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‘Catch and release’ cascades: a resin-mediated three-component cascade approach to small molecules

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Abstract—The application of a ‘catch and release’ approach to palladium-catalysed multi-component cascade reactions leads to diverse libraries of pharmacologically interesting small molecules in high yield and with excellent purity.

1. Introduction

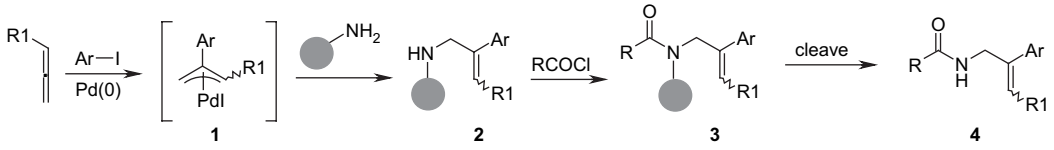
The development of high-throughput screening emphasised the need for new techniques to synthesise compound libraries with ‘drug-like’ properties. Classical multi-step solution-phase synthesis cannot generate large numbers of compounds in a parallel fashion, and thus new methods have been developed to enable rapid synthesis and separation of a desired compound from by-products and/or excess reagents. One way to approach this problem is to attach the desired compound to a solid support, and to separate it from by-products/reagents by filtration. The desired compound is then released from the resin and isolated in high purity.[1–3]

This resin-bound approach has become central to the drug discovery process in the pharmaceutical industry. Reactions can be driven to completion through the use of excess reagents; resin-washing is a very simple way of removing undesired reagents and by-products; physical losses are minimised since the product remains attached to the resin throughout the synthetic process; the process is highly amenable to automation. Nevertheless, there are limitations to undertaking synthetic processes with resin-bound products, in particular the diminished rate of some reactions compared to their solution-phase equivalent, and the often laborious development time for optimising solution-phase chemistry on a solid support.[4,5]

Recent developments in combinatorial synthesis have focused on these limitations. One method, known as ‘resin capture’ or ‘catch and release’, minimises these drawbacks by initiating the synthesis of a library in solution and subsequently transferring the product of the solution-phase synthesis onto solid support for further manipulation and isolation. First published by Armstrong and Brown to synthesise tetrasubstituted ethylenes,[6] the ‘catch and release’ approach enables the facile synthesis of quite complex products with exceptional purity and is now a commonly used combinatorial technique.[7–16]

2. Palladium-catalysed ‘catch and release’ cascade

The objective of the present study was to apply an extended ‘catch and release’ strategy to the palladium-catalysed three-component cascade reaction incorporating aryl iodides, allenes and nitrogen nucleophiles (Scheme 1). Previous work within our group had shown that the three-component catalytic cascade was amenable to solid-phase synthesis when the aryl iodide[17] or allene[18] was pre-attached to the resin. Our envisaged approach would extend this



1 2 3 4

Scheme 1.

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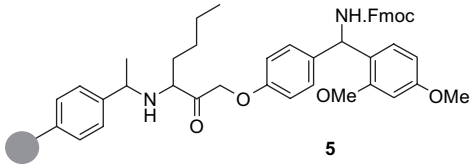
methodology in two ways: by utilising a resin-bound nucleophile to capture the product onto resin; by carrying out further manipulation of the resin-bound product prior to cleavage. It was hoped that this method would allow the rapid construction of diverse libraries of pharmacologically interesting small molecules.

Thus the π-allylpalladium species **1** (formed in solution from an allene and aryl iodide) would be captured by a resin-bound amino group to give resin-bound product **2**. Further manipulation of **2** by, for example, acylation with an acid chloride would provide resin-bound allylic amide **3**. This could be further functionalised or cleaved immediately to give **4**.

2.1. Development of methodology

A good resin for 'catch and release' strategies is Rink Amide MBHA resin **5**. Deprotection of the Fmoc group leaves a primary amino group, which is an ideal nucleophile for our cascade and the presence of the methoxy substituents facilitates cleavage via extended delocalisation of the carbocation via the oxygen lone pairs.



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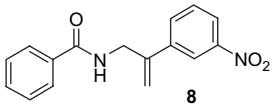
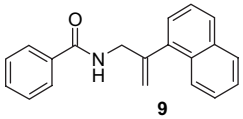
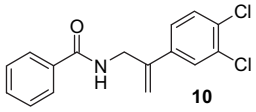
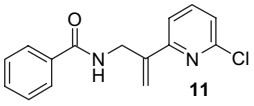
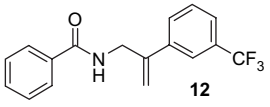
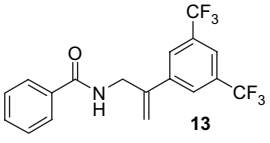
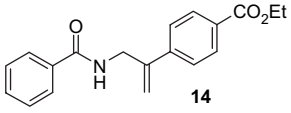
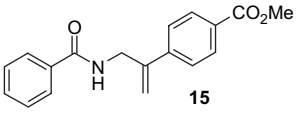
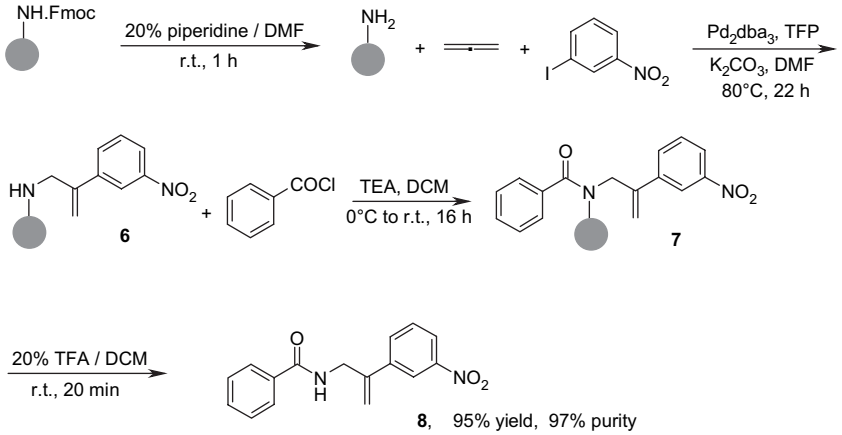
Having selected an appropriate resin, we decided to test the viability of the cascade using allene gas and a simple aryl iodide (Scheme 2).

The resin was deprotected using 20% piperidine in dimethylformamide and, after washing the resin, the three-component catalytic cascade was carried out using very similar reaction conditions to those employed in solution phase. Thus 1.1 equiv of the aryl iodide, 2.0 equiv of potassium carbonate, 2.5 mol % of tris (dibenzylideneacetone) dipalladium(0) and 10 mol % of tri-2-furylphosphine were reacted at 80 °C over 22 h. After washing, the resin-bound product **6** was acylated with excess benzoyl chloride (2 equiv) using triethylamine as base (3 equiv) in dichloromethane to give **7**, which after further washing was cleaved to give allylic amide **8**. The reaction was then repeated using different aryl iodides to provide a small library of allylic amides (Table 1).

Table 1. Cascade products using conditions shown in Scheme 2

Entry	Product	Yield (%)[a]	Purity (%)[b]
1	 **8**	95	97
2	 **9**	64	96
3	 **10**	55	96
4	 **11**	68	99
5	 **12**	75	98
6	 **13**	55	97
7	 **14**	76	98
8	 **15**	82	>99

[a] Isolated yield after column chromatography and/or crystallisation.
[b] HPLC analysis of crude product directly after cleavage.



Scheme 2.

The third column of Table 1 shows that the reaction yields varied from as low as 55% to as high as 95%. These yields represent the isolated yields of the final products after all four synthetic steps (deprotection, the three-component cascade, acylation and cleavage from the resin) and after any subsequent purification. Even the lowest overall yield of 55% represents an average yield exceeding 85% for each individual step. In the circumstances the yields were excellent, and it was pleasing to note that although we were using a primary amine as nucleophile in the cascade, no bis-adduct was formed as a by-product.

We were particularly encouraged by the purity exhibited by the products (the final column in Table 1). Purity was assessed by carrying out an HPLC analysis of the crude product directly after TFA cleavage (the only proviso being that some of the products were washed with ether before being left under high vacuum overnight to remove residual traces of TFA). For all the entries in Table 1, the purity of the compound is at least 95%. Indeed, for the methyl ester **15** the crude product was analytically pure by HPLC with no discernible trace of impurity. All HPLC analyses were recorded at 254 nm using a Luna 5μ (250×4.6 mm) phenyl–hexyl column.

Figure 1 shows the ^{1}H NMR spectrum of **13** recorded directly after cleavage and is typical of the spectra of crude products obtained from this solid-phase synthetic route.

It is noticeable from Table 1 that all of the products are derived from aryl iodides, which are rendered electron deficient by either the presence of an electron withdrawing substituent (entries 1, 3–8) or by extended conjugation (entry 2).

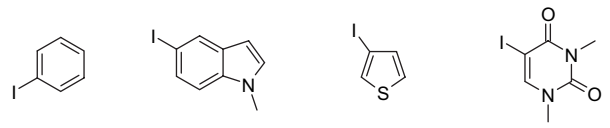


Figure 2.

Numerous attempts to incorporate the aryl/vinyl iodides shown in Figure 2 into the standard protocol proved unsuccessful. A complex mixture of products was obtained on cleavage from the resin, comprising at best 20–30% desired product and often significantly less. Using an excess of aryl iodide (up to 5 equiv), extending the reaction time up to 48 h, altering the solvent (acetonitrile and toluene) and varying the reaction temperature all failed to improve product yield and purity.

Electron withdrawing groups activate the carbon–iodine bond to oxidative addition by the nominally electron-rich palladium(0). However, this cannot alone explain the reaction failure as aryl iodides of the type shown in Figure 2 undergo the three-component cascade reaction using standard nitrogen nucleophiles in solution.[19]

Rather, a combination of both the nature of the nitrogen nucleophile and the nature of the π-allylpalladium intermediate is likely to be decisive here. The resin-bound amino group is sterically hindered, the polymer backbone hinders access of the amino group to the π-allylpalladium species, whilst the close proximity of the sp^2 carbons of the surrounding aryl groups inductively reduces the calculated pK_a, both of which impact adversely on the nucleophilicity of the amine. Therefore, in order for the cascade process to proceed satisfactorily, the π-allylpalladium species (which acts as

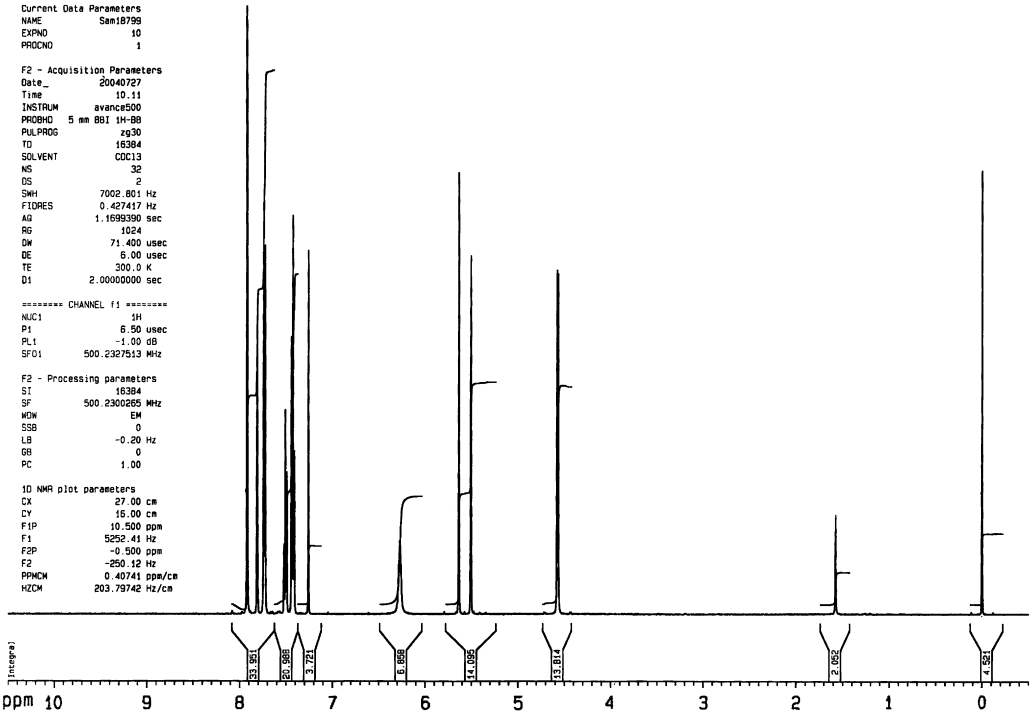


Figure 1. ^{1}H NMR ($CDCl_3$) of compound **13** directly after resin-cleavage.

the electrophile) is likely to require enhanced reactivity. The presence of an electron withdrawing group, which will render that species even more electrophilic, must tip the balance in favour of nucleophilic attack to give the desired cascade product. Thus a combination of steric and electronic factors prevents the cascade from proceeding unless an activated aryl iodide is employed.

2.2. Exploring diversity in the cascade

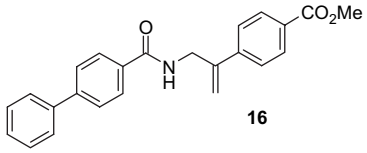
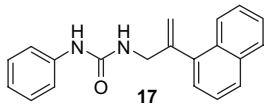
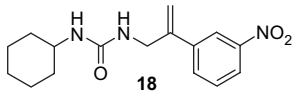
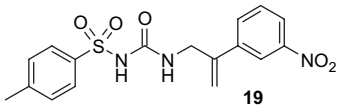
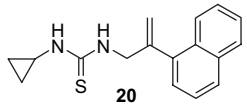
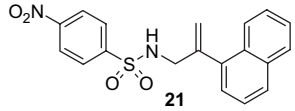
The compounds in Table 1 are derived using benzoyl chloride as the acylating agent. However, it is possible to use other reagents in order to introduce further diversity into the final products (Table 2).

Thus other acid chlorides are tolerated (entry 1) as are aryl and alkyl isocyanates (entries 2 and 3) and sulfonyl isocyanates (entry 4). As before, the products are obtained in high yields and excellent purity.

Attempts to extend the scope of the cascade using isothiocyanates and sulfonyl chlorides as reagents have, thus far, proved less successful (entries 5 and 6). Since both **20** and **21** fell below our purity cut-off they were not processed any further.

An explanation for the poor reactivity of isothiocyanates and sulfonyl chlorides again relates to the nucleophilicity of the resin-bound amino group. Following the three-component catalytic cascade, the resulting secondary amine will have both increased steric hindrance and an even lower pK_a (owing to the inductive effect of the sp^2 carbon of the *exo*-methylene double bond). Therefore, the nucleophilicity of that amino group will be relatively low, explaining why the product can attack the reactive acyl chloride and isocyanate reagents, but not the relatively less reactive isothiocyanate and sulfonyl chloride species. The order of reactivity suggested by these experiments is acyl chloride>isocyanate>isothiocyanate>sulfonyl chloride.

Table 2. Cascade products from alternative acylating agents

Entry	Product	Yield (%)[a]	Purity (%)[b]
1	 **16**	71	94
2	 **17**	90	92
3	 **18**	64	90
4	 **19**	68	>99
5	 **20**	ND	77
6	 **21**	ND	<20

ND=not done (conditions as per Table 1).
[a] Isolated yield after column chromatography and/or crystallisation.
[b] HPLC analysis of crude product directly after cleavage.

We have however managed to incorporate substituted allenes into the cascade (Scheme 3).

Thus cyclohexylallene **22** undergoes the cascade reaction under standard conditions to form resin-bound product **23**.

Acylation with benzoyl chloride proceeded smoothly to give **24**, which after cleavage gave compound **25** in 66% yield and very high purity (97%).

The product was obtained as an 11:1 mixture of *Z*:*E* geometric isomers (as measured by HPLC). NOE studies showed the *Z*-isomer to be the major product (Fig. 3).

The high selectivity for the *Z*-isomer arises from the preferential capture of the *anti*-π-allylpalladium species by the resin-bound nucleophile (Scheme 4).

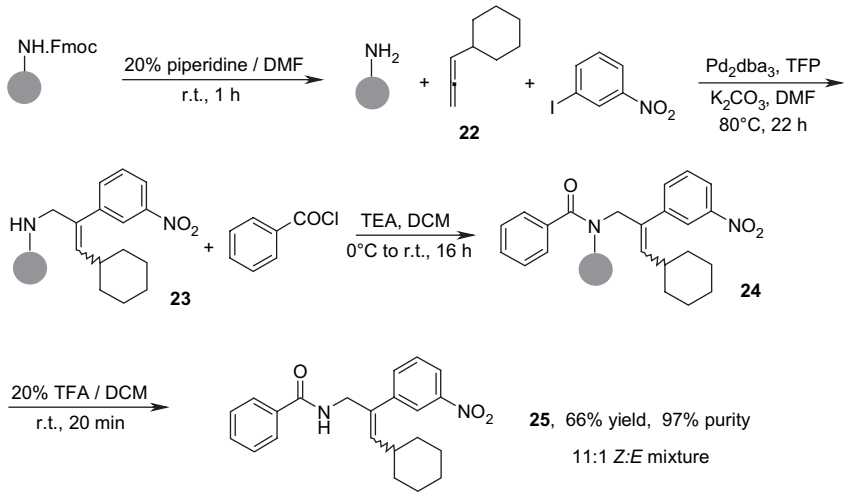
The π-allylpalladium intermediate can interconvert between the sterically congested *syn*-π-allyl **27**, where the cyclohexyl is in very close proximity with the aryl group, and *anti*-π-allyl **26**, where steric congestion is much reduced via η^1-allyl palladium(II) species. Our extensive work in this general area suggests that the *anti*-π-allyl **26** is formed initially and that *anti–syn* isomerisation reflects the rate of nucleophilic attack. Thus steric impediments to nucleophilic attack permit the isomerisation and lead to *Z*/*E* mixtures.

Thus, in the case in hand, steric bulk provided by the Rink amide linker surrounding the amino group is responsible.

Diversity can thus be incorporated into the cascade via the aryl iodide, allene and acylating agent. However, in order to maximise the potential synthetic applicability it was important to develop a strategy, which would allow the synthesis of acids via the cascade approach, thereby allowing further resin-bound coupling reactions.

Standard methods for hydrolysis of the resin-bound aryl esters proved unsatisfactory. Although heating to 65 °C with NaOH in 1:1 EtOH–water did lead to complete hydrolysis of resin-bound ethyl ester **14**, it proved difficult to reliably repeat these results; full conversion was not always achieved and there appeared to be a difficult compromise between solvents which suited the hydroxide base and solvents which allowed the resin to swell sufficiently to undergo hydrolysis.

An alternative literature strategy was to use the *tert*-butyl ester and to hydrolyse with zinc bromide in DCM.[20] Thus 4-iodobenzoic acid *tert*-butyl ester was utilised with allene gas and Rink amide resin in the three-component cascade and was thereafter acylated with benzoyl chloride to give



Scheme 3.

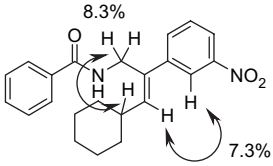
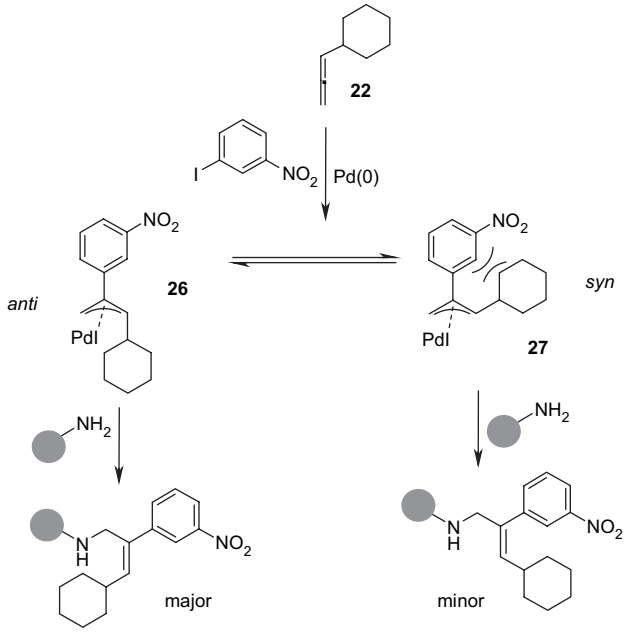


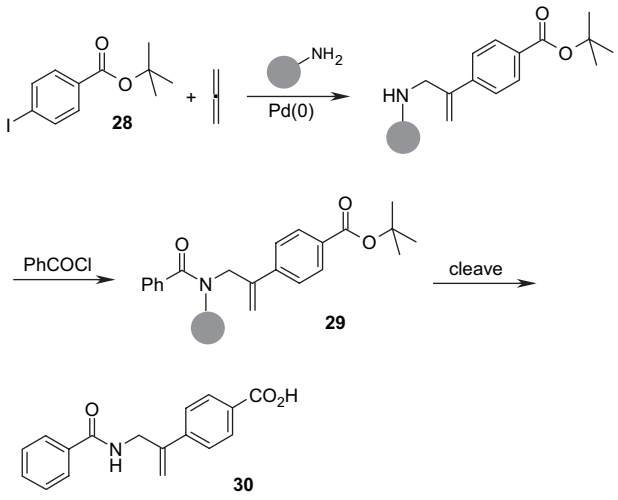
Figure 3.



Scheme 4.

29 (Scheme 5). In order to ascertain whether the cascade had been successful, the product was cleaved from the resin at this stage. Pleasingly, the mild conditions for resin-cleavage (20% TFA in dichloromethane at room temperature for 20 min) were also sufficient to cleave the *tert*-butyl ester, resulting in carboxylic acid **30** in 74% yield and 97% purity.

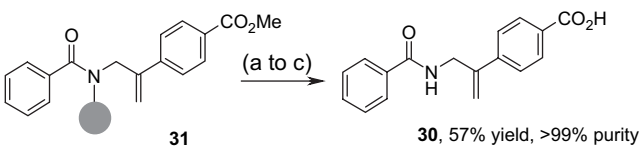
Although this provided a novel combinatorial route to carboxylic acids, our desire to carry out further resin-bound



Scheme 5.

manipulations of these acids for diversity screening, in the synthesis of pharmacologically interesting molecules, required a protocol whereby the esters were hydrolysed without cleaving from the resin.

Although attempts to cleave the ester using zinc bromide in DCM proved unsatisfactory we were able to solve the problem of hydrolysis by using potassium trimethylsilanolate to hydrolyse the methyl ester.[21,22] The cascade incorporating methyl-4-iodobenzoate proceeds very cleanly (Table 1, entry 8) affording resin-bound methyl ester **31**, which was stirred overnight at room temperature with 4 equiv of potassium trimethylsilanolate in dichloromethane (Scheme 6).



Scheme 6. Reagents and conditions: (a) TMSOK, DCM; (b) AcOH–THF (1:2); (c) 20% TFA–DCM.

The resin-bound acid was liberated on work-up using mildly acidic conditions (acetic acid and tetrahydrofuran (1:2 v/v)) to prevent cleavage from the resin. Subsequent resin-cleavage confirmed that the methyl ester had been hydrolysed in 57% yield with purity exceeding 99%.

3. Conclusion

A practical method for the synthesis of diverse libraries of pharmacologically interesting small molecules is described. This method utilises a 'catch and release' approach to resin-bound palladium-catalysed three-component cascade reactions to give products in high yield and with excellent purity.

In the ongoing work by the authors, this resin-mediated reaction has been used to develop potent, novel anti-cancer agents. This work will be outlined in more detail in the near future.

4. Experimental

4.1. General

Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were performed using a Carlo Erba MOD 1106 instrument. Electron ionisation (EI+), fast atom bombardment (FAB+) and accurate molecular weight mass spectra were recorded on a V.G.-AutoSpec instrument operating at 70 eV. Accurate molecular weights were determined using perfluorokerosine as an internal standard. Electrospray (ES+) mass spectra were recorded on a Micro Mass LCT time of flight 'KA111' instrument or a Micro Mass Lynx NT instrument. Chemical ionisation (CI+), EI+ and accurate mass measurements were also performed by the EPSRC National Service, Swansea on a Quattro instrument. Infra-red spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer using a diamond solid-phase transmission accessory unless otherwise specified. HPLC analyses were recorded at 254 nm on a Beckman 163 variable wavelength detector using a Luna 5μ (250×4.6 mm) phenyl–hexyl column unless otherwise stated. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker DRX500 instrument or at 300 MHz on a Bruker DPX300 instrument or at 250 MHz on a Bruker AC250 instrument. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument. Spectra were determined in $CDCl_3$ unless otherwise stated. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (δ 0.00). Coupling constants are given in hertz (Hz). ^{1}H NMR spectra are referenced to tetramethylsilane or residual protonated solvent. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dd=double doublet, dt=double triplet, td=triple doublet, ddd=double double doublet. Dichloromethane (DCM) was distilled from calcium hydride. All other commercially available reagents were used as received and where appropriate anhydrous quality material was purchased. The term ether refers to diethyl ether. All compounds are named according to the IUPAC system and were obtained using the ACD/i-Lab web service.

4.2. General procedure: solid-phase 'catch and release' three-component catalytic cascade

4.2.1. Step A. Removal of the Fmoc protecting group. Piperidine in DMF (20% v/v) was added to Rink Amide MBHA resin (loading 0.73 mmol/g). The solution was agitated at room temperature for 1 h, then filtered and the resin washed with DMF (3×) and DCM (3×). The resin was dried in vacuo at room temperature over 16 h and used directly in Step B.

4.2.2. Step B. Three-component catalytic cascade. A Schlenk tube was charged with the resin from Step A, the aryl iodide (1.1 mol equiv), potassium carbonate (2.0 mol equiv), tri-2-furylphosphine (10 mol %), tris (dibenzylideneacetone) dipalladium(0) (2.5 mol %) and DMF (10 ml) followed, after two freeze, pump, thaw cycles, by allene gas (1 atm, 25 °C). The mixture was allowed to warm to room temperature and then heated at 80–100 °C with gentle stirring for 16–24 h. The mixture was then allowed to cool, vented, filtered and the resin washed with DCM (1×), water (2×), methanol (3×) and DCM (3×). The resin was dried in vacuo at room temperature over 16 h and used directly in Step C.

4.2.3. Step C. Acylation of the cascade product. The acylating agent (2.0 mol equiv) in anhydrous DCM (2 ml) was added dropwise over 2 min to a stirred solution of the resin from Step B, triethylamine (3.0 mol equiv) and anhydrous DCM (10 ml) under nitrogen at 0 °C. The reaction mixture was allowed to warm to room temperature and was agitated for 16–24 h, then filtered and the resin washed with DCM (1×), water (1×), methanol (2×) and DCM (3×). The resin was dried in vacuo at room temperature over 16 h and used directly in Step D.

4.2.4. Step D. Cleavage from the resin. The resin from Step C was slurried in 20% v/v trifluoroacetic acid (TFA) in DCM. The mixture was allowed to stand at room temperature for 20 min, then filtered and the resin washed with DCM (2×). The combined filtrates were concentrated in vacuo to yield the product, which was immediately analysed for purity by HPLC and if necessary further purified by flash chromatography and/or crystallisation.

4.2.4.1. *N*-[2-(3-Nitrophenyl)-allyl]-benzamide (8). Prepared by the general procedure using the following:

Step A: Rink Amide MBHA resin (0.68 g, 0.50 mmol) agitated in 20% v/v piperidine in dimethylformamide (10 ml) for 1 h to give deprotected Rink Amide MBHA resin.
Step B: the product from step A (0.50 mmol), 1-iodo-3-nitrobenzene (137 mg, 1.1 mol equiv), potassium carbonate (138 mg, 2.0 mol equiv), tri-2-furylphosphine (12 mg, 10 mol %), tris (dibenzylideneacetone) dipalladium(0) (12 mg, 2.5 mol %) and allene gas (1 atm, 25 °C) in dimethylformamide (10 ml). The Schlenk tube was heated at 80 °C for 24 h to give **6**.
Step C: benzoyl chloride (0.116 ml, 2.0 mol equiv) in dichloromethane (2 ml) was added dropwise to a gently stirred solution of **6** (0.50 mmol) and triethylamine (0.199 ml, 3.0 mol equiv) in dichloromethane (10 ml) at

0 °C. The mixture was agitated at room temperature for 24 h to give **7**.
Step D: resin **7** (0.50 mmol) was slurried in 20% v/v trifluoroacetic acid in dichloromethane (10 ml) and allowed to stand for 20 min to give the product (purity 97% by HPLC). Crystallisation from ethyl acetate–hexane gave colourless plates (134 mg, 95% overall yield from Step A), mp 111–112 °C.

Found: C, 68.00; H, 5.25; N, 9.80. $C_{16}H_{14}N_2O_3$ requires: C, 68.10; H, 5.00; N, 9.90%.

δ_H (300 MHz): 8.35 (s, 1H, ArH), 8.16 (dd, 1H, *J* 8.2 Hz, ^4J 1.4 Hz, ArH), 7.80 (d, 1H, *J* 7.8 Hz, ArH), 7.71 (d, 2H, *J* 7.5 Hz, ArH), 7.56–7.51 (m, 2H, ArH), 7.42 (t, 2H, *J* 7.7 Hz, ArH), 6.37 (br s, 1H, NH), 5.66 (s, 1H, C=CH), 5.49 (s, 1H, C=CH), 4.60 (d, 2H, *J* 5.7 Hz, NCH_2).

δ_C (75 MHz): 168.4 (C=O), 148.5, 142.3, 140.0, 133.5, 132.1, 132.1, 129.7, 128.8, 126.9, 122.9, 121.1, 116.8, 43.5 (C–N).

m/*z* (ES+, %): 283 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1629 (C=C), 1520+1350 (NO_2).

HPLC: 97% purity; eluted with 1:1 v/v MeCN–H_2O at 0.7 ml/min.

4.2.4.2. *N*-(2-Naphthalen-1-yl-allyl)-benzamide (9). Prepared using the same method as for compound **8** but using 1-iodonaphthalene in step B (purity 96% by HPLC). Further purification by flash chromatography eluting with 3:1 v/v ether–hexane (R_f 0.40) gave a pale yellow oil (134 mg, 64% overall yield from Step A).

Found: C, 83.10; H, 6.10; N, 4.90. $C_{20}H_{17}NO$ requires: C, 83.50; H, 5.96; N, 4.90%.

δ_H (300 MHz): 8.15–8.09 (m, 1H, ArH), 7.87–7.77 (m, 2H, ArH), 7.72–7.67 (m, 2H, ArH), 7.49–7.31 (m, 7H, ArH), 6.58 (t, 1H, *J* 4.6 Hz, NH), 5.60 (d, 1H, ^2J 1.5 Hz, C=CH), 5.24 (d, 1H, ^2J 1.4 Hz, C=CH), 4.43 (d, 2H, *J* 4.7 Hz, NCH_2).

δ_C (75 MHz): 168.0 (C=O), 145.0, 138.9, 134.8, 134.1, 132.0, 131.9, 129.0, 128.8, 128.4, 127.4, 126.8, 126.4, 126.0, 125.9, 125.7, 116.4, 46.4 (C–N).

m/*z* (ES+, %): 310 (M+Na, 78), 288 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1651 (C=O), 1635 (C=C).

HPLC: 96% purity; eluted with 4:1 v/v MeCN–H_2O at 0.4 ml/min.

4.2.4.3. *N*-[2-(3,4-Dichloro-phenyl)-allyl]-benzamide (10). Prepared using the same method as for compound **8** but using 1,2-dichloro-4-iodobenzene in Step B (purity 96% by HPLC). Further purification by crystallisation from dichloromethane–hexane gave colourless prisms (122 mg, 55% overall yield from Step A), mp 105–106 °C.

Found: C, 62.40; H, 4.20; N, 4.40. $C_{16}H_{13}Cl_2NO$ requires: C, 62.70; H, 4.28; N, 4.60%.

δ_H (300 MHz): 7.72 (dd, 2H, *J* 6.9 Hz, ^4J 1.8 Hz, ArH), 7.56 (d, 1H, ^4J 2.0 Hz, ArH), 7.49 (d, 1H, *J* 7.3 Hz, ArH), 7.42–7.39 (m, 3H, ArH), 7.31–7.26 (m, 1H, ArH), 6.37 (br s, 1H, NH), 5.52 (s, 1H, C=CH), 5.36 (s, 1H, C=CH), 4.49 (d, 2H, *J* 5.3 Hz, NCH_2).

δ_C (75 MHz): 168.2 (C=O), 142.7, 138.7, 134.3, 133.2, 132.5, 132.3, 131.0, 129.1, 128.5, 127.3, 125.8, 116.0, 43.8 (C–N).

m/*z* (ES+, %): 306 ($^{35}Cl_2$, M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1629 (C=C).

HPLC: 96% purity; eluted with 4:1 v/v MeCN–H_2O at 0.5 ml/min.

4.2.4.4. *N*-[2-(6-Chloro-pyridin-3-yl)-allyl]-benzamide (11). Prepared using the same method as for compound **8** but using 2-chloro-5-iodopyridine in Step B (purity 99% by HPLC), colourless needles (136 mg, 68% overall yield from Step A), mp 88–89 °C.

Found: C, 65.80; H, 4.95; N, 10.30; Cl, 12.80. $C_{15}H_{13}ClN_2O$ requires: C, 66.10; H, 4.80; N, 10.40; Cl, 13.00%.

δ_H (300 MHz): 8.50 (d, 1H, ^4J 2.4 Hz, ArH), 7.79–7.71 (m, 3H, ArH), 7.54–7.40 (m, 3H, ArH), 7.31 (d, 1H, *J* 8.1 Hz, ArH), 6.27 (br s, 1H, NH), 5.57 (s, 1H, C=CH), 5.43 (s, 1H, C=CH), 4.54 (d, 2H, *J* 5.8 Hz, NCH_2).

δ_C (75 MHz): 167.4 (C=O), 151.0, 147.4, 140.7, 136.3, 133.9, 133.0, 131.8, 128.7, 126.9, 124.0, 116.2, 43.2 (C–N).

m/*z* (ES+, %): 273 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1629 (C=C).

HPLC: 99% purity; eluted with 7:3 v/v MeCN–H_2O at 0.5 ml/min.

4.2.4.5. *N*-[2-(3-Trifluoromethyl-phenyl)-allyl]-benzamide (12). Prepared using the same method as for compound **8** but using 3-iodobenzotrifluoride in Step B (purity 98% by HPLC). Trituration with ether gave a colourless amorphous solid (118 mg, 76% overall yield from Step A), mp 124–125 °C.

Found: C, 73.50; H, 6.05; N, 4.40. $C_{19}H_{19}NO_3$ requires: C, 73.80; H, 6.05; N, 4.50%.

δ_H (300 MHz): 8.03 (d, 2H, *J* 8.3 Hz, ArH), 7.70 (d, 2H, *J* 7.4 Hz, ArH), 7.55 (d, 2H, *J* 8.3 Hz, ArH), 7.49 (t, 1H, *J* 7.5 Hz, ArH), 7.41 (t, 2H, *J* 7.5 Hz, ArH), 6.20 (s, 1H, NH), 5.61 (s, 1H, C=CH), 5.42 (s, 1H, C=CH), 4.57 (d, 2H, *J* 5.6 Hz, NCH_2), 4.37 (q, 2H, *J* 7.1 Hz, OCH_2), 1.39 (t, 3H, *J* 7.1 Hz, CH_3).

δ_C (75 MHz): 167.4 (C=O), 166.3 (C=O), 143.6, 142.6, 134.2, 131.6, 130.0, 129.9, 128.6, 126.9, 126.0, 116.0, 61.0 (C–O), 43.5 (C–N), 14.3 (CH_3).

m/*z* (ES+, %): 310 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1723 (C=O), 1646 (C=O), 1632 (C=C).

HPLC: 98% purity; eluted with 7:3 v/v MeCN–H_2O at 0.6 ml/min.

4.2.4.6. Methyl 4-{1-[benzoylaminomethyl]vinyl} benzoate (15). Prepared using the same method as for compound **8** but using methyl 4-iodobenzoate in Step B (purity >99% by HPLC). Trituration with ether gave a colourless amorphous solid (120 mg, 82% overall yield from Step A), mp 136–137 °C.

Found: C, 71.80; H, 5.85; N, 4.50. $C_{18}H_{17}NO_3 \cdot 0.25H_2O$ requires: C, 72.00; H, 5.80; N, 4.70%.

δ_H (300 MHz): 8.02 (d, 2H, *J* 8.4 Hz, ArH), 7.70 (d, 2H, *J* 7.4 Hz, ArH), 7.55 (d, 2H, *J* 8.4 Hz, ArH), 7.49 (t, 1H, *J* 7.4 Hz, ArH), 7.41 (t, 2H, *J* 7.5 Hz, ArH), 6.20 (br s, 1H, NH), 5.62 (s, 1H, C=CH), 5.43 (s, 1H, C=CH), 4.57 (d, 2H, *J* 5.4 Hz, NCH_2), 3.91 (s, 3H, Me).

δ_C (75 MHz): 167.8 (C=O), 166.4 (C=O), 143.9, 143.2, 134.6, 132.1, 130.3, 130.1, 129.1, 127.3, 126.5, 116.4, 52.6 (C–N), 43.9 (C–O).

m/*z* (ES+, %): 295 (M+H, 100).

HRMS: found [M+H] 295.1199, [$C_{18}H_{17}NO_3$+H] requires 295.1203.

IR (ν_{max}/cm^{-1}): 1720 (C=O), 1643 (C=O), 1626 (C=C).

HPLC: 99.5% purity; eluted with 3:1 v/v MeCN–H_2O at 0.6 ml/min.

4.2.4.7. Methyl 4-(1-{[(biphenyl-4-ylcarbonyl)amino] methyl}vinyl) benzoate (16). Prepared using the same method as for compound **8** but using methyl 4-iodobenzoate in Step B and 4-biphenyl carbonyl chloride in Step C (purity 94% by HPLC). Trituration with ether gave colourless needles (131 mg, 71% overall yield from Step A), mp 198–199 °C.

Found: C, 76.80; H, 5.60; N, 3.70. $C_{24}H_{21}NO_3 \cdot 0.25H_2O$ requires: C, 76.70; H, 5.80; N, 3.70%.

δ_H (300 MHz): 8.03 (dd, 2H, *J* 8.3 Hz, ^4J 1.7 Hz, ArH), 7.70 (d, 2H, *J* 8.3 Hz, ArH), 7.64–7.55 (m, 6H, ArH), 7.46 (t, 2H, *J* 8.3 Hz, ArH), 7.41 (d, 1H, *J* 8.0 Hz, ArH), 6.24 (br s, 1H, NH), 5.64 (s, 1H, C=CH), 5.45 (s, 1H, C=CH), 4.59 (d, 2H, *J* 5.6 Hz, NCH_2), 3.91 (s, 3H, Me).

δ_C (75 MHz): 167.1 (C=O), 166.4 (C=O), 144.5, 143.6, 142.8, 139.9, 133.1, 129.9, 129.7, 128.9, 128.0, 127.4, 127.3, 127.2, 126.1, 116.1 (C=C), 52.26 (C–N), 43.5 (C–O).

m/*z* (EI+, %): 371 (M+H, 100).

HRMS: found [M+H] 371.1519, [$C_{24}H_{21}NO_3$+H] requires 371.1516.

IR (ν_{max}/cm^{-1}): 1715 (C=O), 1639 (C=O), 1607 (C=C).

HPLC: 94% purity; eluted with 3:1 v/v MeCN–H_2O at 0.3 ml/min.

4.2.4.8. *N*-[2-Naphthalen-1-yl-allyl]-3-phenyl-urea (17). Prepared using the same method as for compound **8** but using 1-iodonaphthalene in Step B and phenyl isocyanate in Step C (purity 92% by HPLC). Further purification by flash chromatography eluting with ether (R_f 0.42) gave colourless needles (136 mg, 90% overall yield from Step A), mp 98–99 °C.

Found: C, 79.40; H, 5.80; N, 9.30. $C_{20}H_{18}N_2O$ requires: C, 79.40; H, 6.00; N, 9.30%.

δ_H (300 MHz): 7.99 (dd, 1H, *J* 6.4 Hz, ^4J 3.1 Hz, ArH), 7.88–7.69 (m, 2H, ArH), 7.51–7.38 (m, 3H, ArH), 7.29–7.19 (m, 3H, ArH), 7.10 (t, 1H, *J* 7.4 Hz, ArH), 6.98 (d, 2H, *J* 7.4 Hz, ArH), 5.56 (d, 1H, ^2J 1.0 Hz, C=CH), 5.22 (s, 1H, C=CH), 4.22 (s, 2H, NCH_2).

δ_C (75 MHz): 157.9 (C=O), 145.0, 138.4, 137.2, 134.1, 131.8, 130.0, 128.8, 128.4, 126.8, 126.4, 126.0, 125.7, 125.6, 123.6, 116.7, 47.0 (C–N).

m/*z* (ES+, %): 303 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1683 (C=O), 1621 (C=C).

HPLC: 92% purity; eluted with 4:1 v/v MeCN–H_2O at 0.8 ml/min.

4.2.4.9. 1-Cyclohexyl-3-[2-(3-nitrophenyl)-allyl]-urea (18). Prepared using the same method as for compound **8** but using 3-iodonitrobenzene in Step B and cyclohexyl isocyanate in Step C (purity 90% by HPLC). Further purification by crystallisation from dichloromethane–hexane gave colourless needles (97 mg, 64% overall yield from Step A), mp 95–96 °C.

Found: C, 63.10; H, 7.00; N, 13.60. $C_{16}H_{21}N_3O_3$ requires: C, 63.30; H, 6.98; N, 13.80%.

δ_H (300 MHz): 8.29 (t, 1H, ^4J 2.0 Hz, ArH), 8.15 (dt, 1H, *J* 8.0 Hz, ^4J 2.0 Hz, ArH), 7.78 (dt, 1H, *J* 7.9 Hz, ^4J 1.9 Hz, ArH), 7.52 (t, 1H, *J* 8.0 Hz, ArH), 5.57 (s, 1H, C=CH), 5.41 (s, 1H, C=CH), 4.36 (br s, 1H, NH), 4.30 (d, 2H, *J* 5.4 Hz, NCH_2), 4.27 (br s, 1H, NH), 3.51 (m, 1H, CyH), 1.93–1.89 (m, 2H, CyH), 1.70–1.50 (m, 4H, CyH), 1.41–1.27 (m, 2H, CyH), 1.19–1.06 (m, 2H, CyH).

δ_C (75 MHz): 157.0 (C=O), 148.4, 143.8, 140.5, 132.2, 129.5, 122.7, 121.2, 115.8, 49.4 (C–N), 44.0 (C–N), 33.8 (C–C), 25.5 (C–C), 24.9 (C–C).

m/*z* (ES+, %): 305 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1640 (C=O), 1621 (C=C), 1532+1343 (NO_2).

HPLC: 90% purity; eluted with 4:1 v/v MeCN–H_2O at 0.8 ml/min.

4.2.4.10. 4-Methyl-*N*-({[2-(3-nitrophenyl)prop-2-en-1-yl]amino}carbonyl)benzene sulfonamide (19). Prepared using the same method as for compound **8** but using 3-iodonitrobenzene in Step B and *p*-toluenesulfonyl isocyanate in Step C (purity 99% by HPLC), colourless plates (128 mg, 68% overall yield from Step A), mp 136–137 °C.

Found: C, 54.50; H, 4.80; N, 11.0; S, 8.50. $C_{17}H_{17}N_3O_5S$ requires: C, 54.40; H, 4.56; N, 11.2; S, 8.50%.

δ_H (300 MHz): 8.20 (t, 1H, ^4J 1.9 Hz, ArH), 8.19 (dd, 1H, *J* 8.1 Hz, ^4J 1.7 Hz, ArH), 7.98 (br s, 1H, NH), 7.69 (d, 1H, *J* 7.8 Hz, ArH), 7.59 (d, 2H, *J* 8.3 Hz, ArH), 7.48 (t, 1H, *J* 8.0 Hz, ArH), 7.19 (d, 2H, *J* 8.1 Hz, ArH), 6.80 (t, 1H, *J* 5.4 Hz, NH), 5.57 (s, 1H, C=CH), 5.35 (s, 1H, C=CH), 4.34 (d, 2H, *J* 5.6 Hz, NCH_2), 2.41 (s, 3H, CH_3).

δ_C (75 MHz): 158.0 (C=O), 151.6, 145.5, 142.4, 140.2, 136.6, 132.4, 130.3, 129.9, 127.1, 123.2, 121.5, 117.2, 44.0 (C–N), 22.0 (CH_3).

m/*z* (ES+, %): 398 (M+Na, 91), 376.3 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1695 (C=O), 1631 (C=C), 1549+1344 (NO_2).

HPLC: 99% purity; eluted with 7:3 v/v MeCN–H_2O: 70/30 at 0.5 ml/min.

4.2.4.11. *N*-[(2*Z*)-3-Cyclohexyl-2-(3-nitrophenyl)-prop-2-en-1-yl] benzamide (25). Prepared using the same method as for compound **8** but with the following change to Step B.

Step B: to the resin from Step A was added 3-iodonitrobenzene (137 mg, 1.1 mol equiv), cyclohexylallene (122 mg, 2.0 mol equiv), tris (dibenzylideneacetone) dipalladium (12 mg, 2.5 mol %), tri-2-furylphosphine (12 mg, 10 mol %) and potassium carbonate (138 mg, 2.0 mol equiv). The mixture was agitated under nitrogen for 24 h, filtered and the resin washed with methanol (10 ml), water (10 ml), methanol (2×10 ml), dichloromethane (3×10 ml) and dried in vacuo at room temperature over 16 h.

The combined filtrates following cleavage in Step D were concentrated in vacuo to give an 11:1 mixture of *Z* and *E* stereoisomers (overall purity 97% by HPLC). Crystallisation from acetonitrile yielded the major *Z*-isomer **25** as colourless prisms (120 mg, 66% overall yield from Step A), mp 97–98 °C. Attempted isolation of the minor isomer by flash chromatography proved unsuccessful.

Found: C, 72.30; H, 6.60; N, 7.70. $C_{22}H_{24}N_2O_3$ requires: C, 72.50; H, 6.64; N, 7.70%.

δ_H (300 MHz): 8.28 (t, 1H, ^4J 1.9 Hz, ArH), 8.08 (dd, 1H, *J* 8.1 Hz, ^4J 1.8 Hz, ArH), 7.74 (dd, 1H, *J* 7.9 Hz, ^4J 1.8 Hz, ArH), 7.63 (dd, 2H, *J* 7.6 Hz, ^4J 2.0 Hz, ArH), 7.50–7.45 (m, 2H, ArH), 7.40–7.36 (m, 2H, ArH), 5.95 (d, 1H, *J* 9.5 Hz, C=CH), 5.89 (s, 1H, NH), 4.62 (d, 2H, *J* 5.2 Hz, NCH_2), 2.59–2.53 (m, 1H, CyH), 1.80–1.70 (m, 5H, CyH), 1.42–1.33 (m, 2H, CyH), 1.28–1.21 (m, 3H, CyH).

δ_C (75 MHz): 168.9 (C=O), 148.9, 142.6, 142.1, 134.6, 132.6, 132.0, 129.9, 129.0, 127.2, 122.4, 121.5, 38.8 (C–N), 38.3 (C–C), 33.7 (C–C), 26.2 (C–C), 26.0 (C–C).

m/*z* (ES+, %): 365 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1633 (C=C).

HPLC: 97% purity; eluted with 7:3 v/v MeCN–H_2O at 0.5 ml/min.

4.2.5. 4-[1-(Benzoylamino-methyl)-vinyl] benzoic acid (30).

a. Via hydrolysis of resin-bound *tert*-butyl ester

Prepared using the same method as for compound **8** but using 4-iodobenzoic acid *tert*-butyl ester in Step B (purity 97% by HPLC), colourless amorphous solid (103 mg, 74% overall yield from Step A), mp 194–195 °C.

Found: C, 70.60; H, 5.30; N, 4.70. $C_{17}H_{15}NO_3 \cdot 0.5H_2O$ requires: C, 70.30; H, 5.38; N, 4.80%.

δ_H (DMSO-d_6, 500 MHz): 8.86 (t, 1H, *J* 5.6 Hz, NH), 7.94 (d, 2H, *J* 8.3 Hz, ArH), 7.86 (d, 2H, *J* 7.3 Hz, ArH), 7.67 (d, 2H, *J* 8.3 Hz, ArH), 7.53 (t, 1H, *J* 7.3 Hz, ArH), 7.47 (t, 2H, *J* 7.4 Hz, ArH), 5.64 (s, 1H, C=CH), 5.34 (s, 1H, C=CH), 4.37 (d, 2H, *J* 5.6 Hz, NCH_2).

δ_C (DMSO-d_6, 75 MHz): 167.4 (C=O), 166.6 (C=O), 144.1, 143.2, 134.6, 131.6, 130.3, 129.8, 128.7, 127.6, 126.3, 114.6, 42.5 (C–N).

m/*z* (ES+, %): 282.3 (M+H, 100).

HRMS: found [M+H] 281.1046, [$C_{17}H_{15}NO_3$+H] requires 281.1046.

IR (ν_{max}/cm^{-1}): 3300–2300 (O–H), 1673 (C=O), 1642 (C=O), 1607 (C=C).

HPLC: 98% purity; eluted with 7:3 v/v MeCN–H_2O at 0.3 ml/min.

b. Via hydrolysis of resin-bound methyl ester

Resin-bound methyl ester **31** (0.50 mmol) was prepared by following Steps A, B and C of the procedure for compound **15**.

*Silanolate conversion of methyl ester **31***: resin-bound methyl ester **31** (0.50 mmol) was added to an agitated slurry of potassium trimethylsilanolate (257 mg, 4.0 mol equiv) in dry dichloromethane (10 ml) at room temperature under nitrogen. The reaction mixture was agitated for 16 h and the resin filtered and washed with methanol (10 ml), water (10 ml) and methanol (10 ml). The resin was then acidified with 1:2 v/v acetic acid in tetrahydrofuran, filtered and washed with methanol (10 ml), water (10 ml), methanol

(10 ml) and dichloromethane (2×10 ml). The resin was dried in vacuo at room temperature over 16 h and used directly in the next step.

*Cleavage from the resin to give acid **30***: the resin from the hydrolysis step (0.50 mmol) was slurried in 20% v/v trifluoroacetic acid in dichloromethane (10 ml) and allowed to stand for 20 min to give **30** (purity >99% by HPLC) as a colourless amorphous solid (80 mg, 57% overall yield from Step A).

HPLC: >99% purity; eluted with 7:3 MeCN–H_2O at 0.4 ml/min.

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