, CH_2Cl_2, RT, 16 h; (d) DIEA, CH_2Cl_2, RT, 20 h, 93%; (e) PhSNa, PhSH, DMF, RT, 2 × 10 min.

Scheme 5[a]



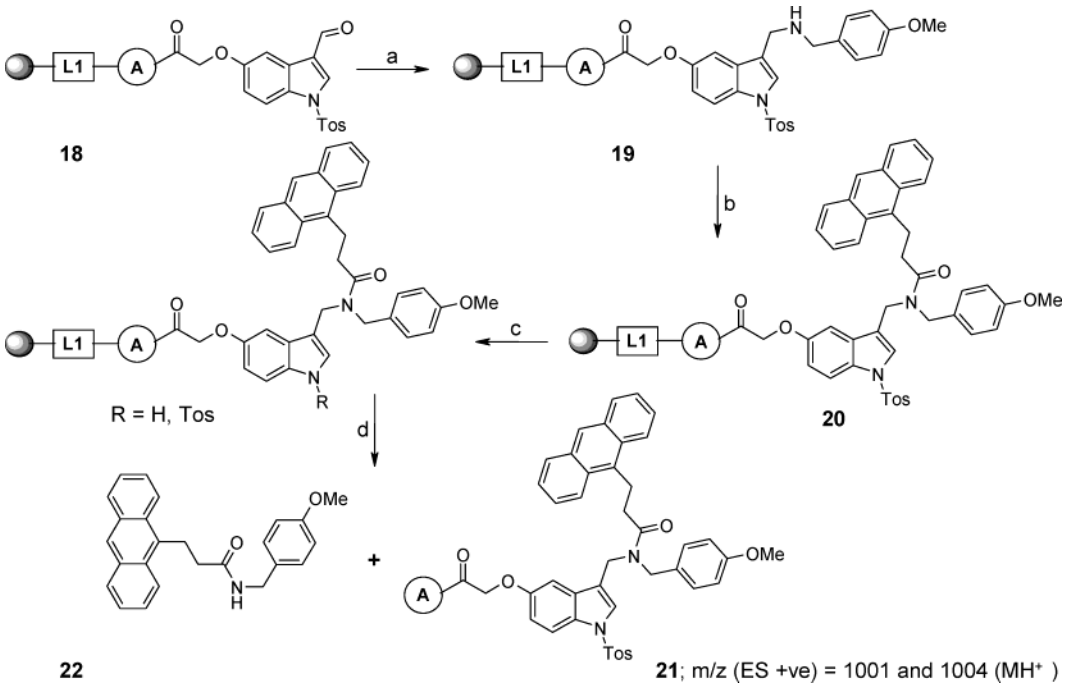
[a] Reagents and Conditions: (a) 4-toluenesulfonyl chloride, Et_3N, 95°C, 1 h, 79%; (b) BCl_3·SMe_2, CH_2Cl_2, room temperature (RT), 3 h, 67%; (c) PS−BEMP, *tert*-butyl bromoacetate, DMF/MeCN, RT, 16 h, 31%; (d) 50% TFA, CH_2Cl_2, RT, 17 h, quant.; (e) **8**, DIC, DMAP, CH_2Cl_2, DMF, RT, 2 × 16 h.

above. The required tosyl-protected indole linker fragment was synthesized from commercial 5-benzyloxyindole-3-carboxaldehyde (Scheme 5). Although protection of this material to give indole **4** in the presence of sodium hydride gave high yields when performed on a small scale (vide infra), *N*-tosylation in triethylamine at 95 °C[30] gave better results upon scale-up. Removal of the benzyl group proceeded smoothly using conditions reported by Congreve et al.[31] to give phenol **15** in good yield. Disappointingly, alkylation of the 5-hydroxyl with *tert*-butyl bromoacetate in the presence of PS−BEMP[32] in DMF and acetonitrile on a small scale gave ester **16** in only low yield (31%). Acidic cleavage of the *tert*-butyl ester gave the required indole linker fragment **17**, which was coupled to the resin-bound secondary amine **8** to give the required analytical construct resin **18**.

With the required analytical construct **18** in hand, the validation chemistry for preparing the anthracene-tagged secondary amide was undertaken (Scheme 6). Each step of the synthesis was followed by analytical cleavage with 1:1 TFA/DCM to release fragments, which were analyzed by HPLC and LCMS. Thus, reductive amination of the resin-bound indole aldehyde **18** with 4-methoxybenzylamine gave secondary amine **19**. Acylation of **19** with 3-anthracen-9-yl-propionic acid[27] in the presence of DIC and catalytic DMAP via double coupling gave the immobilized tertiary amide **20**. Analytical cleavage of **20** gave the corresponding analytical fragment **21**.

Next, the safety-catch release of the linker and liberation of the amide was investigated. For effective removal of the safety catch from the ISC linker, it was necessary to identify mild conditions that would be compatible with a range of substrates immobilized on the linker and with the analytical construct. Cleavage of the widely used *N*-tosyl indole protecting group[33] has been reported under strongly alkaline conditions;[34] with magnesium in methanol;[35] or, more recently, in the presence of TBAF.[36] Samarium iodide has also been reported to de-tosylate amines[37] and was therefore included in the investigation. Because of the heterogeneous nature of the magnesium in methanol system, these conditions were not included in this experiment. Analytical construct **20** was subjected to a range of reaction conditions (Table 1); the resins were then washed and treated with TFA/dichloromethane to release the target amide **22**.

Scheme 6[a]



[a] Reagents and Conditions: (a) (i) 4-methoxybenzylamine, NMP, room temperature (RT), 1 h, (ii) Bu_4NBH_4; (b) 3-anthracen-9-yl-propionic acid, DIC, DMAP, CH_2Cl_2, DMF, RT, 2 × 16 h; (c) TBAF (aq)/THF, 50°C, 17 h; (d) 50% TFA, CH_2Cl_2, RT, 15 min.

Table 1. On-Resin Safety-Catch Release of Tosyl-Protected ISC Linker

entry	conditions	qualitative analysis of reaction washings	% **22** released after treatment with TFA
1	SmI_2, THF, 17 h	small quantity of **21** present	0
2	NaOMe, MeOH, 17 h	small quantity of **21** and **22** (1:1) present	30
3	2M KOH(aq)/THF 17 h	trace quantity of **22** present	0
4	TBAF (aq)/THF, RT[a], 17 h	small quantity of **22** present; no **21** cleaved	50
5	TBAF (aq)/THF, 50 °C, 17 h	small quantity of **22** present; no **21** cleaved	100

[a] Room temperature.

Table 2. Reagents, Equivalents, and Solvents Investigated for Safety-Catch Release

reagent	equiv	mmol	concentration of reagent solution (M)	reagent solution volume (μL)	diluant volume (dry THF, μL)
samarium iodide	10	0.05	0.1	500	0
sodium methoxide	10	0.05	0.5	100	100
potassium hydroxide	40	0.20	2.0	100	100
tetrabutylammonium fluoride	20	0.10	1.0	100	100

Analysis of the washings prior to acidolysis gave an indication of the extent of construct decomposition. Amide **22**[38] was synthesized via solution-phase chemistry for comparison.

In the case of samarium iodide (Table 1, entry 1), HPLC (detection at 386 nm) analysis of the washings after analytical construct cleavage indicated the presence of a small quantity of analytical fragment **21**. However, no **22** was released upon treatment with acid, indicating that this reagent was ineffective at *N*-detosylation of the ISC linker. Under basic conditions (entries 2 and 3), sodium methoxide gave only 30% release of the target amide; however, appreciable quantities of analytical fragment **21** were detected in the resin washings, suggesting that harsher basic conditions at, for example, higher temperature would not be appropriate. Although application of TBAF to the detosylation of the ISC linker at room temperature overnight gave only 50% release of the desired amide, heating at 50 °C for 17 h resulted in no construct decomposition and gave essentially quantitative release of **22** after acidolysis.

In summary, the development of an indole safety-catch linker for the synthesis and release of secondary amides has been described. After an initial solution-phase proof-of-concept study, the power of analytical construct technology was exploited for the rapid and efficient study of the key immobilization and safety-catch cleavage and substrate release steps. Although the tosyl group was shown to be an effective safety-catch protecting group, to be able to apply this linker system to as wide a range of resin-supported chemistry as possible, it is clear that a number of safety-catch groups, stable to different reaction conditions, are required. Equally, aldehyde-based linkers[14] have been exploited for the release of sulfonamides, carbamates, and ureas, as well as secondary amides. Investigations on alternative

Table 3. HPLC and MS Data for Tosyl Safety-Catch Cleavage and Product Release

	resin washings[a]		analytical cleavage[b]	
reagent	HPLC (386 nm)[c]	*m/z*	HPLC (386 nm)	*m/z*
samarium iodide	6.34 (100%)	1002 and 1005	6.32 (100%)	1002 and 1005
sodium methoxide	5.87 (59%)	370	5.99 (22%)	370
	6.31 (41%)	1002 and 1005	6.33 (64%)	1002 and 1005
potassium hydroxide	5.84 (100%)	370	6.29 (75%)	1002 and 1005
tetrabutylammonium fluoride, RT[d]	5.88 (100%)	370	5.99 (43%)	370
			6.33 (42%)	1002 and 1005
tetrabutylammonium fluoride, 50 °C	5.84 (75%)	370	5.93 (86%)	370

[a] Analysis of resin washings prior to analytical cleavage. [b] Analysis of solutions from analytical cleavage (see text). [c] Intensity of HPLC chromatograms of the resin washings was very low. MaU < 50b. [d] Room temperature.

safety-catch groups and the application of this linker family to the synthesis and release of a wider range of functionalities will be reported in a subsequent publication.

Experimental Section

(A) General Methods. All starting materials and reagents were commercially available and used as received without further purification. Where appropriate, reactions were carried out under an inert atmosphere of nitrogen. Thin layer chromatography (TLC) was performed on CamLab SilG/UV254 precoated plates. Flash chromatography was carried out on Merck Kieselgel 60 (0.040−0.063 mm) or by using the Biotage Flash chromatography system under a pressure of nitrogen. Infrared spectra of discrete samples were recorded on a Bio-Rad Win-IR spectrometer by diffuse reflectance on KBr. Infrared spectra of resin samples were obtained by FTIR microspectroscopy using a Perkin-Elmer AutoIMAGE microscope in transmission mode or by ATR using a Perkin-Elmer Spectrum 1 instrument. All ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-400 spectrometer from solutions in deuteriochloroform, except where indicated otherwise. MAS NMR spectra were recorded on a Bruker AM-400 instrument using a Varian Nano NMR probe in deuteriochloroform. The chemical shifts are in δ units relative to TMS ($\delta = 0$) using the indicated solvent as the internal standard. Multiplicities are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; b, broad, and coupling constant *J* values are quoted in hertz. LCMS analyses were performed on a Hewlett-Packard HP 1050 instrument (diode array detection) and a Micromass Platform I (8084) mass spectrometer using electrospray ionization in positive (+ve) and negative (−ve) modes. High-resolution spectra were recorded on a VG Autospec instrument running positive or negative electrospray. Microanalyses were performed by Butterworths Laboratories Ltd., Teddington, Middlesex, U.K. UV spectra for Fmoc determinations were recorded on a Unicam Helios β spectrophotometer. HPLC was run on a Hewlett-Packard 1050 instrument using a Supelco, Supelcosil ABZ+PLUS column (3.3 cm, 4.6 mm ϕ, 3 μm). **Method A.** Eluent: A, water, 0.1% TFA; B, acetonitrile 95%, water 5%, TFA 0.05%. Gradient: from 10 to 95% B in A (1 mL min^{-1}) over 8 min. Detection: UV (diode array: 215, 230, 254, 386 nm). **Method B.** Eluent: A, water, 0.1% TFA; B, acetonitrile 95%, water 5%, TFA 0.05%. Gradient: from 10 to 95% B in A (1 mL min^{-1}) over 18 min. Detection: UV (diode array: 215, 230, 254, 386 nm). Preparative HPLC was run on a Gilson AutoPrep system with a Supelco Supelcosil ABZ+PLUS column (10 cm, 2.12 cm ϕ, 5 μm). **Method A.** Eluent: A, water, 0.1% TFA; B, acetonitrile 95%, water 5%, TFA 0.05%. Gradient: from 10 to 95% B in A (6 mL min^{-1}) over 25 min. Detection: (UV: 215 nm). Melting points were measured on a Mettler FP5 automatic melting point apparatus in open tubes heating from 50 °C at 2 °C min^{-1} and are uncorrected. Evaporation of array samples was carried out in a Genevac HT4 vacuum centrifuge.

(B) Quantification of Resin Loading of Aldehyde Resin. To the swollen (CH_2Cl_2) aldehyde resin (22 mg) was added a solution of 9-fluorenylmethylcarbazate (23 mg, 0.1 mmol) and glacial acetic acid (0.25 mL) in DMF (0.5 mL). The resin was agitated for 20 h; then washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and ether (5 × 5 mL); and then dried in vacuo to give the Fmoc hydrazide derivative.

(C) Analytical Cleavage of the Wang Carbamate Linker. The resin (0.5−2 mg) was incubated in a 20-μL pipet tip containing a filter plug with a solution of TFA in CH_2Cl_2 (20%, 20 μL) for 10 min and then filtered, diluted with HPLC eluant B (70 μL), and analyzed.

(D) Preparation of ISC Linker Building Blocks from 5-Benzyloxy-3-carboxaldehyde. (i) 5-Benzyloxy-1-(toluene-4-sulfonyl)-1H-indole-3-carbaldehyde 4. Procedure A. To a cooled (0 °C) suspension of 5-benzyloxyindole-3-carboxaldehyde (1.00 g, 3.98 mmol) in dry DMF (15 mL) under nitrogen was added sodium hydride (60% dispersion in oil, 187 mg, 4.37 mmol) over 5 min. The reaction mixture was stirred at 0 °C for 30 min and then treated with a solution of *p*-toluenesulfonyl chloride (0.91 g, 4.78 mmol) in DMF (5 mL). After 1.5 h, the reaction was quenched with water (2 mL), and the reaction mixture was diluted with EtOAc (50 mL) and washed with lithium chloride solution (10%, 2 × 25 mL). The aqueous phases were extracted with EtOAc (50 mL), and the combined organic phases were washed with saturated brine (50 mL) and then dried ($MgSO_4$), filtered, and evaporated to a semisolid gum. Flash chromatography (EtOAc/hexane 1:4) gave the title compound as white needles (1.29 g, 80%). mp 170.7 °C. R_f 0.33 [EtOAc/hexane (1:4)]. Found: C, 67.86; H, 4.45; N, 3.42; S, 7.91%. $C_{23}H_{19}NO_4S$ requires C, 68.13; H, 4.72; N, 3.45; S, 7.91%. Found: MH^+, 406.1105; MH, $C_{23}H_{20}NO_4S$ requires 406.1113. ν_{max} (cm^{-1}): 1679 (CHO), 1379, 1176 (SO_2N). δ_H (400 MHz): 10.01

(s, 1H), 8.16 (s, 1H), 7.79−7.85 (m, 4H), 7.41−7.46 (m, 2H), 7.35−7.40 (m, 2H), 7.30−7.39 (m, 1H), 7.28 (d, 2H, J = 8 Hz), 7.08 (dd, 1H, J = 3 + 9 Hz), 5.08 (s, 2H), 2.37 (s, 3H). δ_C (100 MHz): 184.6, 156.0, 145.2, 135.9, 135.8, 133.6, 129.4, 129.0, 127.7, 127.2, 126.8, 126.5, 126.3, 121.4, 115.8, 113.3, 104.5, 69.7, 20.8. LCMS: 6.32 min (electrospray +ve), m/z 406 $(MH)^+$. HPLC (method A): 6.41 min, 100% (230 nm).

Procedure B. A mixture of tosyl chloride (2.91 g, 15.24 mmol), 5-benzyloxyindole-3-carboxaldehyde (2.51 g, 10.00 mmol), and triethylamine (25 mL) was heated at 95 °C for 1 h 15 min and then poured onto ice−water (35 mL). After standing for 2 h at 0 °C, the reaction mixture was filtered, and the residue was washed with water (60 mL), air-dried, and recrystalized from ethyl acetate to give the title compound as white needles (2.24 g). The mother liquors were evaporated and purified by flash chromatography (Biotage, EtOAc/hexane 1:4) to give the title compound as white needles (0.79 g). Total yield = 79%. mp 170.6 °C. R_f 0.33 [EtOAc/hexane (1:4)]. LCMS: 5.62 min (electrospray +ve), m/z 406 $(MH)^+$. HPLC (method A): 6.49 min, 99% (254 nm). ^{1}H and ^{13}C NMR data for this material was found to be identical to that obtained by procedure A.

(ii) 5-Hydroxy-1-(toluene-4-sulfonyl)-1*H*-indole-3-carbaldehyde 15. To a solution of the tosylindole **4** (794.1 mg, 1.96 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen at room temperature was added a solution of boron trichloride dimethyl sulfide in CH_2Cl_2 (2M, 5.0 mL, 10.0 mmol). The reaction mixture was stirred for 3 h and then treated with saturated $NaHCO_3$ solution (10 mL); the mixture was again stirred for 30 min and then diluted with water (60 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with water (50 mL) and saturated brine (50 mL) and then dried ($MgSO_4$), filtered, and evaporated to a white solid. Purification by flash chromatography [Biotage; EtOAc/hexane (1:3)] gave the title compound as a yellow semicrystalline solid (553.4 mg, 90%). R_f 0.11 [EtOAc/hexane (1:4)]. Found: C, 60.99; H, 4.29; N, 4.63; S, 9.91%. $C_{16}H_{13}NO_4S$ requires C, 60.94; H, 4.16; N, 4.44; S, 10.17%. ν_{max} (cm^{-1}): 3300 (OH), 1670 (C=O), 1374, 1167 (SO_2N). δ_H (400 MHz): 10.00 (s, 1H), 9.61 (bs, 1H), 8.75 (s, 1H), 7.95 (d, 2H, J = 8.5 Hz), 7.74 (d, 1H, J = 9 Hz), 7.47 (d, 1H, J = 2.5 Hz), 7.44 (d, 2H, J = 8.5 Hz), 6.88 (dd, 1H, J = 9 + 2.5 Hz), 2.34 (s, 3H). δ_C (100 MHz): 187.5, 156, 147, 139, 133.5, 131, 128.5, 128, 127.5, 122, 116, 114.5), 107, 21.5, LCMS: 4.98 min (electrospray +ve), m/z 316 $(MH)^+$. HPLC (method A): 4.93 min, 100% (230 nm).

(iii) [3-Formyl-1-(toluene-4-sulfonyl)-1*H*-indol-5-yloxy] Acetic Acid *tert*-Butyl Ester 16. To a suspension of the 5-hydroxy indole **15** (843.7 mg, 2.68 mmol) in 10% DMF in CH_2Cl_2 (25 mL) was added PS−BEMP followed by *tert*-butyl bromoacetate (454.0 μL, 2.81 mmol). The reaction mixture was agitated for 20 h and then filtered; the residue was washed with MeCN (100 mL), and the combined filtrates evaporated to a dark gum. Purification by flash chromatography [Biotage, EtOAc/hexane (1:4)] gave the title compound as a white solid (360.8 mg, 31%). mp 144.6 °C. R_f 0.42 [EtOAc/hexane (1:4)]. Found: C, 61.42; H, 5.13; N, 3.15; S, 7.30%. $C_{22}H_{23}NO_6S$ requires C, 61.52; H, 5.40; N, 3.26; S, 7.47%. Found: MH^+, 430.1342; MH, $C_{22}H_{24}NO_6S$ requires 430.1324. ν_{max} (cm^{-1}): 2970 (ArH), 1747 (C=O, ester), 1677 (C=O, aldehyde), 1175 (SO_2N). δ_H (400 MHz): 10.00 (s, 1H), 8.79 (1H), 7.95 (d, 2H, J = 9 Hz), 7.82 (d, 1H, J = 10 Hz), 7.48 (d, 1H, J = 3 Hz), 7.41 (d, 2H, J = 9 Hz), 7.04 (dd, 1H, J = 3 + 10 Hz), 4.65 (s, 2H), 2.31 (s, 3H), 1.38 (s, 9H). δ_C (100 MHz): 187.1, 168.10, 156.0, 146.8, 139.3, 133.6, 130.9, 129.4, 127.5, 127.1, 121.6, 115.9, 114.5, 105.2, 81.9, 65.9, 27.9, 21.4. LCMS: 5.46 min (electrospray +ve), m/z 374 $([M\text{-}t\text{Bu}]H)^+$. HPLC (method A): 6.14 min, 98% (230 nm).

(E) Alternative Procedure Using Potassium Carbonate in DMF. To a suspension of the 5-hydroxy indole **15** (258.5 mg, 0.82 mmol) in DMF (5 mL) was added *tert*-butyl bromoacetate (310.0 μL, 1.80 mmol) followed by potassium carbonate (125.0 mg, 0.90 mmol). The reaction mixture was stirred for 20 h and then poured onto aqueous hydrochloric acid (1 M, 25 mL) and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with lithium chloride solution (10%, 25 mL), water (10 mL), and saturated brine (10 mL) and then dried ($MgSO_4$), filtered, and evaporated to yield a dark gum. Purification by flash chromatography [Biotage, EtOAc/hexane (1:4)] gave the title compound as a white solid (272.5 mg, 77%). The spectral data were in accordance with those of the previously prepared compound.

(i) [3-Formyl-1-(toluene-4-sulfonyl)-1*H*-indol-5-yloxy] Acetic Acid 17. To a solution of the *tert*-butyl ester **16** (1.24 g, 2.90 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL) and water (0.5 mL). The reaction mixture was stirred for 2 h and then evaporated, and the residue was triturated with ether/hexane to give the title compound as a white solid (1.04 g, 96%). mp 158.5 °C. R_f 0.34 [$CHCl_3$: MeOH (9:1)]. Found: MH^+, 374.0709; MH, $C_{18}H_{15}NO_6S$ requires 374.0698. ν_{max} (cm^{-1}): 3290 (OH), 2930 (ArH), 1763 (C=O, acid), 1670 (C=O,aldehyde), 1174 (SO_2). δ_H (400 MHz, DMSO-d_6): 13.00 (bs, 1H), 10.00 (s, 1H), 8.80 (s, 1H), 7.95 (d, 2H, J = 9 Hz), 7.83 (d, 1H, J = 10 Hz), 7.49 (d, 1H, J = 2 Hz), 7.42 (d, 2H, J = 9 Hz), 7.04 (dd, 1H, J = 2 Hz), 4.68 (s, 2H), 2.28 (s, 3H). δ_C (100 MHz, DMSO-d_6): 187.1, 167.9, 153.6, 144.4, 139.4, 136.9, 131.0, 129.2, 128.6, 128.6, 121.7, 115.8, 114.5, 105.3, 66.3, 21.3. LCMS: 5.12 min (electrospray +ve), m/z 374 $(MH)^+$. HPLC (method A): 4.79 min, 97% (215 nm).

(F) Preparation of the Analytical Construct for ISC Linker Investigations. (i) Methyl-[2-(2-nitro-benzenesulfonylamino)ethyl] Carbamic Acid *tert*-Butyl Ester Mixture with Trideuteriomethyl Analogue (1:1) 11. To a solution of (2-aminoethyl)methyl carbamic acid *tert*-butyl ester **9** (3.20 g, 20.0 mmol), (2-aminoethyl)trideuteriomethyl carbamic acid *tert*-butyl ester **10** (3.20 g, 20.0 mmol), and DIEA (8.70 mL, 50.0 mmol) in CH_2Cl_2 (50 mL) was added a solution of *o*-nitrobenzenesulfonyl chloride (9.30 g, 43.0 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 20 h; evaporated in vacuo; dissolved in EtOAc (150 mL); and then washed with aqueous citric acid solution (1 M, 2 × 50 mL), saturated aqueous sodium bicarbonate solution (50 mL), and saturated brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to give a brown

oil. Flash chromatography (EtOAc/hexane, 1:1) gave the title compound as a brown oil (12.1 g, 84%). R_f 0.3 [EtOAc/hexane (1:1)]. Found for the H component: MH^+, 360.1237; MH, $C_{14}H_{21}N_3O_6S$ requires 360.1229. ν_{max} (cm^{-1}): 3300 (NH), 2950 (Ar−H), 1692 (C═O), 1547 (NO_2), 1368, 1174 (SO_2), 742 (SO_2−N). δ_H (400 MHz): 8.08−8.13 (m, 1H), 7.80−7.86 (m, 1H), 7.69−7.75 (m, 2H), 5.5−5.8 (bd, 1H), 3.35−3.40 (m, 2H), 3.25 (bs, 2H), 2.81 (bs, 1.5H), 1.42 (s, 9H), δ_C (100 MHz): 154.0, 148.5, 133.9, 133.1, 131.8, 131.2, 125.7 80.7, 48.6, 42.6, 35.3, 28.7. LCMS: 6.72 min (electrospray +ve), *m*/*z* 276 $(MH)^+$. HPLC (method A): 4.82 min, 100% (230 nm).

(ii) {2-[(3-Anthracen-9-yl-propyl)-(2-nitrobenzenesulfonyl)amino]ethyl}methyl Carbamic Acid *tert*-Butyl Ester Mixture with Trideuteriomethyl Analogue (1:1) 12. To a suspension of the sulfonamide **11** (1.82 g, 5.06 mmol), 3-anthracen-9-yl-propan-1-ol (2.39 g, 10.31 mmol) and PS−triphenylphosphine (4.22 g, 12.65 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added di-*tert*-butylazodicarboxylate (2.33 g, 10.13 mmol). The reaction mixture was allowed to warm to room temperature (RT) over 16 h and then treated with TFA (25 mL). After being stirred for 16 h, the reaction mixture was filtered, the residue was washed with CH_2Cl_2 (2 × 50 mL), and the combined filtrates were evaporated. The residue was dissolved in EtOAc (150 mL) and washed with potassium carbonate solution (2M, 2 × 100 mL), water (100 mL), and saturated brine (100 mL); it was then dried (Na_2SO_4), filtered, and evaporated to a brown gum. Flash chromatography (Biotage, $CHCl_3$/MeOH/Et_3N, 19:1:0.1) gave the title compound as a brown gum (1.64 g, 66%). R_f 0.47 [$CHCl_3$/MeOH (19:1)]. Found for the hydro analogue: MH^+, 478.1805; MH, $C_{26}H_{28}N_3O_4S$ requires 478.1801. ν_{max} (cm^{-1}): 3400 (NH), 3054 (ArH), 1545 (NO_2), 1351, 1162 (SO_2), 734 (SO_2−N). δ_H (400 MHz): 8.32 (s, 1H), 8.14 (d, 2H, J = 8 Hz), 7.98 (d, 2H, J = 8 Hz), 7.88 (d, 1H, J = 9 Hz), 7.40−7.58 (m, 7H), 3.50−3.60 (m, 4H), 3.46 (m, 2H), 2.75 (m, 2H), 2.35 (s, 1.5H), 2.0 (m, 2H). δ_C (100 MHz): 134.5, 134.1, 134.0, 132.4, 131.7, 130.4, 130.2, 126.9, 126.7, 125.8, 124.9, 124.8, 50.5, 48.9, 47.3, 36.7, 30.3, 25.7. LCMS: 4.58 min (electrospray +ve), *m*/*z* 478 and 481 $(MH)^+$. HPLC (method A): 4.47 min, 93% (386 nm).

(iii) Carbonic Acid Wang Polystyrene Resin Ester 4-Nitrophenyl Ester 13. To a washed (dry CH_2Cl_2) suspension of Wang polystyrene resin (1.0 g, loading unknown, assumed 1 mmol g^{-1}, on polystyrene resin) and *N*-methylmorpholine (550 μL, 5.0 mmol) in dry CH_2Cl_2 (5.0 mL) was added a solution of *p*-nitrophenylchloroformate (1.0 g, 5.0 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction was agitated for 16 h, and the resin was washed with CH_2Cl_2 (2 × 10 mL), DMF (5 × 10 mL), and CH_2Cl_2 (5 × 10 mL) and then dried in vacuo to give the title resin as an orange resin (1.30 g). Found: C, 80.38; H, 6.01; N, 1.88%. ν_{max} (cm^{-1}): 1769 (C═O), 1525 (NO_2). Loading = 1.34 mmol g^{-1} by elemental analysis of nitrogen.

(iv) {2-[(3-Anthracen-9-yl-propyl)-(2-nitro-benzenesulfonyl)amino]ethyl}methyl Carbamic Acid Wang Polystyrene Resin Ester Mixture with the Trideuteriomethyl Analogue (1:1) 14. To a suspension of the swollen prewashed (CH_2Cl_2, 3 × 5 mL) resin **13** (1.06 mmol g^{-1}, 1.38 g, 1.46 mmol) in CH_2Cl_2 (5 mL) was added a solution of **12** (1.53 g, 3.20 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was agitated for 20 h and then filtered. The resin was washed with CH_2Cl_2 (3 × 10 mL), DMF (5 × 10 mL), CH_2Cl_2 (5 × 10 mL), and ether (3 × 10 mL) and dried in vacuo to give an orange resin (1.62 g). Analytical cleavage indicated incomplete reaction. The reaction was repeated as above to give the title resin (1.74 g, 93%) as an orange resin. Found: C, 76.90; H, 6.05; N, 3.42; S, 2.55%. ν_{max} (cm^{-1}): 1667 (C═O), 1585 (NO_2). Loading = 0.78 mmol g^{-1} by elemental analysis of sulfur; 0.81 mmol g^{-1} by elemental analysis of nitrogen. Analytical cleavage (method D) gave LCMS: 4.61 min (electrospray +ve), *m*/*z* 478 and 481 $(MH)^+$. HPLC (method A): 4.51 min, 92% (386 nm).

(v) [2-(3-Anthracen-9-yl-propylamino)ethyl]methyl Carbamic Acid Wang Polystyrene Resin Ester Mixture with the Trideuteriomethyl Analogue (1:1) 8. To a suspension of the swollen (DMF) resin **14** (102.3 mg, approx 0.08 mmol) was added a solution of sodium thiophenolate (280.6 mg, 2.12 mmol) and thiophenol (56.0 μL, 0.53 mmol) in DMF (2 mL). The reaction mixture was agitiated for 10 min, after which the resin washed wsa with DMF (3 × 5 mL) and the reaction repeated. Finally, the resin was washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and ether (5 × 5 mL) and then dried in vacuo to give the title resin (83.2 mg, 98%). ν_{max} (cm^{-1}): 3028 (ArH), 1714 (C═O); the resin gave a positive Bromophenol blue test. Analytical cleavage (method A) gave LCMS 3.88 min (electrospray +ve), *m*/*z* 293 and 296 $(MH)^+$. HPLC (method A): 3.31 min, 93% (386 nm).

(vi) [2-((3-Anthracen-9-yl-propyl)-{2-[3-formyl-1-(toluene-4-sulfonyl)-1*H*-indol-5-yloxy]acetyl}amino)ethyl]-methyl Carbamic Acid Wang Polystyrene Resin Ester Mixture with the Trideuteriomethyl Analogue (1:1) 18. To a suspension of the resin **8** (50 mg, 0.62 mmol) in CH_2Cl_2 (1 mL) was added a solution of acid **17** (0.186 mmol), PyBOP (128 mg, 0.246 mmol), and HOBt (33 mg, 0.246 mmol) in DMF (2 mL). After 5 min, DIEA (86 μL, 0.50 mmol) was added, and the reaction mixture was agitated for 17 h. The resin was washed with DMF (5 × 3 mL), CH_2Cl_2 (5 × 3 mL), and ether (5 × 3 mL) and then dried in vacuo to give the title resin (63.4 mg). Analytical cleavage (method D) gave LCMS: 4.65 min (electrospray +ve), *m*/*z* 648 and 651 $(MH)^+$. HPLC (method A): 5.06min, 100% (386 nm).

(G) Solution-Phase Proof-of-Concept Studies Using the Tos-Protected ISC Linker. (i) [5-Benzyloxy-1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]-(4-methoxybenzyl)-amine 5. To a solution of the aldehyde **4** (100 mg, 0.25 mmol) in methanol (2 mL) and CH_2Cl_2 (1 mL) were added 4-methoxybenzylamine (35.5 μL, 0.27 mmol) and (polystyrylmethyl)trimethylammonium cyanoborohydride (124 mg, 0.50 mmol). The reaction mixture was agitated for 24 h, and then a further quantity of (polystyrylmethyl)trimethylammonium cyanoborohydride (124 mg, 0.50 mmol) was added and agitation was continued for 5 days. The reaction mixture was filtered and evaporated to yield a gum. Purification by SPE, eluting with ether, gave the title compound as a clear gum (43.7 mg, 33%). R_f 0.64 [$CHCl_3$/MeOH (9:1)]. ν_{max} (cm^{-1}): 2835 (NH), 1368, 1172 (SO_2). δ_H (400 MHz): 7.88 (d, 1H, J = 9 Hz), 7.71 (d, 2H, J = 9 Hz), 7.40−7.45

(m, 3H), 7.28−7.40 (m, 3H), 7.22 (d, 2H, J = 9 Hz), 7.18 (d, 2H, J = 9 Hz), 7.05 (d, 1H, J = 2.5 Hz), 6.99 (dd, 1H, J = 2.5 + 10 Hz), 6.86 (d, 2H, J = 9 Hz), 5.03 (s, 2H), 3.82 (d, 2H, J = 1 Hz), 3.78 (s, 3H), 3.72 (s, 2H), 2.31 (s, 3H). δ_C (100 MHz): 159.1, 155.9, 145.1, 137.4, 135.7, 132.6, 131.7, 130.2, 129.8, 129.0, 128.4, 128.0, 127.1, 125.0, 122.0, 115.1, 114.8, 114.2, 104.1, 71.0, 55.7, 53.1, 44.0, 21.9. LCMS: 5.09 min (electrospray +ve), m/z 527 $(MH)^+$, 390 $(M\text{-}Tos)NH_4^+$.

(ii) *N*-[5-Benzyloxy-1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]-4-chloro-*N*-(4-methoxybenzyl)benzamide 6. To a solution of the amine **5** (43 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) were added morpholinomethyl polystyrene (94 mg, 0.180 mmol) and PS-DMAP (20 mg) followed by 4-chlorobenzoyl chloride (9.8 μL, 0.088 mmol). The reaction mixture was agitated for 72 h and then filtered and evaporated to yield a white foam. Flash chromatography (EtOAc/hexane, 1:2, Biotage) gave the title compound as a white solid (43.8 mg, 80%). R_f 0.78 [EtOAc/hexane (1:1)]. Found: MH^+, 665.1882; MH, $C_{38}H_{33}N_2O_5SCl$ requires 665.1882. ν_{max} (cm^{-1}): 1629, 1610 (C═O), 1365, 1171 (SO_2N). δ_H (400 MHz): 7.91 (d, 1H, J = 9 Hz), 7.72 (d, 2H, J = 9 Hz), 7.15−7.45 (m, 13H), 7.02 (m, 3H), 6.88 (d, 2H, J = 9 Hz), 5.00 (s, 2H), 4.70 (bs, 2H), 4.20 (bs, 2H), 3.80 (s, 3H), 2.31 (s, 3H). δ_C (100 MHz): 171.2, 159.2, 156.2, 145.5, 137.2, 136.2, 135.5, 134.8, 130.6, 130.3, 129.2, 128.9, 128.6, 128.4, 128.0, 127.1, 118.4, 115.7, 115.2, 114.8, 103.8, 70.8, 55.7, 22.0. LCMS: 6.10 min (electrospray +ve), m/z 667 and 665 $(MH)^+$. HPLC (method A): 7.25 min, 100% (230 nm).

(iii) *N*-(5-Benzyloxy-1*H*-indol-3-ylmethyl)-4-chloro-*N*-(4-methoxybenzyl)benzamide 7. To a solution of the protected indole **6** (16.1 mg, 0.024 mmol) in 1,4-dioxane (1 mL) was added potassium hydroxide solution (0.5 mL). The mixture was heated at 90 °C for 1 h and then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to a clear gum. Flash chromatography (EtOAc/hexane, 1:2) gave the title compound as a yellow gum (6.9 mg, 56%). R_f 0.22 [EtOAc/hexane (1:2)]. Found: MNa^+, 533.1612 MNa, $C_{31}H_{27}N_2ClO_3Na$ requires 533.1608). δ_H (400 MHz): 8.05 (bs, 1H), 7.20−7.50 (m, 16H), 6.95 (dd, 1H, J = 3 + 9 Hz), 5.04 (s, 2H), 4.5−4.8 (bs, 2H), 4.15−4.30 (bs, 2H), 3.78 (s, 3H). LCMS: 5.87 min (electrospray +ve), m/z 511 and 512 $(MH)^+$, 236 $(M\text{-}275)^+$. HPLC (method A): 6.68 min, 95% (230 nm).

(iv) 4-Chloro-*N*-(4-methoxybenzyl)benzamide 3. To a solution of the indole **7** (6.9 mg, 0.014 mmol) in $CDCl_3$ (0.75 mL) was added a mixture of TFA (7.5 μL) and water (10.0 μL). After 2 h, the reaction mixture was evaporated and then purified by flash chromatography [Biotage, EtOAc/hexane (1:2)] to give the title compound as a clear gum (2.5 mg, 65%). R_f 0.61 [EtOAc/hexane (1:2)]. ν_{max} (cm^{-1}): 1630; δ_H (400 MHz): 9.00 (bt, 1H), 7.71 (d, 2H, J = 9 Hz), 7.38 (d, 2H, J = 9 Hz), 7.27 (d, 2H, J = 9 Hz), 6.88 (d, 2H, J = 9 Hz), 4.56 (d, 2H, J = 6 Hz), 3.79 (s, 3H). δ_C (100 MHz): 167.5, 136.2, 133.7, 130.4, 157.2, 128.2, 127.7, 127.4, 112.7, 54.1, 41.2. LCMS: 6.72 min (electrospray +ve), m/z 276 $(MH)^+$. HPLC (method A): 4.82 min, 100% (230 nm).

(H) Solid-Phase Proof-of-Concept Studies Using the Tos-Protected ISC Linker. (i) [2-((3-Anthracen-9-yl-propyl)-{2-[3-[(4-methoxy-benzylamino)-methyl]-1-(toluene-4-sulfonyl)-1*H*-indol-5-yloxy]acetyl}amino)ethyl]methyl Carbamic Acid Wang Polystyrene Resin Ester Mixture with the Trideuteriomethyl Analogue (1:1) 19. To a suspension of the swollen (CH_2Cl_2) aldehyde resin **18** (25.3 mg, approx 0.02 mmol) in NMP (0.25 mL) were added 4-methoxybenzylamine (17 μL, 0.13 mmol) and acetic acid (7.5 μL, 0.13 mmol). The reaction mixture was shaken for 2 h and then treated with a solution of tetrabutylammonium borohydride (33 mg, 0.13 mmol) in NMP (0.25 mL). After 5 h, analytical cleavage of the resin showed the reaction to be complete. The resin was washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL) and ether (5 × 5 mL) and then dried in vacuo to give the title resin (32.8 mg). Analytical cleavage (method D) gave HPLC (method A): 4.40 min, 86% (386 nm).

(ii) {2-[{2-[3-{[(3-Anthracen-1-yl-propionyl)-(4-methoxybenzyl)amino]methyl}-1-(toluene-4-sulfonyl)-1*H*-indol-5-yloxy]acetyl}-(3-anthracen-9-ylpropyl)amino]ethyl}-methyl Carbamic Acid Wang Polystyrene Resin Ester Mixture with the Trideuteriomethyl Analogue (1:1) Ester 20. To a suspension of secondary amine resin **19** (28.0 mg, approximately 0.028 mmol) in DMF (0.25 mL) was added a preformed solution of the anthracene acid (35.0 mg, 0.14 mmol) and DIC (22.0 μL, 0.14 mmol) with catalytic DMAP in CH_2Cl_2 (0.35 mL). After 16 h, the resin was washed with CH_2Cl_2 (2 × 2 mL), DMF (5 × 2 mL), and CH_2Cl_2 (5 × 2 mL), and analytical cleavage showed the reaction was incomplete. The entire reaction was repeated as above, and the resin was dried in vacuo to give the title resin (33.2 mg) as an orange solid. Analytical cleavage (method D) gave LCMS: 5.20 min (electrospray +ve), m/z 1002 and 1005 $(MH)^+$. HPLC (method A): 6.33 min, 74% (386 nm).

(iii) 3-Anthracen-9-yl-*N*-(4-methoxybenzyl)propionamide 22. To a solution of 3-anthracen-9-yl-propionic acid (25.5 mg, 0.102 mmol) and 4-methoxybenzylamine (13.1 μL, 0.10 mmol) in DMF (0.1 mL) and CH_2Cl_2 (2 mL) was added PS−carbodiimide (0.93 mmol g^{-1}, 220.0 mg, 0.21 mmol). The reaction mixture was stirred for 12 h and then filtered and evaporated to give the title compound as a white solid (27.5 mg, 74%). Found: MH^+, 370.1812; MH, $C_{25}H_{24}NO_2$ requires 370.1807. ν_{max} (cm^{-1}): 3299 (NH), 2932 (ArOMe), 1654 (C═O), 1550 (amide II), 1248 (ArOMe). δ_H (400 MHz): 8.35 (bs, 1H), 8.29 (d, 2H, J = 9 Hz), 8.00 (d, 2H, J = 9 Hz), 7.43−7.53 (m, 4H), 6.94 (d, 2H, J = 9 Hz), 6.75 (d, 2H, J = 9 Hz), 5.38 (bm, 1H), 4.26 (d, 2H, J = 7 Hz), 4.02 (m, 2H), 3.76 (s, 3H), 2.65 (m, 2H). δ_C (100 MHz): 172.3, 159.4, 133.4, 132.0, 130.4, 130.0, 129.6, 129.5, 126.7, 126.3, 125.4, 124.5, 114.4, 55.7, 43.7, 38.2, 24.1. HPLC (method A): 5.97 min, 100% (230 nm).

(I) On-Resin Safety-Catch Release of the Tosyl-Protected ISC Linker. Five weighed samples of resin **20** (4.5 mg, approximately 0.005 mmol per reaction) were transferred into the reaction wells of an ACT PLS 4 × 6 organic synthesizer. The tube outlets were connected to a Vacmaster 20 sample processing station fitted with Teflon taps and suba seals. The reaction mixtures were flushed with

nitrogen and then treated with the required reagent and agitated for 19 h either at room temperature or while being heated at 50 °C. The resins were washed with THF (2 × 250 μL) and CH_2Cl_2 (2 × 250 μL). The washings were retained and analyzed by HPLC and LCMS (Table 3), and the washed resins were sampled (approximately 1−2 mg) and cleaved analytically by treatment with 50% TFA in CH_2Cl_2 (20 μL) for 5 min, after which they were diluted with HPLC solvent B (70 μL) and filtered. The filtrate was analyzed by HPLC and LCMS.

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References and Notes

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