Merging Cross-Metathesis and Radical Cyclization: A Straightforward Access to 4-Substituted Benzosultams

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Abstract: *N*-Alkyl-*N*-allyl-2-bromobenzenesulfonamides were functionalized by selective *E*-cross-metathesis with various alkenes. Subsequent radical cyclization initiated by 2,2′-azobis(isobutyronitrile) and tris(trimethylsilyl)silane gave the corresponding 4-substituted benzosultams directly in moderate-to-good yields.

Key words: metathesis, cyclizations, radical reactions, sulfonamides, heterocycles

Sulfonamides and sultams are important classes of pharmacologically active compounds.[1] For example, sultam **1** (Figure 1) is implicated in the inhibition of calpain I, a calcium-activated cysteine protease involved in the degeneration of neurons.[2] Sultam **2** has been recently reported to be a potential inhibitor of aldolase reductase, and might be useful for treatment of complications arising from diabetes.[3] Sultam **3** exhibits activities against HIV,[4] whereas piroxicam (**4**) is a nonsteroidal antiinflammatory drug.[5] Because of these activities, a wide range of synthetic methods have been devised for the synthesis of sultams and related structures.[6]

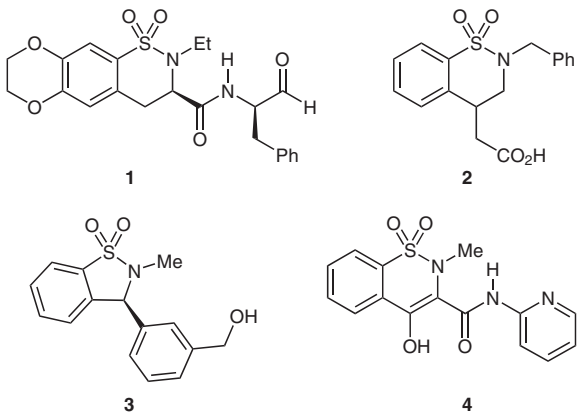
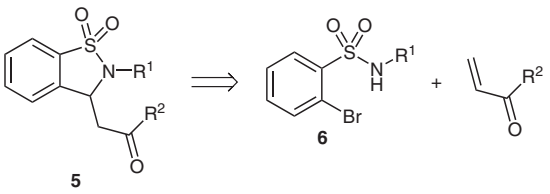


Figure 1 Some representative pharmacologically active sultams

Hanson's group have been very active in this field and they have developed several strategies for preparing libraries of new sultams.[7,8] In particular, they have reported a one-pot procedure that combines a Heck reaction with an aza-Michael cyclization to give benzosultams **5** from the corresponding bromosulfonamide **6** (Scheme 1).[7] Evans's group used a similar Heck cyclization to synthesize the parent structures.[9] More recently, benzosultams have been prepared from less-densely functionalized substrates through processes involving C–H activation,[10,11] mainly promoted by palladium salts,[10] or through intramolecular hydroamination initiated by copper(II), silver(I), or gold(I) catalysts.[12,13] Ring enlargement of saccharin is another suitable route, and this strategy has been used in a synthesis of sultam **2** and its analogues by a relative lengthy route.[3]



Scheme 1 Hanson's approach to benzosultams **5** by sequential Heck reaction and aza-Michael addition

In the last three decades, radical cyclizations have emerged as powerful methods for building heterocyclic structures from unsaturated substrates,[14,15] and these reactions have found a number of direct applications in syntheses of complex natural products. Metathesis is currently the process of choice for the direct functionalization of terminal alkenes or alkynes.[16–18] Therefore, combinations of cross-metathesis and radical cyclization would appear to have potential for developing attractive routes to new heterocyclic structures from readily available compounds in small numbers of steps. To date, however, this combination has been not widely examined.[19,20]

In 2005, we reported a one-pot synthesis of tricyclic fused structures by combining a ring-closing metathesis/isomerization process with a radical cyclization.[21] We have now extended this process by investigating the reactivity of more-flexible structures, such as the *N*-alkyl-*N*-allyl-2-bromobenzenesulfonamides **7**.

Radical cyclizations are governed by Baldwin's rules.[22] We therefore expected that the cyclization mode might be strongly dependent of the substitution of the double bond (Scheme 2). It is important to point out that, even before our first attempts to perform this reaction, the plausibility of the radical process was supported by a result obtained by Ganguly and co-workers,[23] who found that the diallylic

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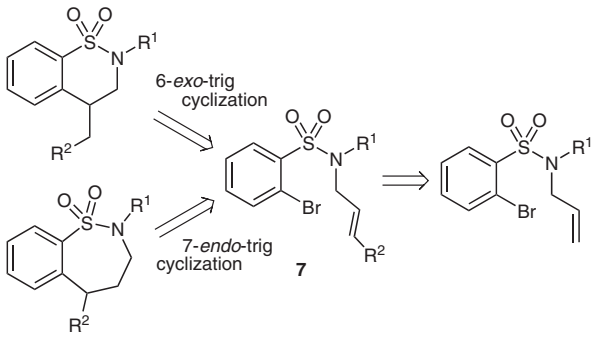
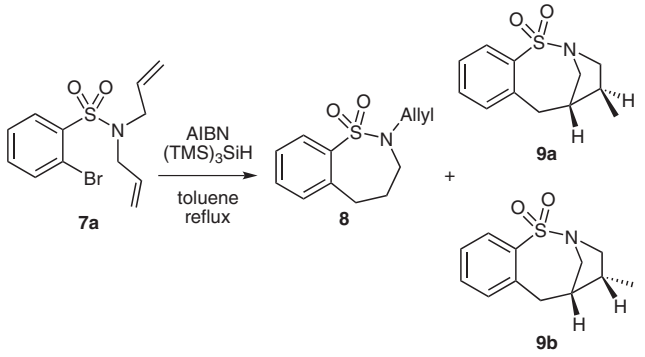


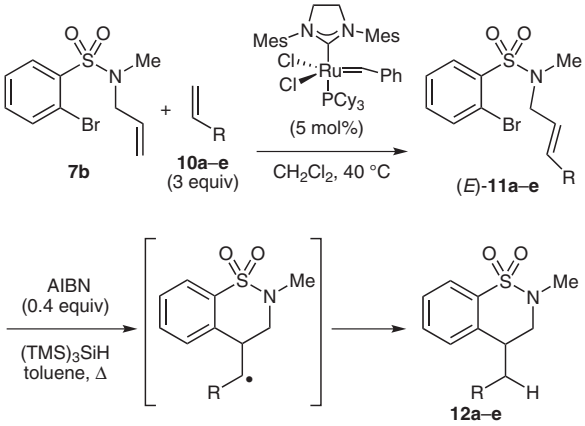
Scheme 2 Cyclization strategy based on a cross-metathesis and a radical cyclization

sulfonamide **7a**[24] underwent an initial 7-*endo*-trig cyclization to give products **8** and **9a**/**9b**. This preliminary study was based on the use of tributylstannane as a radical-chain promoter. However, to facilitate workup of the reaction mixture, we chose to replace tributylstannane with tris(trimethylsilyl)silane, also known also as Chatgilialoglu's reagent.[25] This reagent is easily removed under vacuum during workup, and it eliminates the need to use lipophilic toxic organostannanes derivatives. Interestingly, when we applied our new conditions to substrate **7a**, we obtained compounds **8** and **9a**/**9b** in 50% overall yield, but in a ratio of 15:35, which is significantly different from the value of 56:3 obtained by Ganguly et al. This preliminary result established the feasibility of our intended process (Scheme 3).



Scheme 3 Radical cyclization of substrate **7a**

As pointed out above, substitution of the alkene moiety should have a marked effect on the regioselectivity of the cyclization reaction. Because cross-metathesis usually requires an excess of the alkene partner, it is not possible to perform the cross-metathesis and the radical cyclization as a one-pot process, as this would result in the production of side products from polycondensation reactions. We therefore performed an initial cross-metathesis between sulfonamide **7b** and but-3-en-2-one (**10a**) in the presence of the Grubbs II catalyst (GBII; Scheme 4). The reaction proceeded smoothly and gave the *N*-alkenyl sulfonamide **11a** as a single *E*-isomer. The *E*-configuration of the newly created double bond was assigned from the coupling constant in the ^{1}H NMR spectrum (typical J value = 15.0 Hz). We also tested microwave activation,[26] and the reaction occurred faster but without a significant increase in the chemical yield. With microwave activation, the Hoveyda–Grubbs reagent efficiently catalyzed the reaction to give sulfonamide **11a** in 57% yield and 85% selectivity. We then subjected the functionalized 2-bromosulfonamide **11a** to radical cyclization in toluene, and we obtained sultam **12a** in a reasonable yield.



Scheme 4 Cross-metathesis between **7b** and alkenes **10a**–**e** and subsequent radical cyclization

Next, we examined the cross-metathesis of various alkenes **10b**–**e** in the presence of the Grubbs II catalyst, and we obtained the corresponding *N*-alkenylsulfonamides **11b**–**e** in moderate-to-good yields as single isomers in

Table 1 Preparation of Cross-Adducts **11** and Their Subsequent Radical Cyclization

Alkene reactant		Intermediate product	Yield[a] (%) of **11**	Product	Yield[a] (%) of **12**
10a	CH_2=CHCOMe	**11a**	76[b]	**12a**	63
10b	CH_2=CHCO$_2$Me	**11b**	96	**12b**	73
10c	CH=CH$_2$CO-4-Tol	**11c**	21 (31% conv.)	**12c**	51
10d	CH_2=CHCON(Me)OMe	**11d**	43 (81% conv.)	**12d**	61
10e	CH_2=CHPh	**11e**	53 (95% conv.)	polymers	–

[a] Isolated yields.
[b] Yield was 46% (82% conv.) when performed for 4 h with microwave activation (110 °C) in the presence of the Grubbs II catalyst (5 mol%), and 57% (65% conv.) when performed for 2 h under microwave activation (110 °C) with the Hoveyda–Grubbs catalyst (5 mol%).

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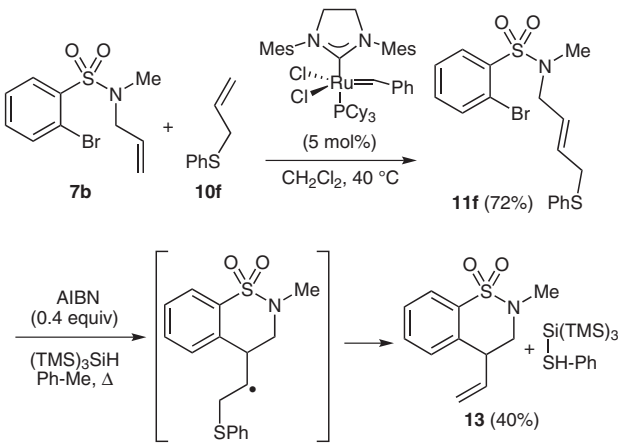
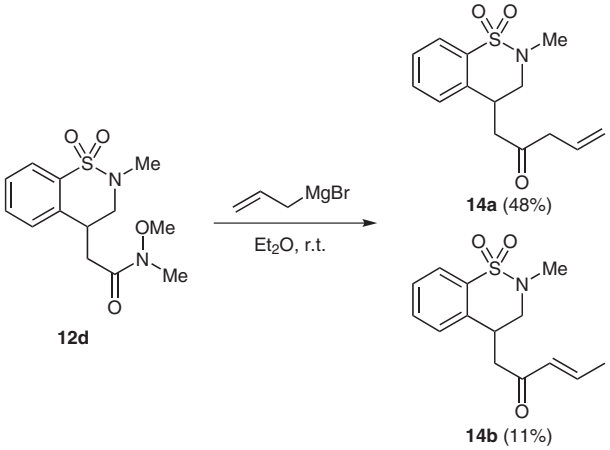
each case (Scheme 4, Table 1). The lower yields observed in some cases were the result of the homodimerization of **7b**. Radical cyclization of **11b–d** gave acceptable yields of sultams **12a–d**, whereas the styrene derivative **11e** gave only polymers.

We also performed the cross-metathesis of **7b** with allyl phenyl sulfide (**10f**) to give the corresponding sulfonamide **11f** in 72% yield. Subsequent radical cyclization–fragmentation reaction of **11f** gave the sensitive 4-vinylbenzosultam **13** in 40% yield (Scheme 5).



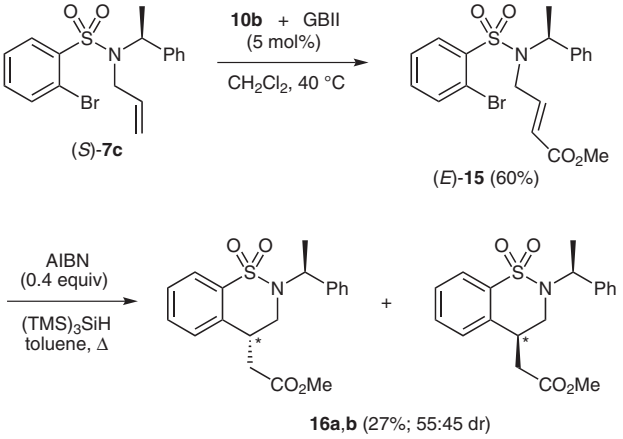
Scheme 5 Synthesis of vinylsultam **13** by cyclization–fragmentation

To enhance the functional diversity of our reaction, we reacted the Weinreb amide **12d** with allylmagnesium bromide. Selective 1,2-addition occurred to give the β,γ-unsaturated ketone **14a** together with isomer **14b**, formed as a result of migration of the terminal carbon–carbon double bond under the basic conditions (Scheme 6).



Scheme 6 Formation of ketones **14a** and **14b** from amide **12d**

In an attempt to control the configuration of the new chiral center that was formed, we developed a diastereoselective approach with (1-phenylethyl)amine as a chiral auxiliary (Scheme 7). Radical cyclization gave an inseparable mixture of sultams **16a** and **16b** in only 27% yield. This low efficiency might be the result of competitive hydrogen abstraction at the benzylic center, followed by intensive polymerization, as reflected by the base line on the thin-layer chromatogram of the reaction mixture. The diastereoselectivity was also poor, probably as a result of insufficient 1,5-asymmetric induction between the (1-phenylethyl)amine moiety and the prochiral sp^2 carbon center.



Scheme 7 Diastereoselectivity in the reaction of sulfonamide **7c**

In conclusion, we have developed a route for the synthesis of 4-substituted benzosultams in moderate-to-high yields through a combination of a cross-metathesis and a radical cyclization reaction. In comparison with alternative pathways, this sequence is straightforward and requires only two steps from readily available substrates. Work is underway to apply this strategy to other important building blocks for drug design.

All commercially available compounds were used without further purification. Solvents were dried by standard procedures. Hexanes refers to a hydrocarbon mixture with a boiling range of 40–60 °C. Column chromatography was performed with silica gel (0.040–0.063 mm). NMR spectra were recorded at 293 K by using a 300-MHz spectrometer (Bruker AMX 300) or a 500-MHz spectrometer (Bruker DRX 500). Shifts are referenced to the residual peaks of the deuterated solvent. Low- and high-resolution mass spectra were recorded in the positive mode by using a Bruker MicrOTOF-Q II XL spectrometer. IR spectra were recorded on a Nicolet IS 100 spectrometer.

2-Bromobenzenesulfonamides 7b and 7c; General Procedure

Et_3N (3 equiv) was added to a 0.2 M soln of alkyl(allyl)amine (1 equiv) in anhyd CH_2Cl_2, and the mixture was stirred at r.t. for 15 min, then being cooled to 0 °C. 2-$BrC_6H_4SO_2Cl$ (1 equiv) was added dropwise, and the mixture was warmed to r.t., stirred for 2 h, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexanes–EtOAc).

***N*-Allyl-2-bromo-*N*-methylbenzenesulfonamide (7b)**

Colorless oil; yield: 2.01 g (99%) from 2-$BrC_6H_4SO_2Cl$ (1.80 g).

IR: 3085, 2918, 1446, 1329, 1154, 919 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 2.0, 7.7 Hz, 1 H), 7.72 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.46–7.33 (m, 2 H), 5.82–5.65 (m, 1 H), 5.27–5.17 (m, 2 H), 3.85 (d, *J* = 6.3 Hz, 2 H), 2.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 135.7, 133.6, 132.8, 132.4, 127.6, 120.3, 119.2, 52.8, 34.0.

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HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{10}H_{12}BrNNaO_2S$ 311.9664; found: 311.9668.

_N_-Allyl-2-bromo-_N_-[(1_S_)-1-phenylethyl]benzenesulfonamide (7c)

Yellow oil; yield: 1.00 g (84%) from allyl[(1*S*)-1-phenylethyl]amine (505 mg);[27] R_f = 0.62 (hexanes–EtOAc, 7:3); $[\alpha]_D^{20}$ –5.1 (*c* = 1.4, $CHCl_3$).

IR: 3057, 1448, 1330, 1265, 1164, 1028, 924 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (dd, *J* = 2.2, 7.4 Hz, 1 H), 7.75 (dd, *J* = 1.8, 7.3 Hz, 1 H), 7.40 (dquint, *J* = 1.8, 7.4 Hz, 2 H), 7.32–7.19 (m, 5 H), 5.70–5.49 (m, 1 H), 5.17 (q, *J* = 7.1 Hz, 1 H), 5.01–4.85 (m, 2 H), 4.05 (dd, *J* = 5.6, 16.6 Hz, 1 H), 3.70 (dd, *J* = 6.9, 16.6 Hz, 1 H), 1.60 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.1, 139.5, 136.0, 135.6, 133.5, 132.8, 128.4, 128.0, 127.9, 127.6, 120.5, 116.9, 56.1, 47.6, 18.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}BrNNaO_2S$: 402.0134; found: 402.0128.

_N_-Allyl-_N_-alkenyl-2-bromobenzenesulfonamides 11a–e; General Procedure

A 0.1 M soln of the appropriate benzenesulfonamide derivative (1 equiv) and alkene derivative (3 equiv) in anhyd CH_2Cl_2 was treated with the Grubbs II catalyst (5 mol%) under argon. The mixture was stirred at reflux under argon atmosphere for 3 h and then a second portion of Grubbs II catalyst (2 mol%) was added and the mixture was stirred at the reflux overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography [silica gel, hexanes–EtOAc].

2-Bromo-_N_-methyl-_N_-[(2_E_)-4-oxopent-2-en-1-yl]benzenesulfonamide (11a)

Light-brown oil; yield: 217 mg (76%) from **7b** (250 mg); R_f = 0.17 (hexanes–EtOAc, 7:3).

IR: 2907, 1661, 1325, 1255, 1158, 933 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 2.0, 7.6 Hz, 1 H), 7.75 (dd, *J* = 1.5, 7.6 Hz, 1 H), 7.52–7.34 (m, 2 H), 6.67 (dt, *J* = 16.0, 5.7 Hz, 1 H), 6.22 (dt, *J* = 16.0, 1.5 Hz, 1 H), 4.09 (dd, *J* = 1.3, 5.7 Hz, 2 H), 2.83 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 141.0, 138.1, 135.9, 134.0, 133.0, 132.7, 127.8, 120.4, 51.4, 34.8, 27.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{14}BrNNaO_3S$: 353.9770; found: 353.9760.

Methyl (2_E_)-4-{[(2-Bromophenyl)sulfonyl](methyl)amino}but-2-enoate (11b)

Light-brown oil; yield: 346 mg (96%) from **7b** (300 mg); R_f = 0.30 (hexanes–EtOAc, 7:3).

IR: 2951, 1720, 1435, 1332, 1273, 1159, 1025, 929 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 2.1, 7.5 Hz, 1 H), 7.75 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.52–7.34 (m, 2 H), 6.85 (dt, *J* = 15.7, 5.6 Hz, 1 H), 6.04 (dt, *J* = 15.7, 1.7 Hz, 1 H), 4.07 (dd, *J* = 1.7, 5.6 Hz, 2 H), 3.74 (s, 3 H), 2.82 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 142.5, 138.2, 135.9, 133.9, 132.7, 127.8, 123.8, 120.4, 51.9, 51.1, 34.6.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{14}BrNNaO_4S$: 369.9719; found: 369.9720.

2-Bromo-_N_-methyl-_N_-[(2_E_)-4-(4-tolyl)-4-oxobut-2-en-1-yl]benzenesulfonamide (11c)

Light-brown oil; yield: 88 mg (21%; 31% conversion) from **7b** (300 mg); R_f = 0.26 (hexanes–EtOAc, 7:3).

IR: 2925, 1671, 1625, 1605, 1448, 1332, 1265, 1162, 1026, 924 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 1.9, 7.7 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 2 H), 7.76 (dd, *J* = 1.4, 7.7 Hz, 1 H), 7.51–7.35 (m, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.12 (dt, *J* = 15.4, 1.5 Hz, 1 H), 6.90 (dt, *J* = 15.4, 5.1 Hz, 1 H), 4.20 (dd, *J* = 1.3, 5.1 Hz, 2 H), 2.90 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.4, 144.2, 141.5, 138.3, 135.9, 134.9, 134.0, 132.7, 129.5, 129.0, 127.8, 127.6, 120.5, 51.6, 34.9, 21.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{18}BrNNaO_3S$: 430.0083; found: 430.0083.

(2_E_)-4-{[(2-Bromophenyl)sulfonyl](methyl)amino}-_N_-methoxy-_N_-methylbut-2-enamide (11d)

Light-brown oil; yield: 145 mg (43%; 81% conversion) from **7b** (345 mg); R_f = 0.35 (hexanes–EtOAc, 5:5).

IR: 2938, 1666, 1634, 1421, 1332, 1266, 978, 922 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 1.9, 7.7 Hz, 1 H), 7.75 (dd, *J* = 1.5, 7.6 Hz, 1 H), 7.50–7.35 (m, 2 H), 6.84 (dt, *J* = 15.5, 5.3 Hz, 1 H), 6.64 (d, *J* = 15.5 Hz, 1 H), 4.11 (dd, *J* = 1.4, 5.3 Hz, 2 H), 3.71 (s, 3 H), 3.24 (s, 3 H), 2.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 140.5, 138.4, 135.9, 133.9, 132.6, 127.8, 121.6, 120.5, 62.1, 51.4, 34.6, 32.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{17}BrN_2NaO_4S$: 398.9985; found: 398.9982.

2-Bromo-_N_-methyl-_N_-[(2_E_)-3-phenylprop-2-en-1-yl]benzenesulfonamide (11e)

Pale-yellow oil; yield: 168 mg (53%; 95% conversion) from **7b** (250 mg); R_f = 0.17 (hexanes–EtOAc, 9:1).

IR: 3059, 1575, 1448, 1331, 1265, 1159, 1026, 967, 926 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 1.9, 7.7 Hz, 1 H), 7.76 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.46 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.40 (dd, *J* = 1.9, 7.6 Hz, 1 H), 7.38–7.24 (m, 5 H), 6.54 (d, *J* = 15.8 Hz, 1 H), 6.14 (dt, *J* = 15.8, 6.7 Hz, 1 H), 4.08–3.99 (m, 2 H), 2.87 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 136.3, 135.8, 134.3, 133.7, 132.6, 128.7, 128.1, 127.7, 126.6, 124.1, 120.5, 52.4, 34.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{16}BrNNaO_2S$: 387.9977; found: 387.9973.

2-Bromo-_N_-methyl-_N_-[(2_E_)-4-(phenylsulfanyl)but-2-en-1-yl]benzenesulfonamide (11f)

Pale-yellow oil; yield: 255 mg (72%; 76% conversion) from **7b** (250 mg); R_f = 0.26 (hexanes–EtOAc, 8:2).

IR: 2010, 1575, 1438, 1331, 1265, 1157, 1025, 964 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 2.0, 7.6 Hz, 1 H), 7.72 (dd, *J* = 1.5, 7.6 Hz, 1 H), 7.51–7.05 (m, 7 H), 5.77–5.59 (m, 1 H), 5.46 (dt, *J* = 15.2, 6.5 Hz, 1 H), 3.77 (d, *J* = 6.5 Hz, 2 H), 3.51 (d, *J* = 6.9 Hz, 2 H), 2.59 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 135.8, 135.3, 133.6, 132.4, 130.6, 130.4, 129.0, 127.9, 127.6, 126.6, 120.4, 51.5, 35.9, 33.6.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}BrNNaO_2S_2$: 433.9855; found: 433.9848.

Methyl (2_E_)-4-{[(2-Bromophenyl)sulfonyl][(1_S_)-1-phenylethyl]amino}but-2-enoate (15)

White viscous liquid; yield: 96 mg (60%; 81% conversion) from **7c** (140 mg); R_f = 0.30 (hexanes–EtOAc, 8:2); $[\alpha]_D^{20}$ +1.5 (*c* = 0.9, $CHCl_3$).

IR: 2950, 2360, 1720, 1448, 1434, 1333, 1267, 1163, 1026, 899 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 2.0, 7.4 Hz, 1 H), 7.77 (dd, *J* = 1.5, 7.3 Hz, 1 H), 7.50–7.35 (m, 2 H), 7.32–7.17 (m, 5 H), 6.63 (dt, *J* = 15.8, 6.0 Hz, 1 H), 5.66 (d, *J* = 15.8 Hz, 1 H),

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5.15 (q, J = 7.0 Hz, 1 H), 4.14 (ddd, J = 1.4, 6.0, 17.6 Hz, 1 H), 3.89 (dd, J = 6.8, 17.6 Hz, 1 H), 3.67 (s, 3 H), 1.55 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 145.5, 139.8, 139.0, 135.8, 133.8, 133.0, 128.7, 128.3, 127.9, 127.8, 122.2, 120.6, 56.1, 51.7, 45.6, 18.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{20}BrNNaO_4S$: 460.0189; found: 460.0189.

Sultams 8, 9a/9b, 12a–d, and 16a/16b; General Procedure

A 0.1 M soln of the appropriate benzene sulfonamide **11** (1 equiv) in toluene was bubbled with a dried stream of N_2 for 10 min. AIBN (0.4 equiv) was then added and the reaction mixture was bubbled again for 10 min. $(TMS)_3SiH$ (1.6 equiv) was added dropwise and the mixture was refluxed for 5 h. The solvent was removed in vacuo and the crude mixture was purified by flash chromatography (silica, hexanes–EtOAc).

2-Allyl-2,3,4,5-tetrahydro-1,2-benzothiazepine 1,1-Dioxide (8)[23]

Yellow oil; yield: 22 mg (15%) from **7a** (200 mg).

^{1}H NMR (300 MHz, DMSO-d_6, 75 °C): δ = 7.79 (d, J = 7.8 Hz, 1 H), 7.58–7.49 (m, 1 H), 7.42 (d, J = 7.8 Hz, 2 H), 5.72 (ddt, J = 10.1, 17.0, 6.0 Hz, 1 H), 5.23 (dq, J = 17.0, 1.6 Hz, 1 H), 5.15 (dq, J = 10.1, 1.6 Hz, 1 H), 3.64–3.54 (m, 2 H), 3.42 (d, J = 6.0 Hz, 2 H), 3.28–3.16 (m, 2 H), 1.83–1.69 (m, 2 H).

MS (ESI): *m/z* (%) = 238.1 $[M + H]^+$ (100).

(10*R,11*R**)-11-Methyl-2-thia-1-azatricyclo[8.2.1.0^{3,8}]trideca-3,5,7-triene 2,2-Dioxide (9a) and (10*R**,11*S**)-11-Methyl-2-thia-1-azatricyclo[8.2.1.0^{3,8}]trideca-3,5,7-triene 2,2-Dioxide (9b)[23]**

Obtained as a 7:3 mixture of **9a** and **9b**.

9a

Orange oil; yield: 53 mg (35%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.89 (dd, J = 1.3, 7.8 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.45 (t, J = 7.8 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 3.90 (d, J = 12.9 Hz, 1 H), 3.32 (ddd, J = 1.6, 4.7, 12.9 Hz, 1 H), 3.24–3.16 (m, 2 H), 3.09 (d, J = 15.8 Hz, 1 H), 2.59 (dd, J = 5.1, 13.7 Hz, 1 H), 2.18 (dd, J = 4.7, 7.5 Hz, 1 H), 1.83–1.75 (m, 1 H), 0.92 (d, J = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 138.8, 136.8, 133.5, 132.7, 129.6, 127.1, 56.2, 55.2, 42.9, 40.9, 34.0, 20.2.

MS (ESI): *m/z* (%): $C_{12}H_{16}NO_2S$: 238.1 $[M + H]^+$ (100), 185.2 (12).

9b

Orange oil: yield: 23 mg (15%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (dd, J = 1.1, 7.9 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.45 (td, J = 7.6, 1.1 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 4.05 (dd, J = 1.9, 14.4 Hz, 1 H), 3.67–3.60 (m, 1 H), 3.56 (dd, J = 1.8, 14.4 Hz, 1 H), 3.00 (s, 1 H), 2.85 (dd, J = 12.3, 14.1 Hz, 1 H), 1.75–1.66 (m, 2 H), 1.52 (tt, J = 6.5, 11.8 Hz, 1 H), 0.70 (d, J = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 139.5, 139.4, 132.3, 129.2, 127.7, 123.3, 54.8, 50.3, 39.7, 32.0, 22.7, 18.1.

MS (ESI): *m/z* (%): $C_{12}H_{16}NO_2S$: 238.1 $[M + H]^+$ (100), 185.2 (12).

1-(2-Methyl-1,1-dioxido-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl)acetone (12a)

Orange oil: yield: 72 mg (63%) from **11a** (150 mg); R_f = 0.11 (hexanes–EtOAc, 7:3).

IR: 2926, 1715, 1330, 1267, 1162, 1139 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.8 Hz, 1 H), 7.47 (td, J = 7.6, 1.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.21 (d, J = 7.8 Hz, 1 H), 3.72 (ddd, J = 6.4, 13.2, 17.6 Hz, 2 H), 3.56 (dd, J = 6.4, 13.2 Hz, 1 H), 2.95–2.85 (m, 2 H), 2.83 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 138.5, 135.7, 132.6, 128.5, 127.8, 124.9, 53.3, 48.9, 35.3, 30.4, 29.8.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{15}NNaO_3S$: 276.0665; found: 276.0668.

Methyl (2-Methyl-1,1-dioxido-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl)acetate (12b)

Yellow oil; yield: 90 mg (73%) from **11b** (160 mg); R_f = 0.16 (hexanes–EtOAc, 7:3).

IR: 2953, 1732, 1438, 1331, 1160 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dd, J = 1.3, 7.8 Hz, 1 H), 7.51 (td, J = 7.6, 1.3 Hz, 1 H), 7.46–7.38 (m, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 3.82 (dd, J = 5.1, 14.0 Hz, 1 H), 3.73 (s, 3 H), 3.72–3.69 (m, 1 H), 3.66–3.56 (m, 1 H), 2.89 (s, 3 H), 2.79–2.74 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 137.7, 136.0, 132.6, 128.5, 128.1, 125.0, 53.1, 52.2, 39.2, 35.3, 31.7.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{15}NNaO_4S$: 292.0614; found: 292.0616.

2-(2-Methyl-1,1-dioxido-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl)-1-(4-tolyl)ethanone (12c)

Yellow oil; yield: 31 mg (51%) from **11c** (75 mg); R_f = 0.33 (hexanes–EtOAc, 3:7).

IR: 2923, 1678, 1477, 1331, 1165, 979 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.82 (m, 3 H), 7.50 (td, J = 7.6, 1.5 Hz, 1 H), 7.41 (td, J = 7.6, 1.2 Hz, 1 H), 7.29 (m, 3 H), 3.97–3.90 (m, 1 H), 3.86 (dd, J = 3.8, 15.1 Hz, 1 H), 3.71–3.56 (m, 1 H), 3.53 (dd, J = 9.0, 18.1 Hz, 1 H), 3.38–3.23 (m, 1 H), 2.87 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 144.9, 139.0, 136.0, 134.0, 132.7, 129.6, 128.8, 128.3, 127.9, 125.0, 53.5, 44.1, 35.3, 30.7, 21.8.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_3S$: 352.0978; found: 352.0980.

***N*-Methoxy-*N*-methyl-2-(2-methyl-1,1-dioxido-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl)acetamide (12d)**

Yellow oil: yield: 94 mg (61%) from **11d** (194 mg); R_f = 0.24 (hexanes–EtOAc, 4:6).

IR: 2939, 1655, 1421, 1332, 1266, 1169, 997, 944 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 3.83 (dd, J = 4.5, 13.4 Hz, 1 H), 3.76–3.66 (m, 2 H), 3.65 (s, 3 H), 3.22 (s, 3 H), 2.88 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 138.7, 135.9, 132.6, 128.8, 127.9, 125.0, 61.5, 53.4, 37.6, 35.3, 32.4, 31.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{18}N_2NaO_4S$: 321.0879; found: 321.0875.

2-Methyl-4-vinyl-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-Dioxide (13)

Pale-yellow oil; yield: 50 mg (46%) from **11f** (200 mg); R_f = 0.29 (PE–EtOAc, 8:2).

IR: 2924, 1473, 1330, 1161, 923 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, J = 1.3, 7.7 Hz, 1 H), 7.49 (dd, J = 1.3, 7.6 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.30 (d, J = 7.7 Hz, 1 H), 5.85–5.67 (m, 1 H), 5.41–5.26 (m, 2 H), 3.98 (dd, J = 10.4, 14.3 Hz, 1 H), 3.90–3.76 (m, 1 H), 3.56 (dd, J = 5.6, 14.3 Hz, 1 H), 2.93 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.9, 136.8, 135.3, 132.3, 129.9, 128.1, 125.1, 119.9, 53.8, 38.7, 35.9.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{13}NNaO_2S$: 246.0559; found: 246.0563.

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Methyl {(4*S*/4*R*)-1,1-Dioxido-2-[(1*S*)-1-phenylethyl]-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl}acetate (16a,16b)
Yellow oil; yield: 19 mg (27%; dr 55:45) from **11f** (87 mg); R_f = 0.18 (hexanes–EtOAc, 2:8).

^{1}H NMR (500 MHz, $CDCl_3$): δ (major) = 7.95–7.81 (m, 1 H), 7.50–7.38 (m, 3 H), 7.38–7.32 (m, 2 H), 7.31–7.21 (m, 2 H), 7.20–7.05 (m, 1 H), 5.53 (q, *J* = 7.0 Hz, 1 H), 3.84 (ddd, *J* = 1.1, 3.7, 14.0 Hz, 1 H), 3.41 (s, 3 H), 3.33 (dd, *J* = 2.9, 14.0 Hz, 1 H), 3.28 (dq, *J* = 10.0, 3.7 Hz, 1 H), 2.23 (dd, *J* = 10.0, 17.7 Hz, 1 H), 2.21–2.12 (m, 1 H), 1.67 (d, *J* = 7.0 Hz, 3 H). δ (minor) = 7.95–7.81 (m, 1 H), 7.50–7.38 (m, 3 H), 7.38–7.32 (m, 2 H), 7.31–7.21 (m, 2 H), 7.20–7.05 (m, 1 H,), 5.41 (q, *J* = 7.0 Hz, 1 H), 3.68 (s, 3 H), 3.53 (dd, *J* = 5.4, 14.4 Hz, 1 H), 3.45–3.41 (m, 1 H), 3.14 (dq, *J* = 10.2, 5.4 Hz, 1 H), 2.71 (dd, *J* = 9.7, 16.6 Hz, 1 H) and 2.61 (dd, *J* = 4.4, 16.6 Hz, 1 H), 1.62 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 and 171.8, 139.4 and 139.0, 138.5 and 138.3, 138.0 and 137.9, 132.4 and 132.2, 128.9, 128.6 and 128.5, 128.3 and 128.10, 128.05 and 127.97, 127.7, 124.0 and 123.9, 53.8 and 52.0 52.1 and 51.6, 45.2 and 43.0, 39.0 and 37.8, 34.4 and 33.9, 18.3 and 15.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_4S$: 382.1063; found: 382.1075.

Ketones 14
A soln of CH_2=$CHCH_2MgBr$ in Et_2O (1 M; 1 mL, 1 mmol) was added to a 0.1 M soln of amide **12d** (94 mg, 0.31 mmol) in anhyd THF at 0 °C. The mixture was stirred at 0 °C until the starting amide was consumed (TLC) and then a 5% soln of HCl in EtOH was added at 0 °C, followed by the addition of a 1:1 mixture of Et_2O (5 mL) and CH_2Cl_2. The organic layer was washed with brine (5 mL) and the aq layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography [silica gel, hexanes–EtOAc (7:3)].

1-(2-Methyl-1,1-dioxido-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl)pent-4-en-2-one (14a)
Colorless oil; yield: 42 mg (48%) from amide **12d** (94 mg); R_f = 0.33 (hexanes–EtOAc, 7:3).

IR: 3058, 1715, 1477, 1331, 1302, 1265, 1168, 929 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 1.2, 7.8 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 1 H), 5.91 (ddt, *J* = 10.2, 17.2, 7.0 Hz, 1 H), 5.30–5.11 (m, 2 H), 3.82–3.62 (m, 2 H), 3.55 (dd, *J* = 6.2, 13.4 Hz, 1 H), 3.20 (d, *J* = 7.0 Hz, 2 H), 3.00–2.87 (m, 2 H), 2.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.4, 138.5, 135.9, 132.7, 129.8, 128.5, 127.9, 125.1, 120.0, 53.3, 48.3, 47.7, 35.4, 30.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{17}NNaO_3S$: 302.0820; found: 302.0821.

(3*E*)-1-(2-Methyl-1,1-dioxido-3,4-dihydro-2*H*-1,2-benzothiazin-4-yl)pent-3-en-2-one (14b)
Pale-yellow oil; yield: 10 mg (11%) from amide **12d** (94 mg); R_f = 0.22 (hexanes–EtOAc, 7:3).

IR: 2916, 1719, 1328, 1161 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 1.2, 7.8 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 1 H), 7.00–6.81 (m, 1 H), 6.16 (dd, *J* = 1.6, 15.8 Hz, 1 H), 3.84–3.69 (m, 2 H), 3.65–3.50 (m, *J* = 6.2 Hz, 1 H), 3.07 (dd, *J* = 8.4, 17.9 Hz, 1 H), 2.93 (dd, *J* = 3.9, 17.9 Hz, 1 H), 2.86 (s, 3 H), 1.92 (dd, *J* = 1.6, 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 144.5, 138.8, 135.9, 132.6, 131.8, 128.7, 127.8, 125.1, 53.4, 45.2, 35.4, 30.3, 18.6.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{17}NNaO_3S$: 302.0820; found: 302.0821.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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