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Skeletal diversity via Pd(0) catalysed three-component cascades of allene and halides or triflates with protected hydroxylamines and formamide

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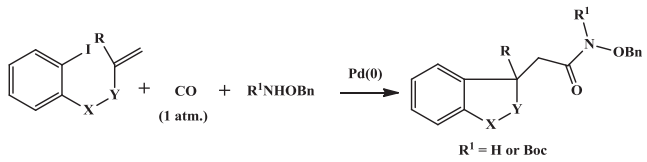
ABSTRACT

The reactions of allene gas (1 atm) and of 1,1-dimethylallene with a range protected hydroxylamines and formamide with aryl/heteroaryl iodides, bromides and triflates under Pd(0) catalysis lead to a skeletally diverse range of products in good yield. The cascades tolerate both electron withdrawing and electron donating substrates and 1,1-dimethylallene reacts regioselectively in all cases.

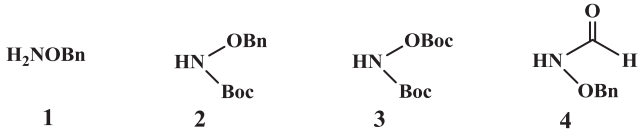
1. Introduction

The hydroxylamine functional group has garnered multiple synthetic applications[1,2] as well as prompting studies of its biology and potential uses in theraputics.[3] We have a long standing interest in hydroxylamines and oximes both as precursors of nitrones, and their subsequent zero waste 1,3-dipolar cycloadditions[4] and as participants in palladium catalysed cascade reactions. We have previously reported both solid phase (Wang resin) and solution phase palladium catalysed, relay switched,[5] three-component cyclisation–carbonylation–hydroxylamine cascades (Scheme 1) and demonstrated that five-component processes are accessible when R^1=H. The carbon monoxide functions as the relay switch in these processes.[6] The latter process results in the formation of six new bonds, two rings and two tetrasubstituted C-centres.[5]



Scheme 1.

We now report a series of three-component cascades in which allene(s) act as the relay switch whilst mono- and bis- protected hydroxylamines **1**–**3** and the formamide **4** are employed as nucleophiles.



1 **2** **3** **4**

1.1. Cascades employing allene gas and monoprotected hydroxylamine 1

Preliminary experiments with nucleophile **1** showed that its use in excess enhanced the yield of the three-component product **5** and suppressed formation of the five-component product **6** (Scheme 2). Reactions were carried out in DMF at 80 °C for 16 h and employed allene (1 atm), **1** (2–3 mol equiv), $Pd_2(dba)_3$ (2.5 mol %), tris-(2-furyl)phosphine (TFP) (10 mol %) and K_2CO_3 (2 mol equiv) (Table 1).

The disparate aryl/heteroaryl halides **7**–**13** were all converted into their corresponding three-component cascade products in excellent yield by using an excess of *O*-benzylhydroxylamine **1** and 1 atm of allene. Thus 2-iodothiophene **8** furnished the desired product **15** in 90% yield (Table 1, entry 2) whilst 5-iodo-1,3-dimethyluracil **11**

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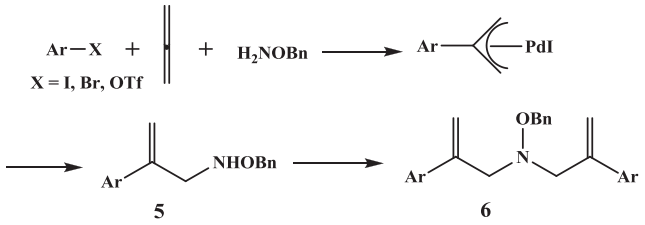
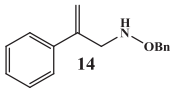
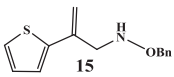
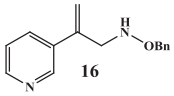
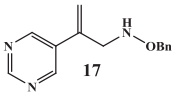
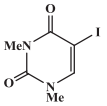
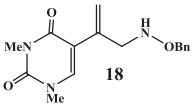
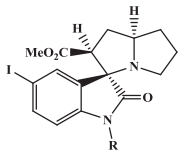
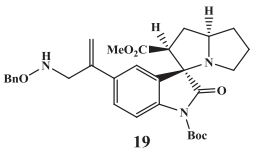
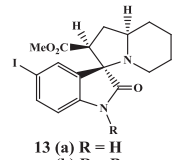
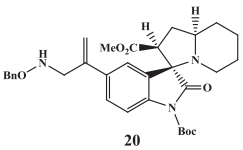


Scheme 2.

Table 1
Three-component Scheme 2 processes employing **1**[a]

Entry	Aryl halide	Product	Yield[b] (%)
1	 7	 14	74
2	 8	 15	90
3	 9	 16	67
4	 10	 17	86
5	 11	 18	85
6	 12 (a) R = H (b) R = Boc	 19	70
7	 13 (a) R = H (b) R = Boc	 20	70

[a] Reactions were carried out for 16 h at 80 °C in DMF under 1 atm of allene gas and in the presence of *O*-benzylhydroxylamine **1** (2–3 mol equiv), Pd_2dba_3 (2.5 mol %), TFP (10 mol %), K_2CO_3 (2 mol equiv).
[b] Isolated yield.

produced allyl hydroxylamine **18** in 85% yield (Table 1, entry 5). Aryl bromides are generally less reactive than aryl iodides in palladium catalysed reactions. However, the more reactive 3-bromopyridine **9** and 5-bromopyrimidine **10** gave the expected products **16** and **17** in good yield under the standard conditions (Table 1, entries 3 and 4) whilst the sterically demanding spirocycles **12b** and **13b** were converted into **19** and **20** in good yield (Table 1, entries 6 and 7). In contrast, phenyl triflate was significantly less reactive and under more forcing conditions (DMF, 110 °C, 85 h) gave the known two component *O*-benzyl-*N*-phenylhydroxylamine product (61%).[7]

Following our earlier report on the application of decarboxylative 1,3-dipolar cycloaddition routes to the spiro-(indole-3,3′-pyrrolizine)-2-one skeleton[8a] there has been substantial activity in this area[8b–i] but to our knowledge the 5-iodo derivatives **12a**,**b** and **13a**,**b** have not been reported (see Experimental).

1.2. Cascades employing allene gas and *N*,*O*-protected hydroxylamines 2

Although using an excess of *O*-substituted hydroxylamine **1** was sufficient to prevent the formation of the five-component product **6** (Scheme 2), it is wasteful and requires the excess reagent to be separated from the product. An alternative strategy employing the *N*,*O*-protected **2** was studied under the standard conditions as for Table 1 except that *N*,*O*-protected hydroxylamine **2** (1.05 mol equiv) was employed (Table 2). Both iodo and bromo substrates gave the desired products in good to excellent yield demonstrating that the cascade tolerates both electron withdrawing and electron donating aryl/heteroaryl substrates (e.g., Table 2, entry 1).

Reactions of *N*-Boc-*O*-benzylhydroxylamine **2** with **10**, **11**, and **12** gave better yields than similar reactions with *O*-benzylhydroxylamine whereas the heterocyclic bromides **9** and **10** gave similar yields with both **1** and **2**.

In one instance we compared the overall two-step yield of **14** via **26a** followed by removal of the Boc group (Scheme 3). The latter two steps route gave **14** (90%) compared to 74% via the direct reaction with *O*-benzylhydroxylamine. The greater reactivity of *N*-Boc-*O*-benzylhydroxylamine **2** compared to **1** was emphasised by the reaction of the former with phenyl triflate to afford **26a** in 80% yield at higher temperature (110 °C) over 84 h (Table 2, entry 10).

1.3. Cascades employing allene gas and *N*,*O*-diBoc-hydroxylamine 3

The reaction of commercially available *N*,*O*-diBoc-hydroxylamine **3** with the iodobenzenes **21a**,**f** and **h** gave the expected products **36a**–**c** using the same conditions as before (Scheme 4).

1.4. Cascades employing allene gas and *N*-benzyloxyformamide 4 as nucleophile

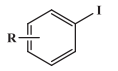
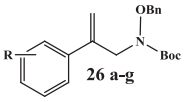
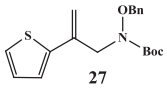
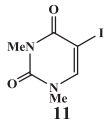
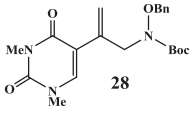
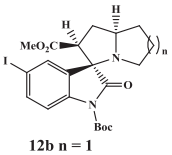
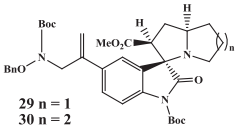
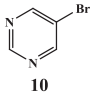
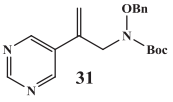
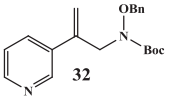
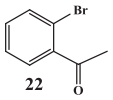
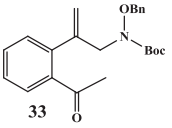
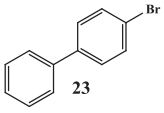
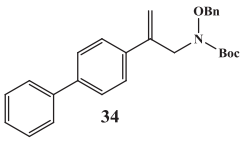
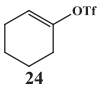
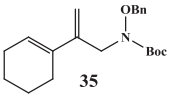
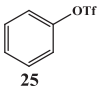
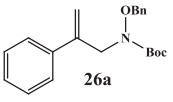
N-Benzyloxyformamide, which exhibits dynamic ^{1}H NMR spectra due to restricted rotation about the amide bond[9] was reacted with an aryl and a heteroaryl iodide (Table 3) under our standard conditions. The iodides **21c** and **8** gave the expected products **37** and **38** in excellent yield (Table 3).

1.5. Reactions employing 1,1-dimethylallene and *O*-benzylhydroxylamine 1 as nucleophile

Mono- or 1,1-disubstituted allenes can give rise to both *syn* and *anti*-π-allyl complexes each of which can be attacked at either terminus giving rise to three possible products (Scheme 5). Generally the *anti*-π-allyl complex is favoured because of the steric clash between the R and Ar groups in the *syn*-π-allyl.

Several aryl iodides and a heterocyclic bromide were reacted with 1,1-dimethylallene (5 mol equiv) and *O*-benzylhydroxylamine using the standard catalyst system in DMF at 80 °C to generate the corresponding allylic hydroxylamines regiospecifically (Table 4). In all cases nucleophilic attack on the π-allyl species **39** occurs at the most substituted site (Scheme 6) in accord with Trost's suggestion that when nucleophilic attack occurs at the most substituted terminus of the π-allyl unit, electronic rather steric effects dominate regioselectivity.[10]

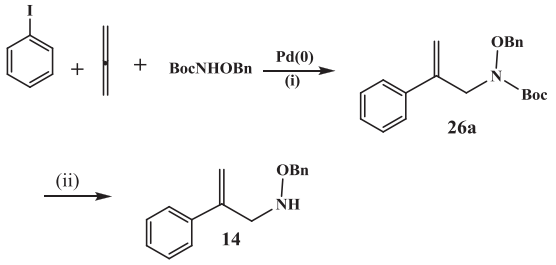
Table 2
Three-component Scheme 3 processes employing **2**[a]

Entry	Aryl halide	Product	Yield[b] (%)
1	 **21** a) R = H b) R = 2-OMe c) R = 4-COMe d) R = 4-CO_2Me e) R = 4-NO_2 f) R = 3-NO_2 g) R = 2-NO_2	 **26 a-g**	94–97
2	 **8**	 **27**	92
3	 **11**	 **28**	96
4	 **12b** n = 1 **13b** n = 2	 **29** n = 1 **30** n = 2	85–88
5	 **10**	 **31**	87
6	 **9**	 **32**	64
7	 **22**	 **33**	81
8	 **23**	 **34**	94
9	 **24**	 **35**	87
10	 **25**	 **26a**	80[c]

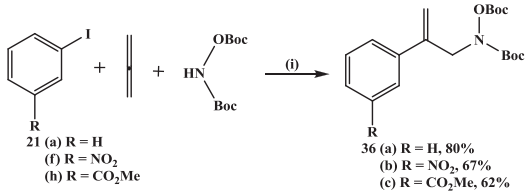
[a] Reactions were carried out for 16 h at 80 °C in DMF under 1 atm of allene gas using *N*-Boc-*O*-benzylhydroxylamine **2** (2–3 mol equiv), Pd_2dba_3 (2.5 mol %), TFP (10 mol %), K_2CO_3 (2 mol equiv).
[b] Isolated yield.
[c] Reaction carried out at 110 °C for 84 h.

2. Conclusion

The application of catalytic cascade chemistry to the assembly of a diverse array of protected hydroxylamines and formamides proceeds in good to excellent yields.

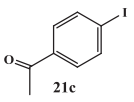
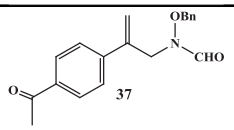
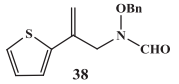


Scheme 3. (i) See footnote a (Table 2); (ii) 10% TFA (5 mol equiv), CH_2Cl_2, rt, 16 h.

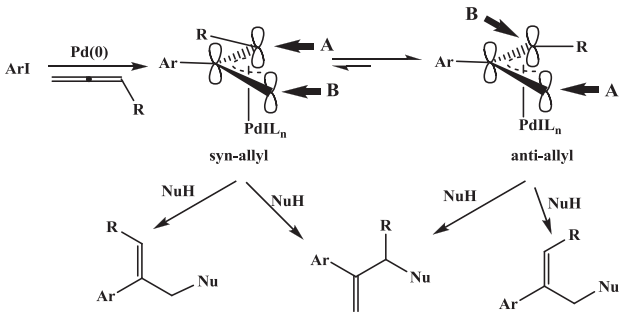


Scheme 4. (i) Conditions as for Table 2.

Table 3
Cascade process involving *N*-benzyloxyformamide **4**[a]

Entry	Aryl halide	Product	Yield[b] (%)
1	 **21c**	 **37**	93
2	 **8**	 **38**	92

[a] All reactions were conducted in a Schlenk tube, with allene (1 atm), nucleophile (1.05 mol equiv), Pd_2dba_3 (2.5 mol %), TFP (10 mol %) and K_2CO_3 (2 mol equiv) in DMF at 80 °C for 16 h.
[b] Isolated yield.



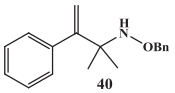
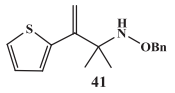
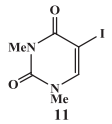
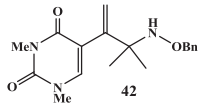
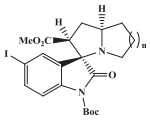
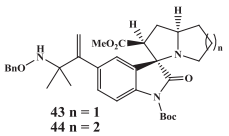
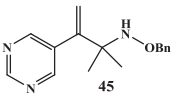
Scheme 5.

3. Experimental

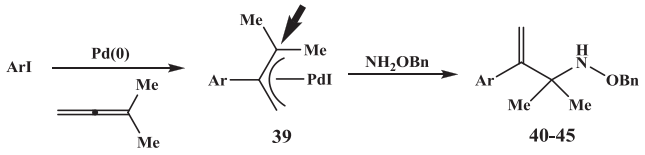
3.1. General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker DPX 300 instrument or at 500 MHz on a Bruker DRX 500 instrument. ^{13}C Nuclear magnetic resonance spectra were recorded at 75 MHz on a Bruker DPX 300 instrument. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts are given in parts per million (δ) down field from tetramethylsilane. ^{1}H spectra are referenced to

Table 4
Reaction of 1,1-dimethylallene with **1** and aryl/heteroaryl halides[a]

Entry	Aryl halide	Product	Yield[b] (%)
1	 22a	 40	83
2	 8	 41	90
3	 11	 42	76
4	 12 n = 1 13 n = 2	 43 n = 1 44 n = 2	47 (n=1) 64 (n=2)
5	 10	 45	76

[a] All reactions were conducted in a Schlenk tube, with 1,1-dimethylallene (5 mol equiv), *O*-benzylhydroxylamine (2–3 mol equiv), Pd_2dba_3 (2.5 mol %), TFP (10 mol %) and K_2CO_3 (2 mol equiv) in DMF at 80 °C for 16 h.
[b] Isolated yield.



Scheme 6.

tetramethylsilane and ^{13}C spectra are referenced to deuterochloroform. Assignments of ^1H signals were made with the aid of 2D COSY spectra where necessary. Assignments of ^{13}C signals were made with the aid of DEPT or APT spectra. Coupling constants are reported to the nearest 0.5 Hz. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Infrared spectra were recorded either neat (for liquids) or as Nujol mulls (for solids) on a Phillips PU 9706 using KBr discs. Mass spectra were recorded on a V.G.-AutoSpec spectrometer using electron impact (EI) operating at 70 eV or fast atom bombardment (FAB), as specified. Accurate molecular weights were determined on the AutoSpec using perfluorokerosene as internal standard. Flash column chromatography was performed on silica gel 60 (Merk 230–400 mesh). Ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40–60 °C. All reagents and solvents were purified according to procedures given in Purification of Laboratory Chemicals, 6th ed., Armarego, W. and Chai, C. L. L., Butterworth–Heinemann, 2009.

3.2. General procedure for the two-step synthesis of spirocycles 12b and 13b via 1,3-dipolar cycloaddition and *N*-Boc protection

3.2.1. Cycloaddition (procedure A). A solution of 5-iodoisatin (5 mmol), proline or pipecolinic acid (1 mol equiv) and methyl acrylate (1 mol equiv) in acetonitrile (100 mL) was heated under reflux for 16 h. The solution was cooled, filtered and the solvent evaporated in vacuo. The residue was purified by flash chromatography eluting with 1:1 v/v ether/ethyl acetate.

*3.2.1.1. Methyl 5-iodo-2-oxo-1,1′,2,2′,5′′,6′,7′,7a′-octahydro-spiro[indole-3,3′-pyrrolizine]-2′-carboxylate (**12a**).* The product crystallized from ether as colourless prisms (1.69 g, 82%); mp 143–144 °C; ^1H NMR δ: 1.56 (m, 1H, 7′-H_A), 1.91 (m, 2H, 2×6′-H), 2.06–2.13 (m, 2H, 7′-H_B and 1′-H_A), 2.37–2.46 (m, 2H, 5′-H_A and 1′-H_B), 2.62 (m, 1H, 5′-H_B), 3.29 (s, 3H, CH_3O), 3.84 (dd, 1H, *J* 6.5 and 12.5 Hz, 2′′-H), 4.05 (m, 1H, 7a′-H), 6.73 (m, 1H, ArH), 7.38 (s, 1H, ArH) and 7.57 (d, 1H, *J* 8.5 Hz, ArH). Found: C, 46.40; H, 4.35; N, 6.90; I, 30.80. $C_{16}H_{17}IN_2O_3$ requires: C, 46.62; H, 4.16; N, 6.80; I, 30.79%. *m*/*z* (%) 412 (M^+, 57), 384 (51), 353 (28), 326 (100), 298 (12), 169 (13), 129 (15) and 83 (74).

*3.2.1.2. Methyl 5-iodo-2-oxo-1,1′,2,5′,6′,7′,8′,8a′-octahydro-2′H-spiro[indole-3,3′-indolizine]-2′-carboxylate (**13a**).* Prepared by general procedure A but with 1.2 mol equiv of methyl acrylate and heating for 120 h. The product crystallized from 2:1 v/v petroleum ether/ethyl acetate as colourless plates (1.38 g, 65%); mp 156–159 °C; ^1H NMR δ: 1.21–1.31 (m, 3H, 2×8′-H and 6′-H_A), 1.50 (m, 1H, 6′-H_B), 1.72–1.75 (m, 1H, 7′-H_A), 1.90–1.93 (m, 1H, 7′-H_B), 2.09–2.20 (m, 2H, 2×1′-H), 2.34–2.39 (m, 2H, 2×5′-H), 3.16–3.19 (m, 1H, 8a′-H), 3.26 (s, 3H, OCH_3), 3.37 (dd, 1H, *J* 8.0 and 10.0 Hz, 2′-H), 6.60–6.63 (m, 1H, ArH), 7.41 (s, 1H, ArH), 7.52 (dd, 1H, *J* 1.5 and 8.0 Hz, ArH); ^{13}C NMR δ: 24.1, 26.0, 32.1, 34.2, 46.0, 51.6, 51.9, 60.0, 73.0, 85.4, 111.7, 132.2, 134.4, 138.1, 172.2. Found: C, 48.10; H, 4.50; N, 6.40; I, 29.70. $C_{17}H_{19}IN_2O_3$ requires: C, 47.90; H, 4.49; N, 6.27; I, 29.77%. *m*/*z* (%): 426 (M^+, 33), 398 (22), 339 (100), 300 (53), 272 (56), 271 (94), 256 (25) and 241 (30).

3.2.2. Boc protection (procedure B). The cycloadduct (2 mmol), di-*tert*-butyl dicarbonate (3 mmol) and triethylamine (3 mmol) were combined in dichloromethane (20 mL) and stirred at reflux for 30 h. The mixture was concentrated in vacuo and the residue purified by flash chromatography eluting with 1:1 v/v petroleum ether/ether.

*3.2.2.1. 1-tert-Butyl 2′-methyl 5-iodo-2-oxo-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indole-3,3′-pyrrolizine]-1,2′-(2H)-dicarboxylate (**12b**).* The product crystallized as colourless prisms from ether (993 mg, 97%); mp 120–121 °C; ^1H NMR δ: 1.60 (m, 1H, 7′-H_A), 1.63 (s, 9H, 3×CH_3), 1.94 (m, 2H, 2×6′-H), 2.02–2.10 (m, 2H, 7′-H_B and 1′-H_A), 2.36–2.48 (m, 2H, 5′-H_A and 1′-H_B), 2.60 (m, 1H, 5′-H_B), 3.29 (s, 3H, CH_3O), 3.87 (dd, 1H, *J* 6.5 and 12.5 Hz, 2′-H), 4.05 (m, 1H, NCH), 6.80 (m, 1H, ArH), 7.40 (s, 1H, ArH), 7.61 (d, 1H, *J* 8.5 Hz, ArH). Found: C, 49.25; H, 5.10; N, 5.35; I, 24.90. $C_{21}H_{25}IN_2O_5$ requires: C, 49.23; H, 4.92; N, 5.47; I, 24.77%. *m*/*z* (%) 512 (M^+, 47), 484 (35), 428 (36), 412 (71), 384 (43), 369 (45), 353 (38), 326 (100), 284 (12), 169 (15) and 83 (92).

*3.2.2.2. 1-tert-Butyl 2′-methyl 5-iodo-2-oxo-1′,5′,6′,7′,8′,8a′-hexahydro-2′H-spiro[indole-3,3′-indolizine]-1,2′(2H)-dicarboxylate (**13b**).* The product was obtained as a colourless amorphous solid from petroleum ether/ether (989 mg, 94%); mp 120–122 °C; ^1H NMR δ: 1.20–1.38 (m, 3H, 2×8′-H and 6′-H_A), 1.50 (m, 1H, 6′-H_B), 1.64 (s, 9H, 3×CH_3), 1.72–1.77 (m, 1H, 7′-H_A), 1.90–1.93 (m, 1H, 7′-H_B), 2.05–2.26 (m, 2H, 2×1′-H), 2.30–2.39 (m, 2H, 5′-H), 3.13–3.19 (m, 1H, 8a′-H), 3.24 (s, 3H, OCH_3), 3.36 (dd, 1H, *J* 8.0 and 10.0 Hz, 2′-H), 7.44 (d, 1H, *J* 1.0 Hz, ArH), 7.60 (m, 2H, ArH); ^{13}C NMR δ: 13.5, 24.0, 25.9, 28.4, 32.2, 34.0, 45.8, 51.9, 52.6, 60.0, 72.5, 77.6, 85.1, 88.1, 116.8, 130.6, 133.9, 138.5, 140.4, 149.3, 171.7, 176.2. Found: C, 50.00; H, 5.15; N, 5.20; I, 24.05. $C_{22}H_{27}IN_2O_5$ requires: C, 50.20; H, 5.17; N, 5.32; I, 24.11%. *m*/*z* (%): 526 (M^+, 18), 498 (23), 442 (28), 426 (40), 397 (77), 339 (74), 213 (20), 97 (100) and 41 (96).

3.2.3. General procedure for reactions using allene gas (procedure C). Nucleophile (1–3 mol equiv), tris-(dibenzylideneacetone) dipalladium (2.5 mol %), tris-(2-furyl)phosphine (10 mol %) and potassium carbonate (2 mol equiv) were added to a solution of the aryl halide (1 mmol) in dry dimethylformamide (10 mL) in a Schlenk tube. The reaction mixture was then degassed using the freeze, pump, thaw (F.P.T.) technique (one cycle). Allene gas was then introduced at the required pressure (1 atm) and the Schlenk tube contents stirred and heated at 80 °C for 16 h. After cooling and venting, DCM (20 mL) was added and the mixture filtered to remove inorganic salts. The filtrate was concentrated in vacuo and the residue was purified by column chromatography.

*3.2.3.1. O-Benzyl-N-(2-phenyl-allyl)-hydroxylamine (**14**).* Prepared by procedure C from iodobenzene (0.24 mL, 2.10 mmol), *O*-benzylhydroxylamine (753 mg, 6.11 mmol) and allene gas (1 atm) in DMF (20 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (371 mg, 74%); ^{1}H NMR δ: 3.94 (s, 2H, NCH_2), 4.67 (s, 2H, OCH_2), 5.29 and 5.47 (2×s, 2×1H, $=CH_2$), 5.62 (br s, 1H, NH), 7.21–7.44 (m, 10H, ArH); ^{13}C NMR δ: 56.6, 76.5, 116.0, 126.6, 128.1, 128.2, 128.7, 128.8, 128.8, 138.3, 139.8, 144.3. Found: C, 80.05; H, 7.00; N, 5.75. $C_{16}H_{17}NO$ requires: C, 80.30; H, 7.16; N, 5.85%. *m*/*z* (%): 240 (100, M+1).

*3.2.3.2. O-Benzyl-N-(2-thiophen-2-yl-allyl)-hydroxylamine (**15**).* Prepared by procedure C from 2-iodothiophene (442 mg, 2.10 mmol), *O*-benzylhydroxylamine (753 mg, 6.11 mmol) and allene gas (1 atm) in DMF (20 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (465 mg, 90%); ^{1}H NMR δ: 3.90 (s, 2H, NCH_2), 4.71 (s, 2H, OCH_2), 5.20 and 5.54 (2×s, 2×1H, $=CH_2$), 5.71 (br s, 1H, NH), 6.95–6.98 (m, 1H, ArH), 7.06–7.08 (m, 1H, ArH), 7.18–7.20 (m, 1H, ArH), 7.28–7.36 (m, 5H, ArH). Found: C, 68.25; H, 6.05; N, 5.60; S, 13.10. $C_{14}H_{15}NOS$ requires: C, 68.54; H, 6.16; N, 5.71; S, 13.07%. *m*/*z* (%): 246 (M+1).

*3.2.3.3. O-Benzyl-N-(2-pyridin-3-yl-allyl)-hydroxylamine (**16**).* Prepared by procedure C from 3-bromopyridine (248 mg, 1.57 mmol), *O*-benzylhydroxylamine (583 mg, 4.74 mmol) and allene gas (1 atm) in DMF (15 mL). Purification by flash column chromatography eluting with 3:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow oil (254 mg, 67%); ^{1}H NMR δ: 3.93 (s, 2H, NCH_2), 4.65 (s, 2H, OCH_2), 5.40 and 5.53 (2×s, 2×1H, $=CH_2$), 5.60 (br s, 1H, NH), 7.21–7.37 (m, 6H, ArH), 7.70 (m, 1H, ArH), 8.51 (dd, 1H, *J* 5.0 and 1.5 Hz, ArH), 8.71 (dd, 1H, *J* 2.5 and 1.0 Hz, ArH); ^{13}C NMR δ: 56.4, 76.7, 117.7, 123.5, 128.2 128.8, 128.9, 133.9 135.5, 138.1, 141.7, 148.1, 149.2. Found: C, 74.70; H, 6.75; N, 11.80. $C_{15}H_{16}N_2O$ requires: C, 74.97; H, 6.71; N, 11.66%. *m*/*z* (%): 240 (M^+, 52), 209 (93), 195 (11), 145 (15), 131 (23), 117 (41), 104 (43), 91 (100) and 77 (49).

*3.2.3.4. O-Benzyl-N-(2-pyrimidin-5-yl-allyl)-hydroxylamine (**17**).* Prepared by procedure C from 5-bromopyrimidine (231 mg, 1.45 mmol), *O*-benzylhydroxylamine (508 mg, 4.13 mmol) and allene gas (1 atm) in DMF (15 mL). Purification by flash column chromatography eluting with 1:1 v/v petroleum ether/ethyl acetate afforded the product as a colourless oil (311 mg, 89%); ^{1}H NMR δ: 3.92 (s, 2H, NCH_2), 4.61 (s, 2H, OCH_2), 5.46 and 5.60 (2×s, 2×1H, $=CH_2$), 7.24–7.40 (m, 5H, ArH), 8.81 (s, 2H, ArH), 9.13 (s, 1H, ArH). Found: C, 69.70; H, 6.35; N, 17.15. $C_{14}H_{15}N_3O$ requires: C, 69.69; H, 6.27; N, 17.41%. *m*/*z* (%): 241 (M^+, 29), 210 (72), 165 (20), 105 (18), 91 (100), 77 (35), 65 (50) and 51 (53).

*3.2.3.5. 5-[1-(Benzyloxy)amino-methyl-vinyl]-1,3-dimethyl-1H-pyrimidine-2,4-dione (**18**).* Prepared by procedure C from 5-iodo-1,3-dimethyluracil (1.01 g, 3.80 mmol), *O*-benzylhydroxylamine (1.43 g, 11.66 mmol) and allene gas (1 atm) in DMF (30 mL). Purification by column chromatography eluting with 3:1 v/v petroleum ether/ethyl acetate afforded the product as a pale orange oil (973 mg, 85%); ^{1}H NMR δ: 3.33 and 3.34 (s, 6H, 2×NCH_3), 3.85 (s, 2H, NCH_2), 4.66 (s, 2H, OCH_2), 5.30 and 5.56 (s, 2×1H, $=CH_2$), 5.64 (br s, 1H, NH), 7.20–7.36 (m, 6H, 5×ArH and =CHN); ^{13}C NMR δ: 28.4, 37.5, 56.7, 76.2, 113.6, 119.2, 128.2, 128.7, 128.8, 138.5, 138.6, 141.1, 151.7, 162.6. Found: C, 63.80; H, 6.35; N, 13.70. $C_{16}H_{19}N_3O_3$ requires: C, 63.77; H, 6.36; N, 13.94%. *m*/*z* (%): 301 (M^+, 18), 283 (10), 210 (14), 194 (38), 180 (51), 165 (10), 109 (15), 91 (100), 77 (18), 51 (16) and 42 (42).

*3.2.3.6. 1-tert-Butyl 2′-methyl 5-(1-{[(benzyloxy)amino]methyl}-vinyl)-2-oxo-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indole-3,3′-pyrrolizine]-1,2′(2H)-dicarboxylate (**19**).* Prepared by procedure C from **12b** (553 mg, 1.08 mmol), *O*-benzylhydroxylamine (345 mg, 2.80 mmol) and allene gas (1 atm) in DMF (10 mL). Purification by flash column chromatography eluting with 3:1 v/v petroleum ether/ethyl acetate afforded the product as a thick pale yellow oil (417 mg, 70%); ^{1}H NMR δ: 1.55 (m, 1H, 7′-H_A), 1.62 (s, 9H, $OC(CH_3)_3$), 1.84 (m, 2H, 2×6′-H), 2.04 (m, 1H, 7′-H_B), 2.13 (m, 1H, 1′-H_A), 2.39–2.42 (m, 2H, 5′-H_A and 1′-H_B), 2.55 (m, 1H, 5′-H_B), 3.17 (s, 3H, CH_3O), 3.88 (dd, 1H, *J* 13.0 and 7.0 Hz, 2′-H), 3.93 (s, 2H, ONHCH_2), 4.05 (m, 1H, 7a′-H), 4.68 (s, 2H, OCH_2), 5.30 and 5.45 (2×s, 2×1H, $=CH_2$), 5.65 (br s, 1H, NH), 7.28–7.45 (m, 7H, ArH), 7.89 (d, 1H, *J* 8.5 Hz, ArH). Found: C, 67.95; H, 6.70; N, 7.80. $C_{31}H_{37}N_3O_6$ requires: C, 67.99; H, 6.81; N, 7.67%. *m*/*z* (%) 547 (M^+, 6), 461 (9), 447 (6), 361 (41), 298 (57), 266 (31) and 91 (100).

*3.2.3.7. 1-tert-Butyl 2′-methyl 5-(1-{[(benzyloxy)amino]methyl}-vinyl)-2-oxo-1′,5′,6′,7′,8′,8a′-hexahydro-2′H-spiro[indole-3,3′-indolizine]-1,2′(2H)-dicarboxylate (**20**).* Prepared by procedure C from **13b** (556 mg, 1.06 mmol), *O*-benzylhydroxylamine (341 mg, 2.77 mmol) and allene gas (1 atm) in DMF (10 mL). Purification by flash column chromatography eluting with 3:1 v/v petroleum ether/ether afforded the product as a thick colourless oil (416 mg, 70%); ^{1}H NMR δ 1.15–1.30 (m, 3H, 2×8′-H and 6′-H_A), 1.45 (m, 1H, 6′-H_B), 1.65 (s, 9H, 3×CH_3), 1.73 (m, 1H, 7′-H_A), 1.89–1.92 (m, 1H, 7′-H_B), 2.10–2.20 (m, 2H, 2×1′-H), 2.28 (m, 2H, 2×5′-H), 3.09 (s, 3H, OCH_3), 3.21 (m, 1H, 8a′-H), 3.38 (dd, 1H, *J* 10.0 and 8.5 Hz, 2′-H), 3.94 (s, 2H, ONHCH_2), 4.68 (s, 2H, OCH_2), 5.28 and 5.47 (2×s, 2×1H, $=CH_2$), 5.65 (br s, 1H, NH), 7.27–7.39 (m, 7H, ArH), 7.74 (d, 1H, *J* 8.5 Hz, ArH). Found: C, 68.70; H, 7.15; N, 7.40. $C_{32}H_{39}N_3O_6$ requires: C, 68.43; H, 7.00; N, 7.48%. *m*/*z* (%): 562 (M+1, 7), 456 (7), 341 (7), 212 (28), 172 (69), 126 (45), 98 (100) and 84 (53).

*3.2.3.8. tert-Butyl benzyloxy(2-phenyl-2-propenyl)carbamate (**26a**).*

(a) Prepared by procedure C from iodobenzene (225 mg, 1.11 mmol), *N*-Boc-*O*-benzylhydroxylamine (272 mg, 1.22 mmol) and allene gas (1 atm) in DMF (10 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as colourless oil (357 mg, 95%).

(b) Prepared by procedure C from phenyl triflate (99 mg, 0.44 mmol), *N*-Boc-*O*-benzylhydroxylamine (105 mg, 0.45 mmol), allene gas (1 atm), potassium carbonate (140 mg, 1.01 mmol) and a catalytic system comprising tris-(dibenzylideneacetone)dipalladium (11 mg, 2.7 mol %) and tris-(2-furyl)phosphine (11 mg, 11 mol %) in DMF (5 mL) at 110 °C for 84 h. Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (120 mg, 80%); ^{1}H NMR δ: 1.48 (s, 9H, 3×CH_3), 4.49 (s, 2H, NCH_2), 4.68 (s, 2H, OCH_2), 5.31 and 5.52 (2×s, 2×1H, $=CH_2$), 7.26–7.50 (m, 10H, ArH); ^{13}C NMR δ: 28.6, 54.3, 77.6, 81.9, 116.0, 126.8, 128.2, 128.7, 128.8, 128.9, 129.8, 135.9, 139.3, 143.6, 156.8. Found: C, 74.00; H, 7.50; N, 3.85.

$C_{21}H_{25}NO_3$ requires: C, 74.31; H, 7.42; N, 4.13%. *m/z* (%) 339 (M^+, <1), 266 (<1), 239 (<1), 206 (20), 193 (8), 91 (100), 57 (80).

*3.2.3.9. tert-Butyl benzyloxy[2-(2-methoxy-phenyl)-2-propenyl] carbamate (**26b**).* Prepared by procedure C from 2-iodoanisole (315 mg, 1.35 mmol), *N*-Boc-*O*-benzylhydroxylamine (308 mg, 1.38 mmol) and allene gas (1 atm) in DMF (10 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (475 mg, 95%); ^{1}H NMR δ: 1.40 (s, 9H, 3×CH_3), 3.80 (s, 3H, OCH_3), 4.43 (s, 2H, NCH_2), 4.74 (s, 2H, OCH_2), 5.22 and 5.33 (2×s, 2×1H, =CH_2), 6.84–6.94 (m, 2H, ArH), 7.20–7.36 (m, 7H, ArH). Found: C, 71.75; H, 7.40; N, 3.75. $C_{22}H_{27}NO_4$ requires: C, 71.52; H, 7.37; N, 3.79%. *m/z* (%) 370 (M+1, 9), 314 (39), 270 (77), 91 (100).

*3.2.3.10. tert-Butyl benzyloxy(2-(4-acetylphenyl)-2-propenyl)carbamate (**26c**).* Prepared by procedure C from 4-iodoacetophenone (467 mg, 1.99 mmol), *N*-Boc-*O*-benzylhydroxylamine (468 mg, 2.09 mmol) and allene gas (1 atm) in DMF (20 mL). Purification by flash column chromatography eluting with 5:1 v/v petroleum ether/ether afforded the product as a colourless oil (725 mg, 96%); ^{1}H NMR δ: 1.49 (s, 9H, 3×CH_3), 2.60 (s, 3H, ArC(O)CH_3), 4.50 (s, 2H, NCH_2), 4.67 (s, 2H, OCH_2), 5.42 and 5.63 (2×s, 2×1H, =CH_2), 7.26–7.31 (m, 5H, ArH), 7.56–7.59 (m, 2H, ArH), 7.92–7.95 (m, 2H, ArH); ^{13}C NMR δ: 27.0, 28.6, 54.1, 77.6, 82.2, 118.1, 126.9, 128.7, 128.9, 129.7, 135.8, 136.7, 142.9, 143.9, 156.7, 198.0. Found: C, 72.25; H, 7.10; N, 3.80. $C_{23}H_{27}NO_4$ requires: C, 72.42; H, 7.13; N, 3.67%. *m/z* (%) 380 (M+1, 2), 326 (21), 282 (21), 161 (7), 91 (100), 57 (44).

*3.2.3.11. Methyl 4-(1-{[(benzyloxy)(tert-butoxycarbonyl)amino] methyl}vinyl)benzoate (**26d**).* Prepared by procedure C from 4-iodobenzoic acid methyl ester (317 mg, 1.21 mmol), *N*-Boc-*O*-benzylhydroxylamine (298 mg, 1.33 mmol) and allene gas (1 atm) in DMF (10 mL). Purification by flash column chromatography eluting with 20:20:1 v/v/v petroleum ether/DCM/ether afforded the product as a colourless oil (469 mg, 97%); ^{1}H NMR δ: 1.48 (s, 9H, 3×CH_3), 3.92 (s, 3H, OCH_3), 4.50 (s, 2H, NCH_2), 4.66 (s, 2H, OCH_2), 5.41 and 5.61 (2×s, 2×1H, =CH_2), 7.26–8.02 (m, 9H, ArH). Found: C, 69.50; H, 6.90; N, 3.60. $C_{23}H_{27}NO_5$ requires: C, 69.50; H, 6.85; N, 3.52%. *m/z* (%): 398 (M+1, <1), 388 (<1), 369 (<1), 342 (28), 310 (12), 298 (29) and 91 (100).

*3.2.3.12. tert-Butyl benzyloxy[2-(4-nitro-phenyl)-2-propenyl]carbamate (**26e**).* Prepared by procedure C from 4-iodonitrobenzene (307 mg, 1.23 mmol), *N*-Boc-*O*-benzylhydroxylamine (304 mg, 1.36 mmol) and allene gas (1 atm) in DMF. Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a pale yellow oil (460 mg, 96%); ^{1}H NMR δ: 1.48 (s, 9H, 3×CH_3), 4.50 (s, 2H, NCH_2), 4.67 (s, 2H, OCH_2), 5.49 and 5.66 (2×s, 2×1H, =CH_2), 7.28–7.34 (m, 5H, ArH), 7.60–7.63 (m, 2H, ArH), 8.17–8.21 (m, 2H, ArH); ^{13}C NMR δ: 28.6, 53.8, 77.6, 82.4, 119.7, 124.0, 127.6, 128.8, 129.0, 129.4 129.7, 130.9, 135.7, 142.2, 145.7, 147.7, 156.7. Found: C, 65.90; H, 6.35; N, 7.35. $C_{21}H_{24}N_2O_5$ requires: C, 65.61; H, 6.29; N, 7.29%. *m/z* (%): 383 (M+1, <1), 329 (24), 285 (8), 235 (12) and 91 (100).

*3.2.3.13. tert-Butyl benzyloxy[2-(3-nitro-phenyl)-2-propenyl]carbamate (**26f**).* Prepared by procedure C from 3-iodonitrobenzene (365 mg, 1.47 mmol), *N*-Boc-*O*-benzylhydroxylamine (336 mg, 1.51 mmol) and allene gas (1 atm) in DMF (15 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a pale yellow oil (536 mg, 94%); ^{1}H NMR δ: 1.49 (s, 9H, 3×CH_3), 4.50 (s, 2H, NCH_2), 4.69 (s, 2H, OCH_2), 5.30 and 5.45 (2×s, 2×1H, =CH_2), 7.30–7.34 (m, 5H, ArH), 7.48–7.53 (m, 1H, ArH), 7.78–7.81 (m, 1H, ArH), 8.13–8.17 (m, 1H, ArH), 8.32–8.34 (m, 1H, ArH). Found: C, 65.80; H, 6.40; N, 7.05. $C_{21}H_{24}N_2O_5$ requires: C, 65.61; H, 6.29; N, 7.29%.

*3.2.3.14. tert-Butyl benzyloxy[2-(2-nitro-phenyl)-2-propenyl]carbamate (**26g**).* Prepared by procedure C from 2-iodonitrobenzene (365 mg, 1.47 mmol), *N*-Boc-*O*-benzylhydroxylamine (345 mg, 1.54 mmol) and allene gas (1 atm) in DMF (15 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a pale yellow oil (428 mg, 94%); ^{1}H NMR δ: 1.31 (s, 9H, 3×CH_3), 4.32 (s, 2H, NCH_2), 4.82 (s, 2H, OCH_2), 5.08 and 5.33 (2×s, 2×1H, =CH_2), 7.33–7.45 (m, 7H, ArH), 7.51–7.54 (m, 1H, ArH), 7.97–8.00 (m, 1H, ArH). Found: C, 65.75; H, 6.55; N, 7.15. $C_{21}H_{24}N_2O_5$ requires: C, 65.61; H, 6.29; N, 7.29%. *m/z* (%): 383 (M−1, <1), 369 (13), 285 (40) and 91 (100).

*3.2.3.15. tert-Butyl benzyloxy[2-(thiophen-2-yl)-2-propenyl]carbamate (**27**).* Prepared by procedure C from 2-iodothiophene (298 mg, 1.41 mmol), *N*-Boc-*O*-benzylhydroxylamine (340 mg, 1.52 mmol) and allene gas (1 atm) in DMF (15 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (451 mg, 92%); ^{1}H NMR δ: 1.51 (s, 9H, 3×CH_3), 4.43 (s, 2H, NCH_2), 4.74 (s, 2H, OCH_2), 5.21 and 5.58 (2×s, 2×1H, =CH_2), 6.98 (dd, 1H, *J* 5.0 and 3.5 Hz, thiophene H), 7.15 (dd, 1H, *J* 1.0 and 3.5 Hz, thiophene H), 7.18 (dd, 1H, *J* 5.0 and 1.0 Hz, thiophene H), 7.30–7.31 (m, 5H, ArH); ^{13}C NMR δ: 28.7, 54.3, 77.8, 82.1, 114.7, 124.7, 125.0 127.9, 128.8, 128.9, 129.8 135.9, 137.2, 143.1, 156.7. Found: C, 66.25; H, 6.90; N, 3.80, S, 9.15. $C_{19}H_{23}NO_3S$ requires: C, 66.06; H, 6.71; N, 4.05, S, 9.28%. *m/z* (%): 363 (M+18, 35), 346 (8, M+1), 307 (100) and 246 (15).

*3.2.3.16. tert-Butyl benzyloxy[2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropydimidin-5-yl)prop-2-enyl]carbamate (**28**).* Prepared by procedure C from 5-iodo-1,3-dimethyluracil (268 mg, 1.01 mmol), *N*-Boc-*O*-benzylhydroxylamine (236 mg, 1.06 mmol) and allene gas (1 atm) in DMF (10 mL). Purification by flash column chromatography eluting with 3:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow oil (402 mg, 96%); ^{1}H NMR δ: 1.47 (s, 9H, 3×CH_3), 3.34 and 3.36 (s, 6H, 2×NCH_3), 4.38 (s, 2H, NCH_2), 4.75 (s, 2H, OCH_2), 5.34 and 5.74 (2×s, 2×1H, =CH_2), 7.32–7.34 (m, 6H, 5×ArH and 1×=CHN). Found: C, 62.60; H, 6.90; N, 10.20. $C_{21}H_{27}N_3O_5$ requires: C, 62.83; H, 6.78; N, 10.47%. *m/z* (%): 419 (M+18, 7), 402 (44, M+1), 302 (100), 239 (40), 222 (50), 196 (38) and 181 (74).

*3.2.3.17. 1-tert-Butyl 2′-methyl 5-(1-{[(benzyloxy)(tert-butoxycarbonyl)amino]methyl}vinyl)-2-oxo-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indole-3,3′-pyrrolizine]-1,2′(2H)-dicarboxylate (**29**).* Prepared by procedure C from **12** (1.123 g, 2.19 mmol), *N*-Boc-*O*-benzylhydroxylamine (500 mg, 2.23 mmol), allene gas (1 atm), potassium carbonate (335 mg, 2.43 mmol), tris-(dibenzylideneacetone) dipalladium (51 mg, 2.5 mol%) and tris-(2-furyl)phosphine (64 mg, 12 mol%). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless glass (1.25 g, 88%); ^{1}H NMR δ: 1.53 (s, 9H, 3×CH_3), 1.60 (m, 1H, 7′-H_A), 1.65 (s, 9H, 3×CH_3), 1.84 (m, 2H, 2×6′-H), 2.05 (m, 1H, 7′-H_B), 2.17 (m, 1H, 1′-H_A), 2.35–2.41 (m, 2H, 5′-H_A and 1′-H_B), 2.55 (m, 1H, 5′-H_B), 3.15 (s, 3H, CH_3O), 3.89 (dd, 1H, *J* 13.0 and 7.0 Hz, 2′-H), 4.05 (m, 1H, 7a′-H), 4.44–4.68 (m, 4H, ONHCH_2 and OCH_2), 5.34 and 5.57 (2×s, 2×1H, =CH_2), 7.26–7.31 (m, 6H, ArH), 7.50–7.54 (m, 1H, ArH), 7.92 (d, 1H, *J* 8.5 Hz, ArH); ^{13}C NMR δ: 28.4, 28.7, 28.9, 32.8, 33.8, 47.6, 51.8, 54.5, 57.7, 65.6, 72.8, 82.2, 84.8, 115.5, 116.3, 123.4, 125.8, 127.7, 128.7, 128.9, 129.6, 134.7, 135.8, 140.3, 142.2, 149.7, 157.2, 170.6, 178.0. Found: C, 66.55; H, 7.10; N, 6.30. $C_{36}H_{45}N_3O_8$ requires: C, 66.75; H, 7.00; N, 6.49%. *m/z* (%): 648 (M+1, 22), 620 (5), 461 (14), 325 (11), 298 (23), 91 (95) and 57 (100).

*3.2.3.18. 1-tert-Butyl 2′-methyl 5-(1-{[(benzyloxy)(tert-butoxycarbonyl)amino]methyl}vinyl)-2-oxo-1′,5′,6′,7′,8′,8a′-hexahydro-2′H-spiro[indole-3,3′-indolizine]-1,2′(2H)-dicarboxylate (**30**).* Prepared by procedure C from **13** (553 mg, 1.05 mmol), *N*-Boc-*O*-benzylhydroxylamine (240 mg, 1.07 mmol), allene gas (1 atm), potassium carbonate (253 mg, 1.83 mmol), tris-(dibenzylideneacetone)dipalladium (28 mg, 3 mol %) and tris-(2-furyl)phosphine (31 mg, 12 mol %). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless glass (592 mg, 85%); ^{1}H NMR δ: 1.20–1.30 (m, 3H, 2×8′-H and 6′-H$_A$), 1.43 (m, 1H, 6′-H$_B$), 1.50 (s, 9H, 3×CH$_3$), 1.65 (s, 9H, 3×CH$_3$), 1.70 (m, 1H, 7′-H$_A$), 1.90–1.93 (m, 1H, 7′-H$_B$), 2.15–2.25 (m, 2H, 2×1′-H), 2.30 (m, 2H, 2×5′-H), 3.09 (s, 3H OCH$_3$), 3.21 (m, 1H, 8a′-H), 3.39 (dd, 1H, *J* 10 and 8.5 Hz, 2′-H), 4.46 (s, 2H, ONHC*H*$_2$), 4.68 (2×d, 2H, *J* 19.5 Hz, OC*H*$_2$), 5.29 and 5.52 (2×s, 2×1H, =CH$_2$), 7.30–7.76 (m, 8H, ArH); HRMS: 662.3430; C$_{37}$H$_{47}$N$_3$O$_8$+H requires: 662.3441. *m*/*z* (%) 661 (M$^+$, <1), 633 (5), 561 (40), 533 (48), 476 (10), 403 (12), 370 (12), 339 (28), 312 (75), 279 (31), 253 (82), 91 (100), 57 (80).

*3.2.3.19. tert-Butyl benzyloxy(2-pyrimidin-5-ylprop-2-enyl)carbamate (**31**).* Prepared by procedure C from 5-bromopyrimidine (209 mg, 1.31 mmol), *N*-Boc-*O*-benzylhydroxylamine (310 mg, 1.38 mmol), allene gas (1 atm), potassium carbonate (219 mg, 1.58 mol), tris-(dibenzylideneacetone)dipalladium (33 mg, 2.8 mol %) and tris-(2-furyl)phosphine (36 mg, 12 mol %). Purification by flash column chromatography eluting with 4:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow oil (392 mg, 87%); ^{1}H NMR δ: 1.49 (s, 9H, 3×CH$_3$), 4.45 (s, 2H, NCH$_2$), 4.71 (s, 2H, OCH$_2$), 5.47 and 5.60 (2×s, 2×1H, =CH$_2$), 7.28–7.38 (m, 5H, ArH), 8.80 (s, 2H, ArH), 9.13 (s, 1H, ArH). Found: C, 66.55; H, 6.80; N, 12.20. C$_{19}$H$_{23}$N$_3$O$_3$ requires: C, 66.84; H, 6.79; N, 12.31%. *m*/*z* (%): 341 (M$^+$, 2), 241 (13), 211 (15), 120 (12), 91 (100) and 57 (90).

*3.2.3.20. tert-Butyl benzyloxy(2-pyridin-3-ylprop-2-enyl)carbamate (**32**).* Prepared by procedure C from 3-bromopyridine (216 mg, 1.37 mmol), *N*-Boc-*O*-Benzylhydroxylamine (322 mg, 1.44 mmol), allene gas (1 atm), potassium carbonate (230 mg, 1.67 mol), tris-(dibenzylideneacetone)dipalladium (33 mg, 2.7 mol %) and tris-(2-furyl)phosphine (36 mg, 11 mol %). Purification by flash column chromatography eluting with 4:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow oil (300 mg, 64%); ^{1}H NMR δ: 1.48 (s, 9H, 3×CH$_3$), 4.47 (s, 2H, NCH$_2$), 4.69 (s, 2H, OCH$_2$), 5.40 and 5.56 (s, 2×1H, =CH$_2$), 7.27–7.33 (m, 6H, ArH), 7.74 (m, 1H, ArH), 8.53 (dd, 1H, *J* 5.0 and 1.5 Hz, ArH), 8.73 (dd, 1H, *J* 2.5 and 1.0 Hz, ArH); HRMS: 341.1865; C$_{20}$H$_{24}$N$_2$O$_3$+H requires: 341.1869. *m*/*z* (%): 341 (M+1, 100), 240 (16).

*3.2.3.21. tert-Butyl benzyloxy(2-(2-acetylphenyl)-2-propenyl)carbamate (**33**).* Prepared by procedure C from 2-bromoacetophenone (303 mg, 1.52 mmol), *N*-Boc-*O*-benzylhydroxylamine (371 mg, 1.66 mmol), allene gas (1 atm), potassium carbonate (250 mg, 1.81 mol), tris-(dibenzylideneacetone)dipalladium (38 mg, 2.7 mol %) and tris-(2-furyl)phosphine (41 mg, 11 mol %). Purification by flash column chromatography eluting with 6:1 v/v petroleum ether/ether afforded the product as a colourless oil (469 mg, 81%); ^{1}H NMR δ: 1.35 (s, 9H, 3×CH$_3$), 2.51 (s, 3H, ArC(O)CH$_3$), 4.32 (s, 2H, NCH$_2$), 4.79 (s, 2H, OCH$_2$), 5.05 and 5.30 (s, 2×1H, =CH$_2$), 7.20–7.62 (m, 9H, ArH). Found: C, 72.15; H, 7.20; N, 3.60. C$_{23}$H$_{27}$NO$_4$ requires: C, 72.42; H, 7.13; N, 3.67%. *m*/*z* (%): 382 (M+1, 9), 326 (8), 282 (100), 173 (15), 159 (60), 57 (47).

*3.2.3.22. tert-Butyl benzyloxy[2-(1,1′-biphenyl-4-yl)prop-2-enyl]carbamate (**34**).* Prepared by procedure C from 4-bromobiphenyl (238 mg, 1.02 mmol), *N*-Boc-*O*-benzylhydroxylamine (240 mg, 1.07 mmol), allene gas (1 atm), potassium carbonate (315 mg, 2.28 mol), tris-(dibenzylideneacetone)dipalladium (27 mg, 2.9 mol %) and tris-(2-furyl)phosphine (26 mg, 11 mol %). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (399 mg, 94%); ^{1}H NMR δ: 1.49 (s, 9H, 3×CH$_3$), 4.53 (s, 2H, NCH$_2$), 4.70 (s, 2H, OCH$_2$), 5.34 and 5.60 (s, 2×1H, =CH$_2$), 7.31–7.37 (m, 8H, ArH), 7.41–7.50 (m, 2H, ArH), 7.58–7.62 (m, 4H, ArH). Found: C, 77.90; H, 7.15; N, 3.15. C$_{27}$H$_{29}$NO$_3$ requires: C, 78.04; H, 7.03; N, 3.37%. *m*/*z* (%): 415 (M$^+$, <1), 282 (45), 269 (7), 206 (74), 178 (83), 152 (48), 105 (17) and 57 (100).

*3.2.3.23. tert-Butyl benzyloxy(2-cyclohex-1-en-1-ylprop-2-enyl)carbamate (**35**).* Prepared from cyclohex-1-enyl triflate (79 mg, 0.34 mmol), *N*-Boc-*O*-benzylhydroxylamine (81 mg, 0.36 mmol), allene gas (1 atm), caesium carbonate (225 mg, 0.69 mmol), tris-(dibenzylideneacetone) dipalladium (8 mg, 2.5 mol %) and tris-(2-furyl)phosphine (8 mg, 10 mol %). in DMF (5 mL) at 105 °C for 96 h. Purification by flash column chromatography eluting with 15:1 v/v petroleum ether/ether afforded the product as a colourless oil (103 mg, 87%); ^{1}H NMR δ: 1.47 (s, 9H, 3×CH$_3$), 1.58–1.69 (m, 4H, cyclohexene 2×CH$_2$), 2.10–2.29 (m, 4H, cyclohexene 2×CH$_2$), 4.28 (s, 2H, NCH$_2$), 4.77 (s, 2H, OCH$_2$), 5.04 and 5.16 (2×s, 2×1H, C=CH$_2$), 5.98 (m, 1H, cyclohexene =CH), 7.32–7.40 (m, 5H, ArH); ^{13}C NMR δ: 22.5, 23.2, 26.2, 26.4, 28.7, 53.0, 77.5, 81.6, 112.5, 125.9, 128.7, 128.8, 129.8, 129.9, 134.7, 136.0, 143.2, 156.7. Found: C, 73.40; H, 8.25; N, 3.80. C$_{21}$H$_{29}$NO$_3$ requires: C, 73.44; H, 8.51; N, 4.08%. *m*/*z* (%): 361 (M+18, 13), 344 (30, M+1), 305 (100), 288 (62), 244 (43), 136 (68) and 91 (48).

*3.2.3.24. tert-Butyl (tert-butoxycarbonyl)oxy(2-phenylprop-2-enyl)carbamate (**36a**).* Prepared by procedure C from iodobenzene (302 mg, 1.48 mmol), *N*-Boc-*O*-Boc-hydroxylamine (364 mg, 1.56 mmol), allene gas (1 atm), potassium carbonate (247 mg, 1.79 mol), tris-(dibenzylideneacetone) dipalladium (35 mg, 2.5 mol %) and tris-(2-furyl)phosphine (36 mg, 10 mol %). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (412 mg, 80%); ^{1}H NMR δ: 1.46 and 1.47 (s, 18H, 6×CH$_3$), 4.64 (s, 2H, OCH$_2$), 5.31 and 5.49 (2×s, 2×1H, =CH$_2$), 7.29–7.46 (m, 5H, ArH); ^{13}C NMR δ: 27.9, 28.4, 28.7, 54.2, 82.8, 115.7, 126.5, 126.6, 126.8, 128.2, 128.7, 139.1, 142.5, 152.5 155.0. Found: C, 65.60; H, 7.90; N, 3.90. C$_{19}$H$_{27}$NO$_5$ requires: C, 65.31; H, 7.79; N, 4.01%. *m*/*z* (%): 349 (M$^+$, <1), 193 (5), 177 (18), 159 (32), 130 (94), 103 (100), 91 (27), 77 (56) and 57 (93).

*3.2.3.25. tert-Butyl (tert-butoxycarbonyl)oxy[2-(3-nitrophenyl)prop-2-enyl]carbamate (**36b**).* Prepared by procedure C from 3-iodonitrobenzene (287 mg, 1.15 mmol), *N*-Boc-*O*-Boc-hydroxylamine (287 mg, 1.23 mmol), allene gas (1 atm), tris-(dibenzylideneacetone)dipalladium (26 mg, 2.5 mol %) and tris-(2-furyl) phosphine (27 mg, 10 mol %) in DMF (10 mL). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (307 mg, 67%); ^{1}H NMR δ: 1.47 (s, 18H, 6×CH$_3$), 4.66 (s, 2H, NCH$_2$), 5.48 and 5.63 (2×s, 2×1H, =CH$_2$), 7.48–7.53 (m, 1H, ArH), 7.77–7.78 (m, 1H, ArH), 8.12–8.16 (m, 1H, ArH), 8.31–8.33 (m, 1H, ArH). Found: C, 57.55; H, 6.80; N, 7.15. C$_{19}$H$_{26}$N$_2$O$_7$ requires: C, 57.86; H, 6.64; N, 7.10%. *m*/*z* (%): 412 (M+18, 100), 312 (27) and 256 (53).

*3.2.3.26. Methyl 3-[1-({(tert-butoxycarbonyl)[(tert-butoxycarbonyl)oxy]amino}methyl)vinyl]benzoate (**36c**).* Prepared by procedure C from methyl 3-iodobenzoate (275 mg, 1.05 mmol), *N*-Boc-*O*-Boc-hydroxylamine (260 mg, 1.11 mmol), allene gas (1 atm), potassium carbonate (205 mg, 1.48 mol), tris-(dibenzylideneacetone)dipalladium (24 mg, 2.5 mol %) and tris-(2-furyl)phosphine (29 mg, 12 mol %). Purification by flash column chromatography eluting with 9:1 v/v petroleum ether/ether afforded the product as a colourless oil (264 mg, 62%); ^{1}H NMR δ: 1.47 (s, 18H, 6×CH$_3$), 3.91 (s, 3H, OCH$_3$),

4.64 (s, 2H, NCH_2), 5.39 and 5.55 (2××s, 2×1H, $=CH_2$), 7.40 (m, 1H, ArH), 7.65 (m, 1H, ArH), 7.96 (m, 1H, ArH), 8.11 (m, 1H, ArH); ^{13}C NMR δ: 27.9, 28.4, 52.5, 54.1, 78.6, 83.0, 85.2 116.9, 127.8, 128.8, 129.3, 130.7, 131.1, 139.4, 141.8, 152.4, 154.9, 167.3. Found: C, 61.85; H, 7.25; N, 3.35. $C_{21}H_{29}NO_7$ requires: C, 61.90; H, 7.17; N, 3.44%. *m*/*z* (%): 408 (M+1).

*3.2.3.27. N-[2-(4-Acetyl-phenyl)-allyl]-N-benzyloxyformamide (**37**).* Prepared by procedure C from 4-iodo-phenyl-ethanone (244 mg, 1.00 mmol), *N*-benzyloxyformamide (156 mg, 1.03 mmol), allene gas (1 atm), tris-(dibenzylideneacetone)dipalladium (23 mg, 2.5 mol %) and tris-(2-furyl)phosphine (23 mg, 10 mol %) in DMF (10 mL). Purification by flash column chromatography eluting with 2:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow oil (287 mg, 93%); ^1H NMR δ: 2.60 (s, 3H, CH_3), 4.30 and 4.67 (2×br s, 2×1H, NCH_2), 4.73 and 4.93 (2×br s, 2×1H, OCH_2), 5.47 and 5.72 (2×s, 2×1H, $=CH_2$), 7.13–7.30 (m, 5H, ArH), 7.56 (br s, 2H, ArH), 7.95 (d, 2H, *J* 8.5 Hz, ArH), 8.13 (br s, 1H, CHO); ^{13}C NMR δ: 27.1, 49.1, 77.6, 78.7, 119.3, 126.8, 129.1, 129.6, 129.8, 137.0, 141.8, 142.7, 163.8, 198.0. Found: C, 73.50; H, 6.20; N, 4.40. $C_{19}H_{19}NO_3$ requires: C, 73.77; H, 6.19; N, 4.53%. *m*/*z* (%): 327 (M+18, 85), 310 (13, M+1), 221 (100), 178 (72) and 161 (30).

*3.2.3.28. N-Benzyloxy-N-(2-thiophen-2-yl-allyl)-formamide (**38**).* Prepared by procedure C from 2-iodothiophene (218 mg, 1.03 mmol), *N*-benzyloxyformamide (158 mg, 1.04 mmol), allene gas (1 atm), tris-(dibenzylideneacetone)dipalladium (24 mg, 2.5 mol %) and tris-(2-furyl)phosphine (24 mg, 10 mol %) in DMF (10 mL). Purification by flash column chromatography eluting with 2:1 v/v petroleum ether/ether afforded the product as a colourless oil (260 mg, 92%); ^1H NMR δ: 4.20 and 4.57 (2×br s, 2×1H, NCH_2), 4.76 and 4.92 (2×br s, 2×1H, OCH_2), 5.24 and 5.63 (2×s, 2×1H, $=CH_2$), 6.99 (dd, 1H, *J* 5.0 and 3.5 Hz, thiophene H), 7.15–7.32 (m, 7H, ArH), 8.14 (br s, 1H, CHO); ^{13}C NMR δ: 49.5, 79.2, 115.9, 124.6, 125.5, 125.6, 128.3, 129.1, 129.5, 130.0, 134.8, 136.3, 142.0, 163.9. Found: C, 65.65; H, 5.40; N, 4.90, S, 11.60. $C_{15}H_{15}NO_2S$ requires: C, 65.91; H, 5.53; N, 5.12, S, 11.73%.

3.2.4. General procedure for reactions using 1,1-dimethylallene (procedure D). Nucleophile (1–3 mol equiv), 1,1-dimethylallene (5 mol equiv), tris-(dibenzylideneacetone)dipalladium (2.5 mol %), tris-(2-furyl)phosphine (10 mol %) and potassium carbonate (2 mol equiv) were added to a solution of the aryl halide (1 mmol) in dry dimethylformamide (10 mL) in a Schlenk tube. The reaction mixture was then stirred and heated at 80 °C for 16 h. After cooling and venting, DCM (20 mL) was added and the mixture filtered to remove inorganic salts. The filtrate was concentrated in vacuo and the residue was purified by column chromatography.

*3.2.4.1. O-Benzyl-N-(1,1-dimethyl-2-phenyl-allyl)-hydroxylamine (**40**).* Prepared by procedure D from iodobenzene (99 mg, 0.48 mmol), *O*-benzylhydroxylamine (196 mg, 1.59 mmol), 1,1-dimethylallene (0.24 mL, 5 mol equiv), tris-(dibenzylideneacetone) dipalladium (11 mg, 2.5 mol %) and tris-(2-furyl)phosphine (11 mg, 10 mol %) in DMF (5 mL). Purification by flash column chromatography eluting with 19:1 v/v petroleum ether/ether afforded the product as a colourless oil (108 mg, 83%); ^1H NMR δ: 1.26 (s, 6H, 2×CH_3), 4.75 (s, 2H, OCH_2), 5.02 and 5.34 (2×s, 2×1H, $=CH_2$), 5.45 (br s, 1H, NH), 7.27–7.35 (m, 10H, ArH). Found: C, 80.55; H, 8.00; N, 5.20. $C_{18}H_{21}NO$ requires: C, 80.86; H, 7.92; N, 5.24%. *m*/*z* (%): 268 (M+1).

*3.2.4.2. O-Benzyl-N-(1,1-dimethyl-2-thiophen-2-yl-allyl)-hydroxylamine (**41**).* Prepared by procedure D from 2-iodothiophene (137 mg, 0.65 mmol), *O*-benzylhydroxylamine (235 mg, 1.92 mmol), 1,1-dimethylallene (0.32 mL, 5 mol equiv), potassium carbonate (131 mg, 0.95 mol), tris-(dibenzylideneacetone)dipalladium (14 mg, 2.5 mol %) and tris-(2-furyl)phosphine (15 mg, 10 mol %) in DMF (5 mL). Purification by flash column chromatography eluting with 30:1 v/v petroleum ether/ether afforded the product as a colourless oil (161 mg, 90%); ^1H NMR δ: 1.33 (s, 6H, 2×CH_3), 4.75 (s, 2H, OCH_2), 5.34 and 5.39 (2×s, 2×1H, $=CH_2$), 5.43 (br s, 1H, NH), 6.97 (dd, 1H, *J* 5.0 and 3.5 Hz, thiophene H), 7.14 (dd, 1H, *J* 3.5 and 1.0 Hz, thiophene H), 7.21 (dd, 1H, *J* 5.0 and 1.0 Hz, thiophene H), 7.28–7.35 (m, 5H, ArH); ^{13}C NMR δ: 25.41, 61.1, 77.1, 116.8, 125.3, 126.6, 126.8, 128.0, 128.6, 128.7, 138.7, 142.7, 147.8. Found: C, 70.35; H, 6.95; N, 5.20; S, 11.80. $C_{16}H_{19}NOS$ requires: C, 70.29; H, 7.00; N, 5.12; S, 11.73%. *m*/*z* (%) 273 (M^+, 1), 258 (10), 242 (32), 164 (72), 151 (34), 97 (42) and 91 (100).

*3.2.4.3. 5-(2-Benzyloxyamino-2-methyl-1-methylene-propyl)-1,3-dimethyl-1H-pyrimidine-2,4-dione (**42**).* Prepared by procedure D from 5-iodo-1,3-dimethyluracil (142 mg, 0.53 mmol), *O*-benzylhydroxylamine (186 mg, 1.51 mmol), 1,1-dimethylallene (0.25 mL, 5 mol equiv), potassium carbonate (152 mg, 1.10 mol), tris-(dibenzylideneacetone)dipalladium (15 mg, 3 mol %) and tris-(2-furyl) phosphine (17 mg, 13 mol %) in DMF (5 mL). Purification by flash column chromatography eluting with 2:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow oil (133 mg, 76%); ^1H NMR δ: 1.28 (s, 6H, 2×CH_3), 3.30 and 3.34 (s, 6H, 2×NCH_3), 4.71 (s, 2H, OCH_2), 5.14 and 5.48 (2×s, 2×1H, $=CH_2$), 5.86 (br s, 1H, NH), 7.15 (s, 1H, =CHN), 7.27–7.37 (m, 5H, ArH). Found: C, 65.40; H, 7.15; N, 12.55. $C_{18}H_{23}N_3O_3$ requires: C, 65.63; H, 7.04; N, 12.76%. *m*/*z* (%) 330 (M+1, <1), 315 (<1), 239(<1), 209 (100), 193 (36), 164 (19), 122 (16), 91 (93).

*3.2.4.4. 1-tert-Butyl 2′-methyl 5-(1-{1-[(benzyloxy)amino]-1-methylethyl}vinyl)-2-oxo-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indole-3,3′-pyrrolizine]-1,2′(2H)-dicarboxylate (**43**).* Prepared by procedure D from **12** (349 mg, 0.68 mmol), *O*-benzylhydroxylamine (240 mg, 1.95 mmol), 1,1-dimethylallene (0.35 mL, 5 mol equiv), potassium carbonate (172 mg, 1.24 mmol), tris-(dibenzylideneacetone)dipalladium (19 mg, 3 mol %) and tris-(2-furyl)phosphine (22 mg, 14 mol %) in DMF (5 mL). Purification by flash column chromatography eluting with 6:1 v/v petroleum ether/ethyl acetate afforded the product as a pale yellow glass (269 mg, 47%); ^1H NMR δ: 1.09 and 1.36 (s, 6H, 2×CH_3), 1.61 (m, 1H, 7′-H_A), 1.64 (s, 9H, 3×CH_3), 1.78 (m, 2H, 2×6′-H), 1.90 (m, 1H, 7′-H_B), 2.08 (m, 1H, 1′-H_A), 2.27 (m, 1H, 5′-H_A), 2.41 (m, 1H, 1′-H_B), 2.55 (m, 1H, 5′-H_B), 3.15 (s, 3H, CH_3O), 3.84 (dd, 1H, *J* 13.0 and 6.0 Hz, 2′-H), 3.97 (m, 1H, 7a′-H), 4.80 (s, 2H, OCH_2), 5.04 and 5.35 (2×s, 2×1H, $=CH_2$), 5.58 (br s, 1H, NH), 7.21–7.41 (m, 7H, ArH), 7.86 (d, 1H, *J* 8.5 Hz, ArH). Found: C, 68.65; H, 7.40; N, 7.40. $C_{33}H_{41}N_3O_6$ requires: C, 68.85; H, 7.18; N, 7.30%. *m*/*z* (%) 575 (M^+, 7), 489 (12), 460(9), 426 (13), 389 (21), 352 (26), 293 (33), 251 (17), 164 (19), 91 (100), 57 (36).

*3.2.4.5. 1-tert-Butyl 2′-methyl 5-(1-{1-[(benzyloxy)amino]-1-methylethyl}vinyl)-2-oxo-1′,5′,6′,7′,8′,8a′-hexahydro-2′H-spiro[indole-3,3′-indolizine]-1,2′(2H)-dicarboxylate (**44**).* Prepared by procedure D from **13** (288 mg, 0.55 mmol), *O*-benzylhydroxylamine (220 mg, 1.79 mmol), 1,1-dimethylallene (0.25 mL, 5 mol equiv), potassium carbonate (118 mg mg, 0.85 mmol), tris-(dibenzylideneacetone) dipalladium (13 mg, 2.5 mol %) and tris-(2-furyl)phosphine (13 mg, 10 mol %) in DMF (5 mL). Purification by flash column chromatography eluting with 3:1 v/v petroleum ether/diethyl ether afforded the product as a colourless glass (207 mg, 64%); ^1H NMR δ: 1.16 and 1.31 (s, 6H, 2×CH_3), 1.20–1.27 (m, 3H, 2×8′-H and 6′-H_A), 1.55 (m, 1H, 6′-H_B), 1.66 (s, 9H, 3×CH_3), 1.70 (m, 1H, 7′-H_A), 1.89 (m, 1H, 7′-H_B), 2.11–2.17 (m, 2H, 2×1′-H), 2.28–2.36 (m, 2H, 2×5′-H), 3.13 (s, 3H OCH_3), 3.18 (m, 1H, 8a′-H), 3.41 (dd, 1H, *J* 10.5 and 8.0 Hz, 2′-H), 4.79 (s, 2H, OCH_2), 5.00 and 5.32 (2×s, 2×1H, $=CH_2$), 5.50 (br s, 1H, NH), 7.22–7.42 (m, 7H, ArH), 7.71 (d, 1H, *J* 8.5 Hz, ArH); ^{13}C NMR δ: 24.1, 24.9, 25.1, 26.1, 28.5, 32.2, 34.3, 45.7, 51.7, 52.8, 59.9, 60.9, 72.7, 77.6, 84.7, 113.9, 115.9, 126.0, 127.7, 127.9, 128.6, 128.7,

130.5, 138.6, 139.5, 149.6, 154.3, 172.1, 177.6. Found: C, 68.95; H, 7.40; N, 7.25. $C_{34}H_{43}N_3O_6$ requires: C, 69.25; H, 7.35; N, 7.13%. *m*/*z* (%) 575 (M^+, 6), 489 (12), 475 (9), 389 (17), 352 (22), 326 (12), 293 (29), 251 (17), 164 (19), 91 (100).

*3.2.4.6. O-Benzyl-N-(1,1-dimethyl-2-pyrimidin-5-yl-allyl)-hydroxylamine (**45**).* Prepared by procedure D from 5-bromopyrimidine (84 mg, 0.53 mmol), *O*-benzylhydroxylamine (183 mg, 1.49 mmol), 1,1-dimethylallene (0.25 mL, 5 mol equiv), potassium carbonate (129 mg, 0.93 mol), tris-(dibenzylideneacetone)dipalladium (19 mg, 3.9 mol %) and tris-(2-furyl)phosphine (22 mg, 18 mol %) in DMF (5 mL). Purification by flash column chromatography eluting with 5:1 v/v petroleum ether/diethyl ether afforded the product as a colourless oil (131 mg, 81%); ^{1}H NMR δ: 1.29 (s, 6H, 2×CH_3), 4.67 (s, 2H, OCH_2), 5.16 and 5.52 (2×s, 2×1H, =CH_2), 5.18 (br s, 1H, NH), 7.29–7.37 (m, 5H, ArH), 8.77 (s, 2H, ArH), 9.14 (s, 1H, ArH). Found: C, 71.05; H, 7.20; N, 15.60. $C_{16}H_{19}N_3O$ requires: C, 71.35; H, 7.11; N, 15.60%. *m*/*z* (%) 270 (M+1, 12), 239(73), 91 (100), 51 (15).

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