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Ring-closing metathesis: development of a cyclisation–cleavage strategy for the solid-phase synthesis of cyclic sulfonamides

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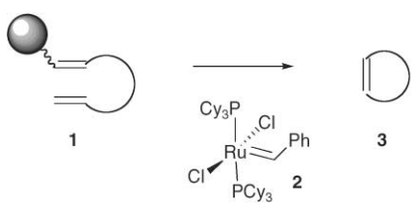
A series of novel 7-membered cyclic sulfonamides have been synthesised using a solid-phase cyclisation–cleavage RCM strategy. Model solution studies indicated the sulfonamides were suitable substrates for RCM using the Grubbs' catalyst **2**. Starting from either 2-carboxyethyl polystyrene (**21**) or Merrifield resin, various seven-membered sulfonamides were prepared in good to excellent yields at low catalyst loadings (2.5–5 mol%) using a flexible spacer between the polymer and the substrate. In addition, a novel double-armed linker was shown to allow efficient RCM cleavage of sulfonamides with as little as 1 mol% of the ruthenium alkylidene complex **2**.

Introduction

In recent years the widespread use of solid-phase techniques within academic research groups and the pharmaceutical industry has provided impetus for the development of methods for the solid-phase synthesis of small organic molecules.[1] Efficient solid-phase synthesis relies heavily on the choice of linker, and many novel linkers and cleavage strategies have been reported.[2] One attractive strategy is cyclisation–cleavage, where the necessary cleavage step has the added benefit of introducing a key structural feature into the target molecule.[3]

Cyclisation–cleavage methods have enjoyed widespread use in solid-phase synthesis, although the majority of applications to date have involved carbon–heteroatom bond formation rather than C–C bond formation (Scheme 1). Ring closing metathesis (RCM) provides an attractive method to achieve cyclisation–cleavage *via* C–C bond formation, and has been used to release cyclic olefins of various ring sizes from the solid-phase.[3–7] Van Maarseveen and co-workers first reported that if an appropriate diene substrate were to be attached to the polymer core through one of its double bonds, RCM would simultaneously form the ring (7-membered lactams) and effect the cleavage from the resin in one step.[5a] However, their early studies suffered from the limitation that large amounts of ruthenium alkylidene complex were required to effect cleavage in satisfactory yields.



Scheme 1 RCM cyclisation–cleavage approach to cyclo-olefins.

Inspection of the RCM reaction pathway on the solid-phase implies that the release of a cyclised product would lead to an intermediate resin-bound ruthenium alkylidene species **5**, which might be inefficient as a propagating species due to site isolation effects within the resin (Scheme 2, pathway A). To solve this problem, Van Maarseveen *et al.* suggested the use of an olefin co-factor to regenerate an active ruthenium species in solution, providing an alternative catalytic pathway.[5a] However, the use of any unwanted additive is undesirable in solid-phase cleavage reactions, and in the case of metathesis reactions, might lead to a variety of cross-metathesis products. In a separate study, Blechert and co-workers reported the cyclisation–cleavage of a cyclic tetrapeptide from Wang resin in only 30% yield.[5b] However, when an 8-carbon spacer was employed between the polymer and the first double bond, the yield increased significantly to 70% without the need for an olefin co-factor. Blechert's results suggested that the use of a flexible spacer may be sufficient to allow efficient catalytic cyclisation–cleavage by RCM.

Isosteric replacement and conformational restriction are commonly employed strategies in drug discovery.[8] Given the prevalence of amides in biologically active molecules, isosteric replacement by sulfonamides and subsequent cyclisation to cyclic sulfonamides should provide interesting novel scaffolds for combinatorial chemistry.[9–11] Our interest in cyclisation–cleavage strategies in general, and more specifically in developing efficient RCM-based approaches, led us to examine the solid-phase synthesis of seven-membered cyclic sulfonamides.[5h,11] As part of our investigation, we chose to evaluate a strategy employing a novel double-armed linker, the idea being that a domino-sequence of RCM reactions would regenerate a catalytically active alkylidene carbene complex in solution (Scheme 2, pathway B). In order to determine whether any benefit was realised from the use of a double-armed linker, the corresponding single-armed analogue would also be prepared for comparison. Here we provide a full account of these studies, part of which was communicated previously.[5h]

Results and discussion

Our synthetic approach began with the assembly of the single- and double-armed substrates **19** and **20** in solution prior to attachment to the solid-phase, to ensure that the key RCM reaction was viable (Scheme 3). The final approach would require the substrate to be directly assembled on the solid-phase, attached through a robust linkage that would be stable to a broad range of conditions. However, the development of the solid-phase chemistry was simplified by initially employing an ester linkage that would allow facile cleavage of intermediates from the resin in order to monitor the success of the individual solid-phase steps. As a solid support for the preliminary studies, we chose to make use of a 2-carboxyethyl polystyrene (**21**) which is readily prepared from Merrifield resin.[12]

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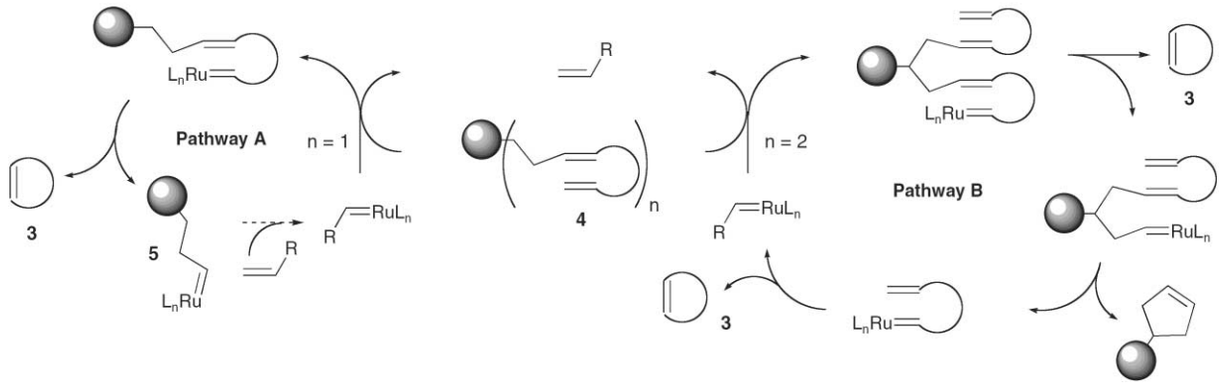
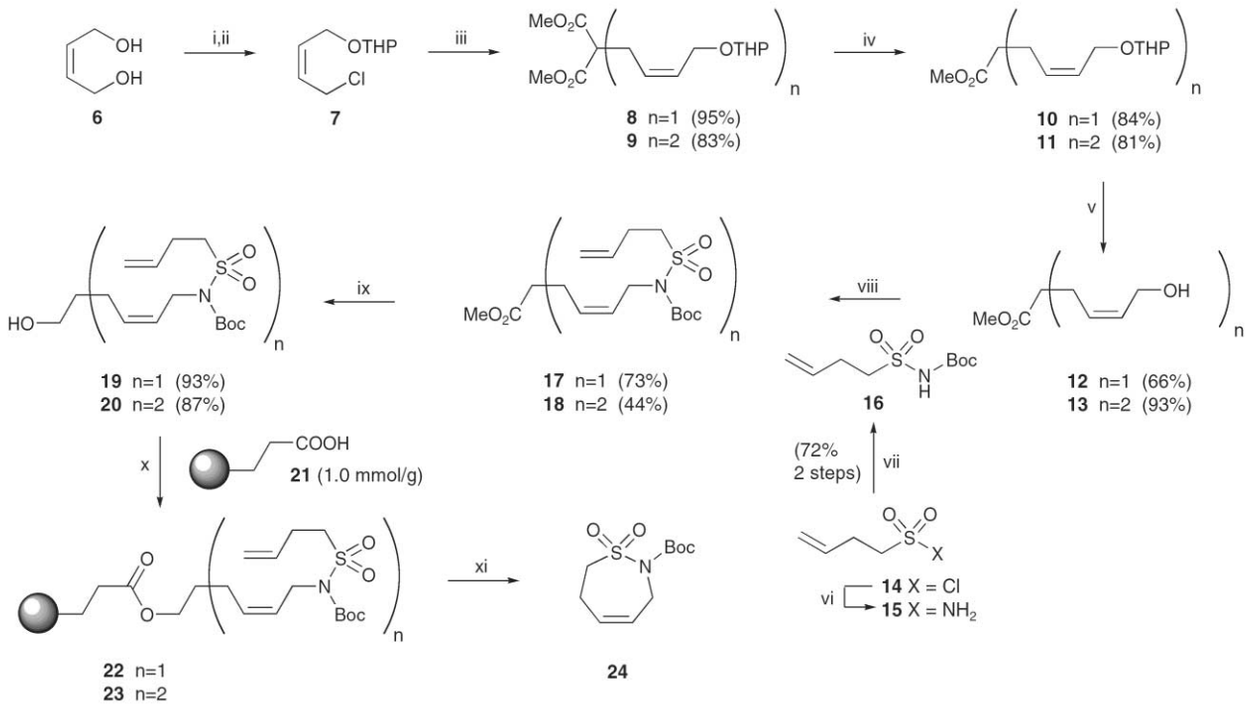


Scheme 2 Possible pathways for cyclisation–cleavage reactions on single- and double-armed substrates.



Scheme 3 *Reagents*: i, DHP, *p*-TSA, THF, CH_2Cl_2; ii, MsCl, *i*-Pr_2NEt, CH_2Cl_2; iii, dimethyl malonate, NaH, DMF; iv, KOAc, DMSO, heat; v, *p*-TSA, MeOH; vi, NH_4OH (aq.); vii, $(Boc)_2O$, *i*-Pr_2NEt, DMAP, CH_2Cl_2; viii, DEAD, PPh_3, THF; ix, $LiAlH_4$, Et_2O; x, **21**, DIC, DMAP, CH_2Cl_2; xi, **2** (50 mol%), CH_2Cl_2.

The synthesis began by monoalkylation and dialkylation of dimethyl malonate with the known allylic chloride **7**, which provided malonates **8** and **9**.[13] Krapcho dealkoxycarbonylation of **8** and **9** afforded the monoesters **10** and **11** in 84% and 81% yield respectively.[14] Removal of the protecting groups provided the alcohols **12** and **13**, which underwent Mitsunobu coupling with sulfonamide **16** prepared from 3-butene-1-sulfonyl chloride.[15–17] Reduction of the ester groups present in **17** and **18** proceeded smoothly, allowing multigram quantities of alcohols **19** and **20** to be prepared for solid-phase coupling. The resin-bound RCM precursors **22** and **23** were obtained in the first instance by coupling alcohols **19** and **20** to the 2-carboxyethyl polystyrene (**21**) using a mixture of DIC and excess DMAP. IR spectroscopy and $LiBH_4$ reductive cleavage of the alcohols **19** and **20** from the resin confirmed success of these coupling reactions.

At this point we wanted to verify that metathesis reaction of the linker-diene adduct **17** would give the desired cyclic sulfonamide **24** in solution, and to determine the influence of concentration on the cyclisation. Treatment of the substrate **17** with 1 mol% of the Grubbs' catalyst **2** at concentrations of 0.1, 0.5 and 1.0 mM with respect to the substrate in CH_2Cl_2 all proceeded to give **24** in excellent yield (>90%). For the preliminary solid-phase RCM cyclisation–cleavage studies, resins **22** and **23** were refluxed in CH_2Cl_2 with 50 mol% Grubbs' catalyst **2** and we were pleased to observe formation of the desired 7-membered sulfonamide **24**.

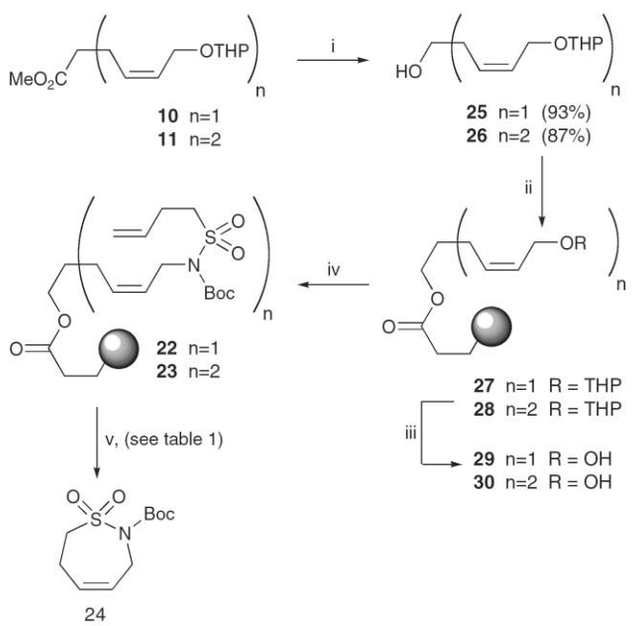
Having confirmed the viability of the cyclisation–cleavage reaction, attention turned to the synthesis of the linker and substrates directly on the solid-phase (Scheme 4). The esters **10** and **11** were reduced to the alcohols **25** and **26** in good yields using $LiAlH_4$ and subsequently coupled to 2-carboxyethyl polystyrene (**21**) under standard conditions. Consecutive THP deprotection and Mitsunobu reaction with sulfonamide **16** afforded the resin-bound RCM precursors **22** and **23**. IR spectroscopy or $LiBH_4$ reduction confirmed the success of the different reactions throughout the sequence and provided estimated loadings for **22** and **23**.[18]

The resins **22** and **23** were submitted to different amounts of Grubbs catalyst **2** (2.5–50 mol%) in refluxing CH_2Cl_2 (see Table 1). In addition, a co-factor, 1-octene,[5a] was also added to the reactions containing the single-armed resin **22** to determine whether this additive had any beneficial effect. The yields were generally satisfactory; however, little difference was observed between the single- and double-armed linker. No real benefit was obtained in the cleavage reactions of the single-armed linker substrate **22** containing the olefin co-factor and the purity of the crude sulfonamide **24** was reduced, probably

Table 1 Ring-closing metathesis cyclisation–cleavage reactions of resins **22** and **23**

Entry	Substrate	Co-factor[a]	Catalyst (mol%)[b]	Yield (%)[c]
1	**22**	No	2.5	66
2	**22**	No	5.0	61
3	**22**	No	10.0	62
4	**22**	No	50.0	41
5	**22**	Yes	2.5	53
6	**22**	Yes	5.0	38
7	**22**	Yes	10.0	56
8	**23**	No	2.5	61
9	**23**	No	5.0	43
10	**23**	No	10.0	52
11	**23**	No	50.0	55

[a] One equivalent of 1-octene was used as the olefin co-factor were indicated. [b] Quantities are calculated on the basis of the theoretical loadings of resins **22** and **23** (0.76 and 1.24 mmol S g^{-1}) calculated from 2-carboxyethylpolystyrene (1.0 mmol CO_2H g^{-1}). [c] Yields refer to purified material.



Scheme 4 *Reagents*: i, $LiAlH_4$, THF; ii, **21**, DIC, DMAP, CH_2Cl_2; iii, *p*-TSA, MeOH; iv, **16**, DEAD, PPh_3, THF; v, **2** (2.5–50 mol%), CH_2Cl_2.

due to the presence of cross metathesis by-products. In fact, when the metathesis product **24** was resubmitted to the Grubbs' catalyst **2** in the presence of 1-octene, slow degradation was observed.

The use of 2-carboxyethyl polystyrene (**21**) had proved successful in our initial RCM studies by allowing us to monitor individual solid-phase reaction steps as well as permitting direct attachment of an RCM precursor to the solid-phase. However, the ester linkage does not display sufficient stability under basic and nucleophilic conditions to be broadly applicable in solid-phase synthesis. To provide a more robust attachment to the resin, alcohols **25** and **26** were coupled directly to Merrifield resin **31** by reaction of the corresponding sodium alkoxides in DMF at 60 °C (Scheme 5). The resin-bound alcohol **34** and diol **35** were obtained by deprotection of the THP ethers **32** and **33** respectively,[19] and Mitsunobu coupling with sulfonamide **16** afforded the RCM precursors **36** and **37**.[20]

Resins **36** and **37** were then submitted to varying quantities of Grubbs' catalyst **2** in refluxing CH_2Cl_2 (see Table 2). An olefin co-factor was not used, since it had not proved advantageous with the 2-carboxyethyl polystyrene-supported substrates. The RCM cyclisation–cleavage from ether-linked resins **36** and **37** proceeded in better yields than those seen

Table 2 Ring-closing metathesis cyclisation–cleavage reactions of resins **36** and **37**

Entry	Substrate	Catalyst (mol%)[a]	Yield (%)[b]
1	**36**	1.0	31
2	**36**	2.5	45
3	**36**	5.0	100 (100)[c]
4	**36**	50.0	53 (60)[c]
5	**37**	1.0	91
6	**37**	2.5	100
7	**37**	5.0	100 (100)[c]
8	**37**	50.0	78 (84)[c]

[a] Quantities are calculated on the basis of the estimated loadings of resins **36** and **37**.[20] [b] Yields estimated by GC analysis of the crude reaction mixture. [c] Isolated yields.[20]

for 2-carboxyethyl resins **22** and **23**, and we were delighted to obtain quantitative cleavage of the product **24** in some instances.[21] The most striking observation was that when less than 5.0 mol% of catalyst **2** was used, higher yields were obtained for the double-armed linker in comparison to the single-armed analogue. Hence the double-armed linker appeared to be more efficient than the single-armed linker when a low amount of the ruthenium complex **2** is used.

In order to extend the methodology to provide a small collection of cyclic sulfonamides we examined the synthesis of a series of *N*-alkylated analogues starting from resins **36** and **37**. Removal of the Boc group was achieved under standard conditions to afford immobilised sulfonamides **38** and **39** (Scheme 5). Subsequent *N*-alkylation with a range of alkyl halides was initially performed using DBU as the base,[22] however subsequent RCM cleavage reactions showed the alkylation step to be incomplete (about 50% alkylated product obtained after a double alkylation). Replacing DBU with *t*-BuOK and performing double couplings proved much more effective, providing a series of *N*-alkylated RCM precursors **40**–**47**.[23] To demonstrate that several steps could be carried out on our resin-bound sulfonamides, sulfonamide **38** was subjected to *N*-alkylation with *t*-butyl bromoacetate followed by removal of the *t*-butyl ester and subsequent amide bond formation with benzylamine to give the diene **56** (Scheme 6). A variety of resins bearing single and double-armed linkers **38**–**47**, **53** and **56** were then submitted to the cyclisation–cleavage conditions, and the corresponding sulfonamides obtained in good to excellent yields (Schemes 5 and 6, Table 3). Again, it appeared that at lower catalyst loading the double-armed linker outperformed the single-armed linker (see entries 4 and 5, Table 3).

To gain some insight into the rate of cyclisation–cleavage, the release of the cyclic sulfonamide **24** was monitored over time by removal of aliquots and GC analysis using phenanthrene as an internal standard. Although the RCM cyclisation–cleavage reactions were typically left for 15 h, it was shown that the release of **24** from resins **36** and **37** was 70–80% complete after 1 h using 5 mol% of the Grubbs' catalyst **2** and 90% complete after 3 hours.

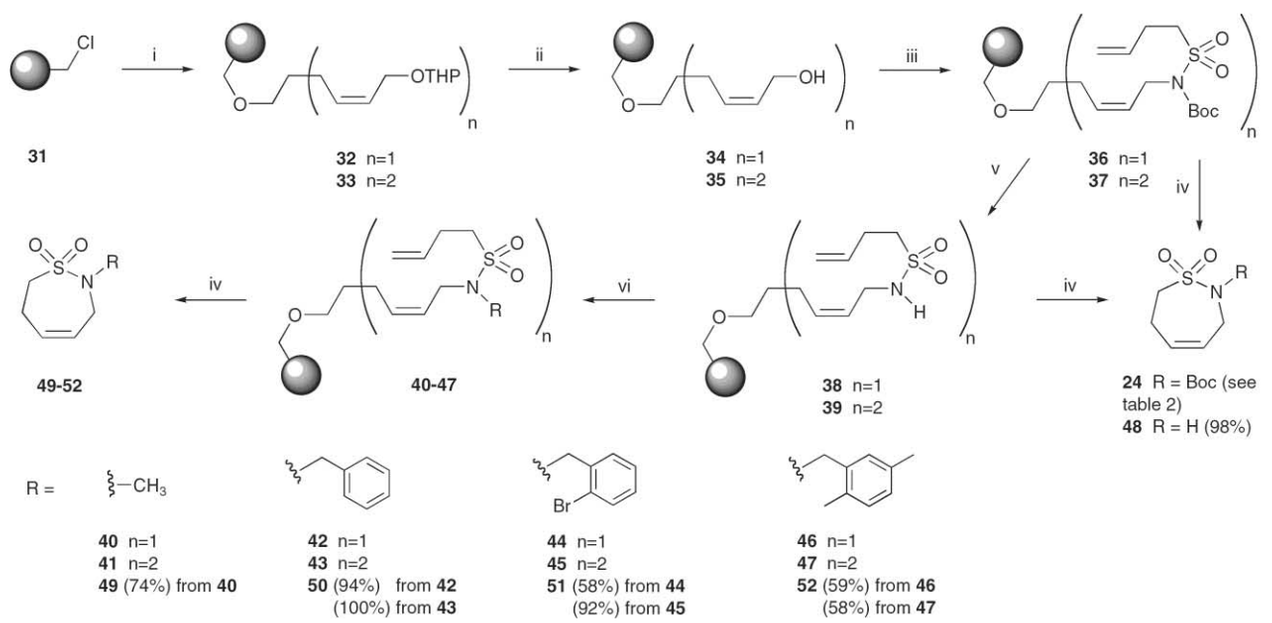
An important issue with any cleavage protocol is the presence of impurities derived from the reagents or catalyst in the final product. In the present case, all crude products (and the recovered resin) obviously contained ruthenium-derived impurities,[24] which were removed by column chromatography. However, removal of these coloured impurities was less straightforward when higher catalyst loadings were employed, underscoring the importance of developing conditions that allow efficient catalytic cyclisation–cleavage. Future studies relating to the RCM cyclisation–cleavage approach should address the issue of catalyst removal, particularly if high-throughput approaches are to be applied.[24]

It was mentioned above that the resins recovered after RCM cleavage were typically coloured brown, suggesting that some

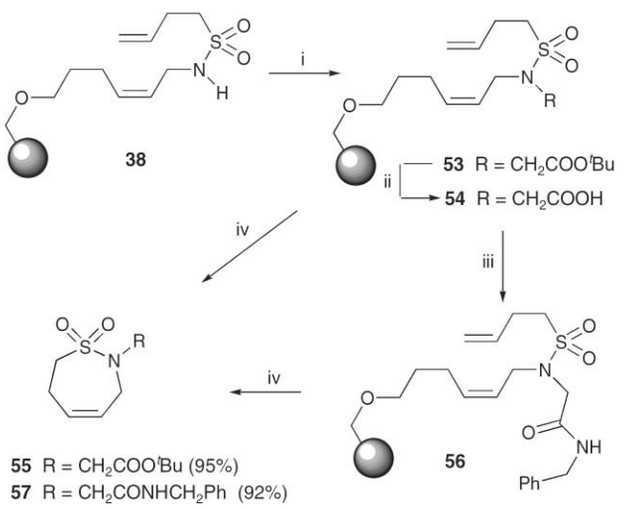
Table 3 Ring-closing metathesis cyclisation–cleavage reactions to form *N*-substituted sulfonamides **48**–**52**, **55** and **57**

Entry	Substrate	Product	R	Catalyst (mol%)[a]	Yield (%)[b]
1	**38**	**48**	H	5.0	98
2	**39**	**48**	H	5.0	97
3	**40**	**49**	CH_3	5.0	[74][c]
4	**42**	**50**	CH_2Ph	1.0	[45][c]
5	**43**	**50**	CH_2Ph	1.0	[100][c]
6	**42**	**50**	CH_2Ph	2.5	[94][c]
7	**43**	**50**	CH_2Ph	2.5	[100][c]
8	**42**	**50**	CH_2Ph	5.0	[100][c]
9	**43**	**50**	CH_2Ph	5.0	[100][c]
10	**44**	**51**	$CH_2(o\text{-Br})C_6H_4$	5.0	58
11	**45**	**51**	$CH_2(o\text{-Br})C_6H_4$	5.0	92
12	**46**	**52**	$CH_2(2,5\text{-}(CH_3)_2)C_6H_3$	5.0	59
13	**47**	**52**	$CH_2(2,5\text{-}(CH_3)_2)C_6H_3$	5.0	58
14	**53**	**55**	$CH_2CO_2{}^tBu$	2.5	95
15	**56**	**57**	$CH_2CONHCH_2Ph$	5.0	92

[a] Quantities are calculated on the basis of the calculated loadings of resins **38**–**47**, **53** and **56**. [b] Isolated yields. [c] GC yields.



Scheme 5 *Reagents*: i, **25** or **26**, NaH, DMF, 60 °C; ii, *p*-TSA, MeOH; iii, **16**, DEAD, PPh_3, THF; iv, **2** (1.0–50 mol%), CH_2Cl_2; v, TFA, CH_2Cl_2; vi, *t*-BuOK, MeI or BnBr or 2-bromobenzyl bromide or 2,5-dimethylbenzyl chloride, THF.



Scheme 6 *Reagents*: i, *t*-BuOK, *t*-butyl bromoacetate, THF; ii, TFA, CH_2Cl_2; iii, $BnNH_2$, DIC, DMAP, THF; iv, **2** (2.5–5 mol%), CH_2Cl_2.

ruthenium species had been trapped/attached within the resin.[25] To determine whether the recovered resins could be used as metathesis catalysts themselves, the coloured resins were added to a solution of 1-octene in refluxing CH_2Cl_2 and in all the experiments the dimerisation product (*E*)-7-tetradecene was observed. It may also be of interest to note that the coloured resins were stored open to the air for several months prior to these cross metathesis experiments.

Conclusions

A series of novel 7-membered cyclic sulfonamides have been prepared by a solid-phase approach in good to excellent yields using an RCM cyclisation–cleavage reaction as the key step. Initial model studies in solution indicated the sulfonamide-linker adducts were suitable substrates for RCM. Transferring the model to the solid-phase, firstly using an ester linkage and then an ether linkage, we were pleased to observe that the yields for the cyclisation–cleavage were good to excellent without the use of an olefin co-factor. Two flexible linkers have been studied and both produced good yields of sulfonamides using 5.0 mol% of catalyst **2**. The introduction of the double-armed linker was justified by the realisation of efficient RCM cleavage using very low amounts of catalyst (1–2.5 mol%). Although we can not confirm that the hypothetical RCM pathway B (Scheme 2) is operating, the present study does show that efficient cyclisation–cleavage of sulfonamides can be achieved using the double-armed linker at low catalyst loadings.

Experimental

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate accessory or a Nicolet Impact 400 instrument using a Thunderdome accessory. UV studies were carried out on a Perkin-Elmer Lambda 2 UV/VIS spectrometer or a Hewlett-Packard 8452A diode array spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL GX270, Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers. Low resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. Melting points were measured on a Gallenkamp electrothermal melting point apparatus. GC analyses were carried out on a Varian 3800 fitted with a 30 m x 0.25 mm DB120 fused silica column. All loadings of resins, amounts of reagents and yields in solid-phase reactions are calculated from the measured loadings of intermediate resins **21**, **34**, and **35**, assuming quantitative conversion for subsequent solid-phase reactions.

Dimethyl 2,2-di[(*Z*)-4-tetrahydro-2*H*-2-pyranyloxy)-2-butenyl] propanedioate (9)

To a solution of dimethyl malonate (1.1 mL, 10.0 mmol) in DMF (100 mL) was added a 60% dispersion of NaH in mineral oil (1 g, 25.0 mmol). When the gas evolution had ceased, chloride **7** (5.75 g, 30.0 mmol) was added and the reaction mixture was stirred at rt for 15 h. The reaction was quenched with water (50 mL) and the product was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel flash chromatography (5 × 5 cm; hexane : Et_2O 1 : 0 to 1 : 1) afforded a colourless oil (3.65 g, 8.3 mmol, 83%). ν_{max} (film) 2944, 1734 (s, CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.71–5.63 (m, 2H, C*H*=CH), 5.43–5.34 (m, 2H, CH=C*H*), 4.58 (t, 2H, *J* = 3.3 Hz, OCH), 4.21 (dd, 2H, *J* = 12.5, 5.9 Hz, C*H*HO), 4.01 (dd, 2H, *J* = 12.5, 7.3 Hz, CH*H*O), 3.87–3.79 (m, 2H, C*H*HO), 3.68 (s, 6H, OCH_3), 3.48–3.43 (m, 2H, CH*H*O), 2.66 (d, 4H, *J* = 8.1 Hz, $(CH_2)_2C(CO_2Me)_2$), 1.83–1.46 (m, 12H, $CH_2CH_2CH_2$); ^{13}C NMR (75MHz, $CDCl_3$) 171.3 (CO), 130.4 (*C*H=CH), 125.9 (CH=*C*H), 98.2 (OCHO), 62.8 (CH_2O), 62.3 (CH_2O), 57.4 ($C(CO_2Me)_2$), 52.7 (OCH_3), 30.9 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 19.6 (CH_2); *m*/*z* (ES$^+$) (rel. intensity) 463.4 ([M + Na]$^+$, 100); HRMS *m*/*z* (ES$^+$) 463.2303; $C_{23}H_{36}O_8Na$ requires 463.2302; $C_{23}H_{36}O_8$ requires C: 62.71; H: 8.24; found C: 62.36; H: 8.53%.

Methyl (*Z*)-6-(tetrahydro-2*H*-2-pyranyloxy)-2-[(*Z*)-4-(tetrahydro-2*H*-2-pyranyloxy)-2-butenyl]-4-hexenoate (11)

To a solution of malonate **9** (4.79 g, 10.8 mmol) and water (400 µL) in DMSO (30 mL) was added KOAc (2.15 g, 22 mmol). The mixture was stirred at 140 °C for 5 h. The solution was allowed to cool to rt and poured into water (250 mL). The product was extracted with a 1 : 1 (v/v) mixture of Et_2O and hexane (3 × 100 mL). The combined organic layers were washed with water (75 mL), sat. aq. $NaHCO_3$ (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel flash chromatography (4 × 5 cm; hexane : Et_2O 1 : 0 to 1 : 1) afforded a colourless oil (3.35 g, 8.7 mmol, 81%). ν_{max} (film)/cm^{-1} 2942, 1735 (s, CO); ^{1}H NMR (300 MHz, $CDCl_3$) 5.67–5.56 (m, 2H, C*H*=CH), 5.55–5.45 (m, 2H, CH=C*H*), 4.60 (br s, 2H, OCH), 4.22 (dt, 2H, *J* = 12.4, 6.4 Hz, C*H*HO), 4.13–3.99 (m, 2H, CH*H*O), 3.88–3.81 (m, 2H, C*H*HO), 3.68 (s, 3H, OCH_3), 3.51–3.47 (m, 2H, CH*H*O), 2.49–2.23 (m, 5H, CH_2CHCO_2Me), 1.85–1.50 (m, 12H, $CH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 175.2 (CO), 129.4 (*C*H=CH), 128.6 (CH=*C*H), 98.0 (OCHO), 62.7 (CH_2O), 62.2 (CH_2O), 51.7 (OCH_3), 45.5 (*C*HCO$_2$Me), 30.7 (CH_2), 29.7 (CH_2), 25.6 (CH_2), 19.6 (CH_2); *m*/*z* (ES$^+$) (rel. intensity) 400.4 ([M + NH_4]$^+$, 65), 405.4 ([M + Na]$^+$, 100); HRMS *m*/*z* (ES$^+$) 405.2253; $C_{21}H_{34}O_6Na$ requires 405.2247.

Methyl (*Z*)-6-hydroxy-4-hexenoate (12)

To an ice-cooled solution of ester **10** (200 mg, 0.88 mmol) in CH_3OH (10 mL) was added 4-toluenesulfonic acid (36 mg, 0.18 mmol). The ice bath was removed and the solution was stirred for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and the product extracted twice with Et_2O (25 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel flash chromatography (1.5 × 3 cm; hexane : Et_2O 1 : 1) afforded a colourless oil (84 mg, 0.58 mmol, 66%). ν_{max} (film)/cm^{-1} 3411 (br, OH), 2953, 1736 (s, CO), 1438 (m), 1365, 1166 (m), 1094, 1025 (m), 984, 850; ^{1}H NMR (300 MHz, $CDCl_3$) 5.71–5.62 (m, 1H, C*H*=CH), 5.50–5.41 (m, 1H, CH=C*H*), 4.17 (d, 2H, *J* = 6.6 Hz, CH_2OH), 3.44 (s, 3H, OCH_3), 2.92 (br s, 1H, OH), 2.40–2.38 (m, 4H, $CH_2CH_2CO_2Me$); ^{13}C NMR (75 MHz, $CDCl_3$) 173.9 (CO), 130.6 (CH), 130.2 (CH), 58.2 (CH_2OH), 51.8 (OCH_3), 33.7 (CH_2), 22.7 (CH_2); *m*/*z* (EI) (rel. intensity) 84 ([(M − CO_2Me) + H]$^+$, 100); HRMS *m*/*z* (ES$^+$) 167.0678; $C_7H_{12}O_3Na$ requires 167.0678.

Methyl (*Z*)-6-hydroxy-2-[(*Z*)-4-hydroxy-2-butenyl]-hexanoate (13)

To an ice-cooled solution of ester **11** (3.44 g, 9 mmol) in MeOH (70 mL) was added PTSA (340 mg, 1.8 mmol). The ice bath was removed and the solution stirred for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The product was extracted with Et_2O (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel flash chromatography (3 × 5 cm; hexane–Et_2O) afforded a colourless oil (1.79 g, 8.4 mmol, 93%). ν_{max} (film)/cm^{-1} 3348 (br, OH), 2953, 1725 (s, CO); ^{1}H NMR (300 MHz, $CDCl_3$) 5.65 (dt, 2H, *J* = 11.0, 7.0 Hz, C*H*=CH), 5.37 (dt, 2H, *J* = 11.0, 7.0 Hz, CH=C*H*), 4.12 (dd, 2H, *J* = 13.0, 7.0 Hz, CH_aH_bOH), 4.05 (dd, 2H, *J* = 13.0, 7.0 Hz, CH_aH_bOH), 3.60 (s, 3H, OCH_3), 2.50 (q(5), 1H, *J* = 7.0 Hz, COC*H*), 2.39 (dt, 2H, *J* = 14.0, 7.5 Hz, $CHCH_aH_b$), 2.23 (dt, 2H, *J* = 14.0, 7.5 Hz, $CHCH_aH_b$), 2.20 (br, 2H, CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$) 175.8 (CO), 131.3 (*C*H=CH), 128.5 (CH=*C*H), 58.2 (CH_2OH), 51.9 (OCH_3), 45.0 (*C*HCO), 29.1 (*C*H_2CH); *m*/*z* (EI) (rel. intensity) 237.1 ([M + Na]$^+$, 100); HRMS *m*/*z* (ES$^+$) 237.1102; $C_{11}H_{18}O_4Na$ requires 237.1097.

3-Butene-1-sulfonamide (15)

Sulfonyl chloride **14**[15] (4.0 g, 26.0 mmol) was added to an ice cooled 30% solution of ammonia in water (40 mL). The reaction mixture was stirred for 10 minutes. The product was extracted with CH_2Cl_2 (20 mL), Et_2O (20 mL) and EtOAc (20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid (2.53 g, 19 mmol, 72%). mp 41–42 °C; ν_{max} (film)/cm^{-1} 3346 (m), 3255 (m), 3070, 2986, 1640, 1301 (s, SO_2), 1133 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 5.84 (ddt, 1H, *J* = 16.9, 10.4, 6.5 Hz, C*H*=CH_2), 5.20–5.11 (m, 2H, CH=C*H*$_2$), 4.93 (br s, 2H, NH_2), 3.25–3.19 (m, 2H, CH_2SO_2), 2.65–2.58 (m, 2H, $CH_2CH_2SO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 134.1 (*C*H=CH_2), 117.4 (CH=*C*H_2), 54.4 (CH_2SO_2), 28.2 (*C*$H_2CH_2SO_2$); $C_4H_9NO_2S$ requires C: 35.54; H: 6.71; N: 10.36; found C: 35.70; H: 6.77; N: 10.40%.

N-(3-Butene-1-sulfonyl) *tert*-butylcarbamate (16)

To an ice cooled solution of sulfonamide **15** (1.35 g, 10 mmol), DMAP (12 mg, 0.1 mmol) and diisopropylethylamine (1.73 mL, 12 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (2.5 g, 11 mmol) in CH_2Cl_2 (10 mL). The ice bath was removed. The reaction

mixture was stirred for 2.5 h and was then concentrated *in vacuo*. The residue was partitioned between EtOAc (60 mL) and a 1 M aqueous solution of HCl (40 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica gel flash chromatography (3 × 5 cm, hexane : Et_2O 1 : 0 to 1 : 1) afforded a colourless oil (2.35 g, 10 mmol, 100%). ν_{max} (film)/cm^{-1} 3236 (br, NH), 2982, 1740 (s, CO), 1643, 1346 (s, SO_2), 1135 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (br s, 1H, NH), 5.79 (ddt, 1H, J = 16.9, 9.9, 6.6 Hz, C*H*=CH_2), 5.18–5.08 (m, 2H, CH=C*H*$_2$), 3.49–3.43 (m, 2H, CH_2SO_2), 2.61–2.53 (m, 2H, C*H*$_2$$CH_2SO_2$), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 150.1 (CO), 133.7 (*C*H=CH_2), 117.7 (CH=*C*H$_2$), 84.4 (O*C*$(CH_3)_3$), 52.2 (CH_2SO_2), 28.1 ($C(CH_3)_3$), 27.6 (*C*H$_2$$CH_2SO_2$); *m*/*z* ($ES^+$) 493 ($[2M + Na]^+$); HRMS *m*/*z* ($ES^+$) 258.0772; $C_9H_{17}NO_4SNa$ requires 258.0770; $C_9H_{17}NO_4S$ requires C: 45.94; H: 7.28; N: 5.95; found C: 45.51; H: 7.41; N: 5.81%.

Methyl (*Z*)-6-[*N*-(3-butene-1-sulfonyl)-*N*-(*tert*-butoxycarbonyl)-amino]-4-hexenoate (17)

To a solution of alcohol **12** (91 mg, 0.63 mmol), PPh_3 (165 mg, 0.63 mmol) and Boc-sulfonamide **16** (148 mg, 0.63 mmol) in THF (6 mL) was added dropwise a solution of DEAD (250 µL, 0.63 mmol) in THF (2 mL) at rt. The solvent was removed *in vacuo*, triphenylphosphine oxide was precipitated by addition of Et_2O and collected by filtration.. The filtrate was concentrated *in vacuo* to give a yellow oil. Purification by silica gel flash chromatography (2 × 4 cm; hexane : Et_2O 1 : 0 to 1 : 1) afforded a colourless oil (166 mg, 0.46 mmol, 73%). ν_{max} (film)/cm^{-1} 1727 (s, CO), 1357 (s, SO_2), 1147 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 5.76 (ddt, 1H, J = 16.9, 10.3, 6.6 Hz, C*H*=CH_2), 5.52 (dt, 1H, J = 10.3, 5.9 Hz, C*H*=CH), 5.49 (dt, 1H, J = 10.3, 5.9 Hz, CH=C*H*), 5.19–5.08 (m, 2H, CH=C*H*$_2$), 4.31 (d, 2H, J = 5.9 Hz, CH_2N), 3.67 (s, 3H, OCH_3), 3.53–3.45 (m, 2H, CH_2SO_2), 2.60–2.36 (m, 6H, C*H*$_2$$CH_2SO_2$ & C*H*$_2$C*H*$_2$$CO_2$Me), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 173.5 (COO), 151.5 (NCO), 133.8 (*C*H=CH_2), 131.5 (*C*H=CH), 126.2 (CH=*C*H), 117.6 (CH=*C*H$_2$), 84.7 (O*C*$(CH_3)_3$), 53.5 (CH_2SO_2), 51.7 (OCH_3), 43.3 (CH_2N), 33.7 (CH_2), 28.1 ($C(CH_3)_3$), 27.7 (*C*H$_2$$CH_2SO_2$), 22.9 ($CH_2$); *m*/*z* (ES) (rel. intensity) 384 ($[M + Na]^+$, 28), 379 ($[M + NH_4]^+$, 100); HRMS *m*/*z* (CI) 362.16303 $C_{16}H_{28}NO_6S$ requires 362.16373.

Methyl 2,2-di-{(*Z*)-4-[*N*-(3-butene-1-sulfonyl)-*N*-(*tert*-butoxycarbonyl)-amino]-but-2-en-1-yl} ethanoate (18)

The procedure described above for the preparation of sulfonamide **17** was followed using diol **13** (1.7 g, 8 mmol) and Boc-sulfonamide **16** (3.76 g, 16 mmol). Purification by silica gel flash chromatography (4 × 8 cm; hexane : Et_2O 1 : 0 to 1 : 1) afforded a colourless oil (2.28 g, 3.5 mmol, 44%). ν_{max} (film)/cm^{-1} 2978, 1724 (s, CO), 1643, 1354 (s, SO_2), 1144 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (ddt, 2H, J = 16.9, 10.3, 6.6 Hz, C*H*=CH_2), 5.54–5.51 (m, 4H, CH=CH), 5.17–5.09 (m, 4H, CH=C*H*$_2$), 4.37–4.20 (m, 4H, CH_2N), 3.66 (s, 3H, OCH_3), 3.53–3.48 (m, 4H, CH_2SO_2), 2.56–2.34 (m, 9H, C*H*$_2$C*H*CO_2Me & C*H*$_2$$CH_2SO_2$), 1.53 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 175.3 (COO), 151.5 (NCO), 133.8 (*C*H=CH_2), 129.9 (*C*H=CH), 127.2 (CH=*C*H), 117.6 (CH=*C*H$_2$), 84.8 (O*C*$(CH_3)_3$), 53.6 (CH_2SO_2), 51.8 (OCH_3), 45.3 (*C*HCO_2Me), 43.3 (CH_2N), 29.7 (*C*H$_2$CHCO_2Me), 28.2 ($C(CH_3)_3$), 27.7 (*C*H$_2$$CH_2SO_2$); *m*/*z* (ES) (rel. intensity) 671 ($[M + Na]^+$, 100), 666 ($[M + NH_4]^+$, 83); HRMS *m*/*z* (CI) 671.26376 $C_{29}H_{48}N_2O_{10}S_2Na$ requires 671.26426.

(*Z*)-6-[(*N*-(3-Butene-1-sulfonyl)-*N*-(*tert*-butoxycarbonyl)-amino]-4-hexen-1-ol (19)

To an ice-cooled solution of $LiAlH_4$ (25 mg, 0.66 mmol) in Et_2O (2 mL) was added dropwise a solution of ester **17** (200 mg, 0.55 mmol) in Et_2O (1 mL). The ice bath was removed and the solution was stirred at rt for 6 h. Excess $LiAlH_4$ was carefully destroyed at 0 °C with vigorous stirring by dropwise addition of water (0.5 mL), a 15% aqueous solution of NaOH (0.5 mL) and after 5 min water (1.5 mL). The product was then extracted twice with Et_2O and CH_2Cl_2 (5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. After column chromatography **19** was obtained as a colourless oil (170 mg, 0.51 mmol, 93%). ν_{max} (film)/cm^{-1} 3424 (br, OH), 2935, 1725 (s, CO), 1642, 1357 (s, SO_2), 1147 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (ddt, 1H, J = 16.9, 10.3, 6.6 Hz, C*H*=CH_2), 5.58–5.48 (m, 2H, CH=CH), 5.18–5.09 (m, 2H, CH=C*H*$_2$), 4.31 (d, 2H, J = 5.9 Hz, CH_2N), 3.63 (t, 2H, J = 6.2 Hz, C*H*$_2$OH), 3.54–3.48 (m, 2H, CH_2SO_2), 2.57–2.50 (m, 2H, C*H*$_2$$CH_2SO_2$), 2.26 (q, 2H, J = 6.6 Hz, C*H*$_2$$CH_2CH_2OH$), 2.05 (br s, 1H, OH), 1.66 (quintet, 2H, J = 6.6 Hz, C*H*$_2$$CH_2OH$), 1.53 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 151.6 (CO), 133.8 (CH), 133.3 (CH), 125.4 (CH), 117.6 (CH=C*H*$_2$), 85.0 (O*C*$(CH_3)_3$), 61.6 (CH_2OH), 53.6 (CH_2SO_2), 43.5 (CH_2N), 32.1 (*C*H$_2$$CH_2OH$), 28.1 ($C(CH_3)_3$), 27.7 (*C*H$_2$$CH_2SO_2$), 23.4 (*C*H$_2$$CH_2CH_2OH$); *m*/*z* (ES) (rel. intensity) 351 ($[M + NH_4]^+$, 100); $C_{15}H_{27}NO_5S$ requires C: 54.03; H: 8.16; N: 4.20; found C: 53.59; H: 8.19; N: 4.14%.

2,2-Di-{(*Z*)-4-[*N*-(3-butene-1-sulfonyl)-*N*-(*tert*-butoxycarbonyl)-amino]-but-2-en-1-yl} ethanol (20)

The procedure described above for the reduction of **17** to **19** was followed, using ester **18** (620 mg, 0.95 mmol). Purification by silica gel flash chromatography (2 × 4 cm; hexane–Et_2O) afforded **20** as a colourless oil (513 mg, 0.83 mmol, 87%). ν_{max} (film)/ 3538 (br, OH), 2979, 1722 (s, CO), 1642, 1353 (s, SO_2) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (ddt, 2H, J = 16.9, 10.3, 6.6 Hz, C*H*=CH_2), 5.61–5.47 (m, 4H, CH=CH), 5.18–5.10 (m, 4H, CH=C*H*$_2$), 4.40–4.25 (m, 4H, CH_2N), 3.54–3.48 (m, 6H, CH_2SO_2 & C*H*$_2$OH), 2.57–2.50 (m, 4H, C*H*$_2$$CH_2SO_2$), 2.36–2.26 (m, 2H, C*H*HCHCH_2OH), 2.18–2.09 (m, 2H, CH*H*CH-CH_2OH), 1.99 (br s, 1H, OH), 1.69–1.59 (m, 1H, C*H*CH_2OH), 1.54 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 151.6 (CO), 133.8 (*C*H=CH_2), 131.8 (*C*H=CH), 126.3 (CH=*C*H), 117.6 (CH=*C*H$_2$), 85.0 (O*C*$(CH_3)_3$), 63.5 (CH_2OH), 53.6 (CH_2SO_2), 43.7 (CH_2N), 41.3 (*C*HCH_2OH), 28.8 (*C*H$_2$CH-CH_2OH), 28.2 ($C(CH_3)_3$), 27.7 (*C*H$_2$$CH_2SO_2$); *m*/*z* (ES) (rel. intensity) 643 ($[M + Na]^+$, 100).

Functionalised carboxyethyl resin 22

From 19. To a suspension of carboxyethyl resin **21** (200 mg, 1.0 mmol OH g^{-1}, 0.2 mmol) in CH_2Cl_2 (4 mL) were added DIC (100 µL, 0.6 mmol), DMAP (74 mg, 0.6 mmol) and alcohol **19** (200 mg, 0.6 mmol). The mixture was stirred for 15 h. The resin was collected by filtration, washed with CH_2Cl_2 (3 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. For on-bead IR data see below.

From 29. To a suspension of resin **29** (200 mg) swollen in THF (3 mL) was added PPh_3 (140 mg, 0.5 mmol) and **16** (166 mg, 0.5 mmol). DEAD (80 µL, 0.5 mmol) was added dropwise and the mixture stirred at rt for 15 h. The resin was collected by filtration, washed with MeOH (2 × 10 mL) and CH_2Cl_2 (2 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2922, 1727 (s), 1602, 1360 (s), 1147 (s); sulfur combustion analysis gave an estimated loading of 0.72 mmol S g^{-1}; reductive cleavage of **19** gave an estimated loading of: 0.73 mmol S g^{-1}. The results were in good agreement with the theoretical loading of the resin **22**, which was calculated to be 0.76 mmol g^{-1} based on the loading of carboxyethyl resin **21**.

Functionalised carboxyethyl resin 23

From 20. To a suspension of carboxyethyl resin **21** (200 mg, 1.0 mmol OH g^{-1}, 0.2 mmol) in CH_2Cl_2 (4 mL) were added DIC

(100 μL, 0.6 mmol), DMAP (74 mg, 0.6 mmol) and alcohol **20** (372 mg, 0.6 mmol). The mixture was stirred for 15 h. The resin was collected by filtration, washed with CH_2Cl_2 (3 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. For on-bead IR data see below.

From 30. To a suspension of resin **30** (200 mg) swollen in THF (3 mL) was added PPh_3 (280 mg, 1 mmol) and **16** (235 mg, 1.0 mmol). DEAD (160 μL, 1.0 mmol) was added dropwise and the mixture stirred at rt for 15 h. The resin was collected by filtration, washed with MeOH (2 × 10 mL) and CH_2Cl_2 (2 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2922, 1730 (s), 1602, 1362 (s), 1147 (s); sulfur combustion analysis gave an estimated loading of 1.13 mmol S g^{-1}; reductive cleavage of **20** gave an estimated loading of: 1.1 mmol S g^{-1}. The theoretical loading of resin **23**, was calculated to be 1.24 mmol S g^{-1}.

tert-Butyl 1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-2-carboxylate (24)

To a suspension of the resin **37** (187 mg, 0.127 mmol theoretical) in CH_2Cl_2 (2 mL) was added ruthenium complex **2** (1.1 mg, 0.0013 mmol) and the suspension was heated at reflux for 15 h. The mixture was then filtered, washing the resin with CH_2Cl_2 (5 × 3 mL). The solvent was then removed from the combined solutions and the resulting brown oil was purified by column chromatography to afford the title compound **24** as a pale oil (28.8 mg, 0.116 mmol, 91%). ν_{max} (neat)/cm^{-1} 2926, 1732 (s, CO), 1362 (s, SO_2), 1140 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 5.93 (dt, 1H, J = 11.5, 5.0 Hz, C*H*=CH), 5.86 (dt, 1H, J = 11.5, 6.2 Hz, CH=C*H*), 4.25 (d, 2H, J = 5.0 Hz, CH_2N), 3.30–3.26 (m, 2H, CH_2SO_2), 2.51–2.46 (m, 2H, $CH_2CH_2SO_2$), 1.50 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 151.6 (CO), 131.7 (CH), 130.4 (CH), 84.5 ($OC(CH_3)_3$), 51.6 (CH_2), 45.0 (CH_2), 28.1 ($C(CH_3)_3$), 22.2 ($CH_2CH_2SO_2$); *m*/*z* (ES) 270 ([M + Na]$^+$); HRMS *m*/*z* (CI) 270.0776 $C_{10}H_{17}NO_4SNa$ requires 270.0770.

(*Z*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-4-hexen-1-ol (25)

The procedure described above for the reduction of **17** to **19** was followed, using ester **10** (2.58 g, 11.3 mmol). Purification by silica gel flash chromatography (5 × 6 cm, hexane : Et_2O 1 : 0 to 1 : 1) afforded a colourless oil (2.10 g, 10.5 mmol, 93%). The spectroscopic data were consistent with that reported in the literature.[26]

(*Z*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-2-[(*Z*)-4-(tetrahydro-2*H*-2-pyranyloxy)-2-butenyl]-4-hexenol (26)

The procedure described above for the reduction of **17** to **19** was followed, using ester **11** (3.24 mg, 8.5 mmol). Purification by silica gel flash chromatography (3.5 × 4 cm; hexane : Et_2O 1 : 0 to 1 : 2) afforded a colourless oil (2.63 g, 7.4 mmol, 87%). ν_{max} (neat)/cm^{-1} 3461 (br, OH), 2939 (m); ^{1}H NMR (400 MHz, ($CDCl_3$) 5.71–5.57 (m, 4H, CH=CH), 4.66–4.62 (m, 2H, OCHO), 4.32–4.19 (m, 2H, C*H*HOTHP), 4.14–4.01 (m, 2H, CH*H*OTHP), 3.90–3.82 (m, 2H, $CH_2CH_2CH_2CHHO$), 3.52–3.49 (m, 4H, $CH_2CH_2CH_2CHHO$ & CH_2OH), 2.96 (br s, 1H, OH), 2.26–2.07 (m, 4H, CH_2CHCH_2OH), 1.85–1.51 (m, 13H, $CH_2CH_2CH_2$ & $CHCH_2OH$); ^{13}C NMR (100 MHz, ($CDCl_3$) 132.7 (*C*H=CH), 127.2 (CH=*C*H), 98.3 (OCHO), 63.4 (CH_2O), 62.6 (CH_2O), 62.3 (CH_2O), 41.1 (*C*HCH$_2$OH), 30.6 (CH_2), 28.9 (CH_2), 25.5 (CH_2), 19.5 (CH_2); $C_{20}H_{34}O_5$ requires C: 67.76; H: 9.67; found C: 67.29; H: 9.77%.

Resin 27. Carboxyethyl resin **21** (750 mg, 1.0 mmol OH g^{-1}, 0.75 mmol) was swollen in CH_2Cl_2 (5 mL). Alcohol **25** (450 mg, 2.25 mmol), DIC (350 μL, 2.25 mmol) and DMAP (280 mg, 2.25 mmol) were added and the reaction stirred at rt for 15 h. The resin was collected by filtration, washed three times with CH_2Cl_2 (10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2920, 1731 (s), 1601.

Resin 28. Procedure as described for the synthesis of resin **27** using resin **21** (750 mg, 1.0 mmol OH g^{-1}, 0.75 mmol) and diol **26** (797 mg, 2.25 mmol). ν_{max} (neat)/cm^{-1} 2926, 1731 (s), 1601.

Alcohol functionalised resin 29. To a suspension of **27** (740 mg) swollen in a 5 : 1 (v/v) mixture of DME and MeOH (6 mL) was added PTSA (250 mg, 1.5 mmol). The mixture was stirred at rt for 15 h. The resin was collected by filtration, washed twice with MeOH and CH_2Cl_2 (10 mL each) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 3335 (br), 2922, 1729 (s), 1602.

Diol functionalised resin 30. The procedure described for the preparation of **29** was followed using resin **28** (740 mg). ν_{max} (neat)/cm^{-1} 3336 (br), 2920, 1730 (s), 1601.

Resin 32. To a solution of alcohol **25** (280 mg, 1.38 mmol) in DMF (10 mL) was added NaH (60 mg, 1.5 mmol). When the gas evolution ceased, the solution was added dropwise to Merrifield resin (200 mg, loading 2.3 mmol Cl g^{-1}, 0.5 mmol) swollen in THF (5 mL). The reaction mixture was stirred at 60 °C for 15 h. Excess NaH was carefully quenched by dropwise addition of water. The resin was collected by filtration and washed with DMF (10 mL), H_2O (10 mL), DMF (10 mL) and CH_2Cl_2 (10 mL). The resin was then dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2921, 1601.

Resin 33. The procedure described for the preparation of **32** was followed using **26** (490 mg, 1.38 mmol). ν_{max} (neat)/cm^{-1} 2921, 1601.

Alcohol functionalised resin 34. To a suspension of the resin **32** (300 mg) in MeOH (5 mL) was added *p*-TSA (180 mg, 0.95 mmol). The mixture was stirred at rt for 15 h. The resin was collected by filtration, washed with CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 3340 (br), 2920, 1601; The loading of the resin was estimated to be 1.02 mmol OH g^{-1}.[19]

Diol functionalised resin 35. Following the procedure described for the preparation of **34** using resin **33** (325 mg), MeOH (10 mL) and *p*-TSA (360 mg, 1.9 mmol). ν_{max} (neat)/cm^{-1} 3334 (br), 2920, 1601; The loading of the resin was estimated as 0.97 mmol OH g^{-1}.[19]

Resin 36. To a suspension of the resin **34** (150 mg, 1.02 mmol OH g^{-1}, 0.15 mmol) swollen in THF (5 mL) was added PPh_3 (165 mg, 0.6 mmol) and **16** (150 mg, 0.6 mmol). DEAD (0.1 mL, 0.6 mmol) was added dropwise. The mixture was stirred at rt for 15 h. The resin was collected by filtration, washed with CH_2Cl_2 (3 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2921, 1723 (s), 1601, 1358 (s), 1148 (s). The resin loading was estimated to be 0.88 mmol S g^{-1} by sulfur combustion analysis.[20]

Resin 37. Procedure as described for **36** using **35** (150 mg, 0.97 mmol OH g^{-1}, 0.14 mmol). ν_{max} (neat)/cm^{-1} 2925, 1724 (s), 1602, 1358 (s), 1145 (s). The resin loading was estimated to be 1.05 mmol S g^{-1} by sulfur combustion analysis.[20]

Resin 38. To a suspension of resin **36** (150 mg) swollen in CH_2Cl_2 (2 mL) was added a 50% solution of TFA in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 30 min. The resin was collected by filtration, washed with H_2O (2 × 5 mL), Et_3N (2 × 5 mL), CH_2Cl_2 (2 × 5 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2915, 1601, 1321 (s), 1143 (s).

Resin 39. Following the procedure described for the preparation of resin **38** using **37** (150 mg). ν_{max} (neat)/cm^{-1} 2914, 1601, 1321 (s), 1141 (s).

Resin 40. Sulfonamide resin **38** (150 mg) was swollen in THF (5 mL) then KO*t*-Bu (167 mg, 1.5 mmol) was added followed by methyl iodide (90 μL, 1.5 mmol). The reaction mixture was stirred at rt for 15 h. The resin was collected by filtration, washed with CH_2Cl_2 (3 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2918, 1601, 1321 (s), 1139 (s).

Resin 41. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **39** (150 mg) and methyl iodide (90 μL, 1.5 mmol) gave resin **41**. ν_{max} (neat)/cm^{-1} 2916, 1601, 1320 (s), 1137 (s).

Resin 42. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **38** (150 mg) and benzyl bromide (180 μL, 1.5 mmol) gave resin **42**. ν_{max} (neat)/cm^{-1} 2918, 1600, 1328 (s), 1141 (s).

Resin 43. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **39** (150 mg) and benzyl bromide (180 μL, 1.5 mmol) gave resin **43**. ν_{max} (neat)/cm^{-1} 2920, 1600, 1492, 1450 (m), 1337 (s), 1141 (s), 742, 697 (s).

Resin 44. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **38** (150 mg) and 2-bromobenzyl bromide (375 mg, 1.5 mmol) gave resin **44**. ν_{max} (neat)/cm^{-1} 2922, 1601, 1321 (s), 1140 (s).

Resin 45. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **39** (150 mg) and 2-bromobenzyl bromide (375mg, 1.5 mmol) gave resin **45**. ν_{max} (neat)/cm^{-1} 2922, 1601, 1492, 1448 (m), 1318 (s), 1140 (s), 1026, 910 (m), 697 (s).

Resin 46. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **38** (150 mg) and 2,5-dimethylbenzyl chloride (220 μL, 1.5 mmol) gave resin **46**. ν_{max} (neat)/cm^{-1} 2915, 1603, 1492, 1449 (m), 1319 (s), 1141 (s), 912 (m), 697 (s).

Resin 47. Following the general procedure for the alkylation of resin **38** to give resin **40**, reaction of sulfonamide resin **39** (150 mg) and 2,5-dimethylbenzyl chloride (220 μL, 1.5 mmol) gave resin **47**. ν_{max} (neat)/cm^{-1} 2908, 1602, 1492, 1450 (m), 1327 (s), 1140 (s), 910 (m), 697 (s).

2,3,6,7-Tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione (48)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **38** and catalyst **2** (5.0 mol%) gave a white solid (98%) or resin **39** and catalyst (5.0 mol%) gave a white solid (97%). Mp 66–67 °C; ν_{max} (neat)/cm^{-1} 3274 (NH), 2930, 1316 (s, SO_2), 1135 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 6.09–5.96 (m, 2H, CH=CH), 4.58 (br, 1H, NH), 3.67 (dd, 2H, J = 6.6, 5.2 Hz, CH_2NH), 3.16–3.12 (m, 2H, CH_2SO_2), 2.58–2.53 (m, 2H, CH_2CH_2SO_2); ^{13}C NMR (75 MHz, $CDCl_3$) 132.6 (*C*H=CH), 132.3 (CH=*C*H), 52.7 (CH_2), 42.0 (CH_2), 22.1 (*C*H_2CH_2SO_2); *m*/*z* (ES$^+$) (rel. intensity) 170 ([M + Na]$^+$, 100); $C_5H_9NO_2S$ requires C: 40.80; H: 6.16; N: 9.51; found C: 40.78; H: 6.34; N: 9.29%.

2-Methyl-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione (49)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **40** and catalyst (5.0 mol%) gave a colourless oil (74%). ν_{max} (neat)/cm^{-1} 2954 (s), 1471 (m), 1346 (s), 1332 (s, SO_2), 1158 (s), 1139 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 6.17–6.08 (m, 1H, C*H*=CH), 5.95 (dt, 1H, J = 11.8, 5.9 Hz, CH=C*H*), 3.80 (d, 2H, J = 5.9 Hz, CH_2NMe), 3.04–2.99 (m, 2H, CH_2SO_2), 2.77 (s, 3H, NCH_3), 2.56–2.50 (m, 2H, CH_2CH_2SO_2); ^{13}C NMR (75 MHz, $CDCl_3$) 133.5 (CH), 130.1 (CH), 47.0 (CH_2), 46.4 (CH_2), 35.1 (NCH_3), 22.2 (*C*H_2CH_2SO_2); *m*/*z* (CI) (rel. intensity) 162 ([M+H]$^+$, 100); HRMS *m*/*z* (EI) 161.0503 $C_6H_{11}NO_2S$ requires 161.0510.

2-Benzyl-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione (50)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **42** and catalyst (2.5 mol%) gave a colourless oil (94%) or resin **43** and catalyst (1.0 mol%) gave a colourless oil (100%). ν_{max} (neat)/cm^{-1} 2926, 1347 (s), 1330 (s, SO_2), 1157 (s), 1140 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.43–7.21 (m, 5H, C_6H_5), 6.16 (dt, 1H, J = 11.0, 6.6 Hz, C*H*=CH), 5.87 (dt, 1H, J = 11.0, 5.9 Hz, CH=C*H*), 4.24 (s, 2H, NCH_2Ph), 3.63 (d, 2H, J = 5.9 Hz, CH_2NBn), 3.14–3.10 (m, 2H, CH_2SO_2), 2.61–2.55 (m, 2H, CH_2CH_2SO_2); ^{13}C NMR (75 MHz, $CDCl_3$) 135.5 (C), 133.7 (CH), 130.4 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 50.5 (CH_2), 49.1 (CH_2), 42.0 (CH_2), 22.3 (*C*H_2-CH_2SO_2); *m*/*z* (CI) (rel. intensity) 238 ([M + H]$^+$, 28), 172 (27), 132 (100); HRMS *m*/*z* (EI) 237.0823 $C_{12}H_{15}NO_2S$ requires 237.0823.

2-(2-Bromobenzyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione (51)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **44** and catalyst (5.0 mol%) gave a white solid (58%) or resin **45** and catalyst (5.0 mol%) gave a white solid (92%). Mp 96–97 °C; ν_{max} (neat)/cm^{-1} 2931, 1350 (s), 1331 (s, SO_2), 1155 (s), 1139 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.60 (d, 1H, J = 8.1 Hz, C_6H_3), 7.56 (d, 1H, J = 8.1 Hz, C_6H_3), 7.36 (br t, 1H, J = 7.4 Hz, C_6H_3), 7.18 (br t, 1H, J = 8.1 Hz, C_6H_3), 6.18 (dt, 1H, J = 11.0, 6.6 Hz, C*H*=CH), 6.00 (dt, 1H, J = 11.0, 5.9 Hz, CH=C*H*), 4.39 (s, 2H, NCH_2Ph), 3.69 (d, 2H, J = 5.9 Hz, CH_2NAr), 3.18–3.14 (m, 2H, CH_2SO_2), 2.64–2.58 (m, 2H, CH_2CH_2SO_2); ^{13}C NMR (75 MHz, $CDCl_3$) 135.3 (C), 133.7 (CH), 133.0 (CH), 130.8 (CH), 130.3 (CH), 129.5 (CH), 128.1 (CH), 123.6 (C), 50.3 (CH_2), 49.8 (CH_2), 42.8 (CH_2), 22.3 (*C*H_2CH_2SO_2); *m*/*z* (CI) (rel. intensity) 318 (50), 316 ([M + H]$^+$, 100); $C_{12}H_{14}BrNO_2S$ requires C: 45.58; H: 4.46; N: 4.43; found C: 45.67; H: 4.39; N: 4.24%.

2-(2,5-Dimethylbenzyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepine-1,1-dione (52)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **46** and catalyst (5.0 mol%) gave a white solid (59%) or resin **47** and catalyst (5.0 mol%) gave a white solid (58%). Mp 118 °C; ν_{max} (neat)/cm^{-1} 2959, 1348 (s), 1329 (s, SO_2), 1158 (s), 1140 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.11–7.04 (m, 3H, C_6H_3), 6.19 (dt, 1H, J = 13.2, 6.6 Hz, C*H*=CH), 5.88 (dt, 1H, J = 11.0, 5.9 Hz, CH=C*H*), 4.22 (s, 2H, NCH_2Ar), 3.58 (d, 2H, J = 6.6 Hz, CH_2NCH_2Ar), 3.15–3.12 (m, 2H, CH_2SO_2), 2.62–2.56 (m, 2H, CH_2CH_2SO_2), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 135.6 (C), 134.7 (C), 133.7 (CH), 132.7 (C), 130.9 (CH), 130.5 (CH), 129.0 (CH), 48.6 (CH_2), 48.5 (CH_2), 41.7 (CH_2), 22.2 (*C*H_2CH_2SO_2), 20.9 (CH_3), 18.7 (CH_3); $C_{14}H_{19}NO_2S$ requires C: 63.37; H: 7.22; N: 5.28; found C: 63.31; H: 7.33; N: 5.21%.

Resin 53. Following the general procedure for the alkylation of resin **38** to give resin **40** (double coupling), sulfonamide resin **38** (150 mg) and *tert*-butyl bromoacetate (220 μL, 1.5 mmol) gave resin **53**. ν_{max} (neat)/cm^{-1} 2915, 1735 (s), 1601, 1338 (s), 1140 (s).

Resin 54. To a suspension of resin **55** (150 mg) swollen in CH_2Cl_2 (2 mL) was added a 50% solution of TFA in CH_2Cl_2

(5mL). The mixture was stirred at rt for 3 h. The resin was collected by filtration, washed with CH_2Cl_2 (2 × 5 mL), Et_3N (2 × 5 mL), CH_2Cl_2 (2 × 5 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2907, 1727 (s), 1600, 1337 (s), 1141 (s).

Resin 56. Benzylamine (186 μL, 1.7 mmol) was added to a suspension of resin **56** (160 mg) in THF (5 mL) in the presence of DMAP (200 mg, 1.7 mmol) and DIC (260 μL, 1.7 mmol). The reaction mixture was left at rt for 15 h. The resin was collected by filtration, washed with CH_2Cl_2 (2 × 10 mL) and dried *in vacuo* at 50 °C for 5 h. ν_{max} (neat)/cm^{-1} 2918, 1673 (s), 1602, 1324 (s), 1141 (s).

tert-Butyl 2-(1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepin-2-yl) acetate (55)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **53** the title compound **55** was obtained as a colourless oil (95%). ν_{max} (neat)/cm^{-1} 2977, 1744 (s, CO), 1348 (s), 1331 (s, SO_2), 1137 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 6.11 (dt, 1H, J = 11.0, 6.6 Hz, C*H*=CH), 5.95 (dt, 1H, J = 11.0, 5.9 Hz, CH=C*H*), 3.92 (d, 2H, J = 5.9 Hz, CH_2NCH_2CO_2^{t}Bu), 3.80 (s, 2H, NCH_2CO_2^{t}Bu), 3.13–3.09 (m, 2H, CH_2SO_2), 2.59–2.53 (m, 2H, CH_2CH_2SO_2), 1.48 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 133.7 (*C*H=CH), 130.1 (CH=*C*H), 82.4 (O*C*(CH_3)$_3$), 50.5 (CH_2), 49.5 (CH_2), 44.4 (CH_2), 28.2 (C(*C*H_3)$_3$), 22.3 (*C*H_2CH_2SO_2); *m*/*z* (ES) 279 ([M + NH_4]$^+$); HRMS *m*/*z* (CI) 284.0930; $C_{11}H_{19}NO_4SNa$ requires 284.0926.

N-Benzyl-2-(1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6,2-thiazepin-2-yl) acetamide (57)

Following the general procedure for RCM cyclisation–cleavage to give **24**, using resin **56** and catalyst **2** (5.0 mol%) gave **57** as a colourless oil (92%). ν_{max} (neat)/cm^{-1} 3251 (br, NH), 2933, 1650 (s, CO), 1325 (s, SO_2), 1158 (s), 1138 (s, SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.34–7.21 (m, 5H, C_6H_5), 6.93 (br, 1H, NH), 6.09 (dt, 1H, J = 11.0, 6.6 Hz, C*H*=CH), 5.94 (dt, 1H, J = 11.0, 5.9 Hz, CH=C*H*), 4.43 (d, 2H, J = 5.9 Hz, NHCH_2Ph), 3.73 (d, 2H, J = 5.9 Hz, CH_2N), 3.68 (s, 2H, NCH_2CONH), 3.03–2.98 (m, 2H, CH_2SO_2), 2.54–2.43 (m, 2H, CH_2CH_2SO_2); ^{13}C NMR (75 MHz, $CDCl_3$) 171.8 (CO), 137.8 (C), 134.4 (CH), 129.8 (CH), 128.5 (CH), 127.8 (CH), 51.0 (CH_2), 49.5 (CH_2), 44.9 (CH_2), 43.6 (CH_2), 22.1 (*C*H_2CH_2SO_2); *m*/*z* (ES) 295 ([M + H]$^+$); $C_{14}H_{18}N_2O_3S$ requires C: 57.12; H: 6.16; N: 9.51; found C: 56.92; H: 6.28; N: 9.19%.

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19 The loadings of resins **34** and **35** were estimated as 1.02 mmol OH g^{-1} and 0.97 mmol OH g^{-1} respectively, by coupling with cinnamoyl chloride followed by cleavage (KOTMS, MeOH, CH_2Cl_2) and GC analysis of the cleaved alcohol.

20 The loadings of resins **36** and **37** were estimated as 0.88 mmol of S g^{-1} and 1.05 mmol of S g^{-1} respectively by combustion analysis. The values obtained were lower than the theoretical loadings of 0.83 mmol S g^{-1} (**36**) and 0.68 mmol S g^{-1} (**37**) based on **34** and **35**.

21 The fact that some yields obtained were so high probably reflects an under estimation of the loading of the hydroxyl resins **34** and **35**, although the RCM reaction must still be efficient process based on the loadings obtained for **36** and **37**.

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