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α -Haloarylsulfonamides: Multiple Cyclization Pathways to Skeletally Diverse Benzofused Sultams

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Abstract

The development of new methods to skeletally diverse sultams based on a central α -halo benzene sulfonamide building block is reported. Several salient features of this building block are utilized in multiple reaction pathways, including the Heck reaction, *C*- and *O*-arylation, Sonogashira-Pauson-Khand, Sonogashira-intramolecular hydroamination, lithiative cyclization and domino aza-Michael Heck for the generation of 5-, 6- and 7-membered benzofused bicyclic and tricyclic sultams.

1. Introduction

In recent years, there has been a rapidly growing demand for libraries of small molecules for high-throughput screening (HTS). This demand has presented challenging opportunities in molecular library development. In this regard, Diversity-Oriented Synthesis (DOS)ⁱ⁻ⁱⁱ has emerged as an enabling platform for the production of multiple scaffolds displaying skeletal diversity, where a lack thereof has been cited as a bottleneck in the drug discovery process.ⁱ Among several features that define DOS, functional group pairingⁱⁱⁱ has surfaced as a significant component, which aims to selectively pair functional groups resulting in the generation of multiple scaffolds. Interest in the facile production of new sultams for biological screening has provided recent impetus for exploring new FG-pairing cyclization pathways of α -halo benzene sulfonamides. We herein report studies towards this goal revealing α -halo benzene sulfonamides as versatile starting materials whose features can be exploited in multiple reaction pathways to produce an array of 5-, 6- and 7-membered benzofused sultams. Ultimately, we aim to utilize these methods in a broader DOS strategy for library production of sultams.

Sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties.^{iv} In particular, a number of benzofused sultams have recently been reported that exhibit broad inhibitory properties against a variety of enzymes including: COX-2,^v HIV integrase,^{vi} lipoxygenase,^{vii} Calpain I^{viii} and MMP-2.^{ix} Moreover, a number of additional sultams have shown promising bioactivity, such as antiviral,^x anticancer,^{xi} antimicrobial,^{xii} antimalarial,^{xiii} antileukemic^{xiv} and AMPA receptor modulatory

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properties with potential for treating disorders of the brain.^{xv} This impressive biological profile is augmented by a number of chemical properties inherent to sulfonamides including facile coupling/alkylation pathways for sulfonamide formation, stability to hydrolysis, polarity and their crystalline nature.^{xvi}

α -Haloarylsulfonamides represent an attractive building block for the production of benzofused sultams,^{xvii} due to a number of key features. The most prominent include: (i) click coupling between starting α -halobenzenesulfonyl chlorides and amines under mild conditions generating the corresponding sulfonamides in quantitative yield, (ii) the α -halo group enhances the acidity of the aryl sulfonamide N-H enabling Mitsunobu and conventional alkylation reactions to occur under mild conditions, (iii) the α -halo group can be utilized in metal-catalyzed cross coupling or Li-halogen exchange chemistry and (iv) a number of substituted α -halo benzene sulfonyl chlorides are commercially available. Taken collectively, these attributes guided our efforts in this study.

2. Results and discussion

As outlined in Scheme 1, we began our initial investigation exploring Pd(0)-catalyzed Heck reactions with olefin containing sulfonamides **2**, **3** and **4** (Scheme 1). Substrates **2** and **3** were designed to alleviate any potential issues with regioselective Heck reactions. Substrate **4** was a more promiscuous Heck substrate and deserves mention first. Sulfonamide **4** was prepared via simple coupling of sulfonyl chloride **1** with L-amino methyl ester•HCl under standard conditions (CH₂Cl₂, Et₃N, DMAP) and allylation with allyl bromide. Subsequent Heck conditions were explored [Pd(OAc)₂, Et₃N, 0.25 M in CH₃CN at 100 °C in a microwave] and produced a mixture of products via 6-*exo*-trig (**5**) and 7-*endo*-trig (**6**) pathways, along with product **7** resulting from deallylation.^{xviii}

The regioselectivity concern of 6-*exo* versus 7-*endo* cyclization was not an issue when sulfonamide **2** was subjected to standard Heck reaction conditions. Thus, treatment of **1** with L-amino methyl ester•HCl under the aforementioned conditions, followed by alkylation with ethyl 4-bromocrotonate, yielded the alkylated sulfonamide **2**, which upon subjection to Heck conditions in refluxing CH₃CN, afforded the desired δ -sultam **8** as the sole product via a selective 6-*exo* cyclization pathway.

The straightforward syntheses of the 7-membered sultams **9** were also readily prepared as outlined in Scheme 1. Homo-allylation of the sulfonamide with 4-bromo-1-butene produced the alkylated product **3** in low yield. However, we found that performing the Mitsunobu reaction with 3-buten-1-ol in the presence of DIAD and PPh₃ gave superior yields of **3**.^{xix} Subsequent intramolecular Heck reaction of **3**, cleanly afforded the 7-*exo*-trig cyclization products **9** in excellent yields (Table 1). Ozonolysis of **9** produced the benzothiazepenones **10** in good to excellent yields. Similarly, the inseparable mixture of Heck products **5–6** was subjected to ozonolysis furnishing benzothiazeneone **11** in pure form after isolation.

The chemistry of benzenesulfonamide was further extended to an intramolecular arylation reaction whereby the α -bromo aryl sulfonamide group was paired with an aromatic group.^{xx} The literature contains a single example of a 6-membered sultam produced from an α -halobenzenesulfonamide using Pd(0)-catalysis.^{xxi} However, in this intramolecular direct C-arylation, the yield was low. Treating **1** with aniline and subsequent alkylation with methyl iodide or ethyl iodide produced the corresponding sulfonamide **12**, which was subjected to Pd(OAc)₂, PPh₃, Cs₂CO₃ in toluene at 110 °C affording cyclized product **13** via a C-arylation pathway. The present method offers a practical method for synthesis of dibenzothiazine dioxides in excellent yields (Table 2).

With this result in hand, we attempted the direct C-arylation to furnish a 7-membered sultam **15**. Treatment of **1** with benzyl amine and subsequent alkylation with methyl iodide furnished **14**, which was again subjected to Pd(OAc)₂ conditions at 110 °C for 24 h to afford the 7-membered benzofused sultam **15** in 85% yield.

The method was next applied to an intramolecular O-arylation reaction^{xxii} whereby the α -bromo aryl sulfonamide group was paired with an alcohol. Thus, **1** was coupled with phenylalanine methyl ester, followed by Mitsunobu reaction with 3-buten-1-ol and reduction with LiAlH₄ to furnish sulfonamide **16** in 41% over 3 steps. Sulfonamide **16** was treated with CuI (20 mol%) in the presence of HOCH₂CH₂OH as a ligand in DMF at 120 °C to afford the O-arylation, cyclized product **17** in 49 % yield.

The chemistry of α -halobenzenesulfonamide was further extended to both Pauson-Khand (PK) and intramolecular hydroamination (IHA) reactions.^{xxiii} In this method, the α -bromoaryl sulfonamide group was attached to an alkyne under Sonogashira conditions and subsequently paired with both an alkene (PK) as well as an N-H (IHA). The reaction sequence began with the sulfonylation of methylamine with tosyl chloride **18** followed by iodination to afford 2-iodosulfonamide **19** in 80% over 2 steps.^{xxiv} Compound **19** was subjected to Sonogashira reaction with trimethylsilyl acetylene in presence of PdCl₂(PPh₃)₂ and CuI to furnish sulfonamide **20**.^{xxv} Alkylation of **20** with allyl bromide in presence of K₂CO₃ in CH₃CN at 50 °C afforded allylated enyne product **21** along with a small amount of the corresponding IHA product **22**. However, when the reaction of **20** was carried out in the same conditions in the absence of allyl bromide, sultam **22** was produced as the sole product in 78% yield, representing a formal intramolecular hydroamination of an acetylene via a 5-*exo*-cyclization pathway. Finally, treatment of sulfonamide enyne **21** with [Co₂(CO)₈] under thermal conditions (90 °C) furnished the tricyclic Pauson-Khand product **23** in 67% yield.

The production of sultam **22** via an intramolecular hydroamination pathway prompted us to explore the development of a one-pot protocol that would take advantage of the inherent nucleophilicity of the sulfonamide N-H. In this regard, we have previously reported a one-pot domino Heckaza-Michael protocol for the synthesis of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides **24**.^{xxvi} Such domino protocols are attractive strategies for the incorporation of multiple points of diversity in a one-pot multi-component transformation. Thus, we investigated the application of α -haloaryl sulfonamides toward a domino aza-Michael-Heck protocol, where by initial Michael addition of the sulfonamide into methyl propiolate, followed by an intramolecular Heck reaction yields the corresponding benzofused sultam. Thus, *N*-benzyl-2-iodobenzenesulfonamide was reacted with methyl propiolate under standard reaction conditions at 110 °C to cleanly afford the desired sultam **25** in 74% yield. We are currently investigating additional variants of this protocol.

As a final example, we explored additional chemistry of the 7-membered benzothiazepenes using a classical aldol reaction to produce enone **26**. The underlying principle behind this was a reagent-based DOS approach towards skeletal diversity. Thus, treatment of **10e** with benzaldehyde in the presence of KOH furnished **26** bearing an unsaturated ketone as a single isomer in 80% yield. This aldol condensation set the stage for further modifications as outlined in Scheme 5.^{iiia} Subsequent hetero-Diels-Alder (HDA) reaction of ethyl vinyl ether and **26** under neat conditions at 70 °C generated the tricyclic benzosultam **27** as a single regio- and diastereoisomer in 62% yield. Condensation reaction of **26** with phenyl hydrazine produced the pyrolozine-containing sultam **28** in 82% yield as a 1:1 mixture of diastereomers.^{xxvii} Finally, reaction of malononitrile with **26** produced the tricyclic sultams **29** in 68% yield.

Conclusion

In conclusion, we have developed a variety of new reaction pathways toward the synthesis of skeletally diverse benzofused sultams. These methods employ commercially available α -haloaryl sulfonyl chlorides in achieving multiple reaction pathways such as Heck, lithiation, Sonogashira-NH addition, Sonogashira-Pauson-Khand, *C*- and *O*-arylations to produce 5, 6, 7-membered sultams in good to excellent yields. We also demonstrated that Heck reaction products undergo facile ozonolysis/aldol to produce an intermediate unsaturated ketone, which was utilized in a reagent-based DOS approach to furnish additional diverse sultams. All the sultam reported herein have been submitted to NIH biological outreach partners for biological screening through the NIH Molecular Library Screening Network (NIH-MLSCN). The utilization of the reported method is currently being employed in library production and the results will be reported in due course.

3. Experimental Section

General 3.1

All reactions were carried out in flame-dried glassware under argon. Toluene, THF, Et₂O, and CH₂Cl₂ were purified by passage through a purification system (Solv-Tek) employing activated Al₂O₃. Et₃N was distilled from CaH₂. Flash column chromatography was performed with Merck silica gel (230–400 mesh). Thin layer chromatography was performed on silica gel 60F₂₅₄ plates. ¹H and ¹³C spectra were recorded in CDCl₃ on either a Bruker DRX-400 or a Bruker AM-500 spectrometer operating at 400/100 MHz and 500/125 MHz, respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Infrared data was obtained on a Nicolet 320 Fourier Transform Infrared Spectrophotometers. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

3.2 Synthetic Studies

(*S,E*)-ethyl-4-(2-bromo-*N*-(1-methoxy-3-methyl-1-oxobutan-2-yl)phenylsulfonamido)but-2-enoate (2)—Into a flame dried flask was added, **1** (2.0 g, 7.82 mmol), H-Leu-OMe (1.42 g, 7.82 mmol) and CH₂Cl₂ (20 mL). After stirring for 5 mins at RT, Et₃N (2.32 mL, 16.4 mmol) was added and the reaction flask stirred at RT for 2 h. The crude reaction mixture was filtered and concentrated under reduced pressure. A portion of the crude material (208 mg, 0.56 mmol) was added to a flame-dried flask, to which Cs₂CO₃ (294 mg, 1.165 mmol) and dry CH₃CN (6 mL, 0.1 M) was added. After stirring for 5 mins, (*E*)-ethyl 4-bromobut-2-enoate (0.66 mmol) was added and the reaction mixture was stirred at 60 °C until completion of reaction (as monitored by TLC). The crude reaction mixture was filtered through a pad of Celite, washed with CH₂Cl₂, concentrated under reduced pressure and subjected to flash chromatography (1:1 EtOAc: Hexane) to provide **2** (201 mg, 0.44 mmol, 78%) as a clear oil. FTIR (neat): 2972, 1739, 1720, 1342, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.11 (dd, *J* = 1.7, 7.9, 1H), 7.71 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.43 (td, *J* = 7.7, 1.3 Hz, 1H), 7.37 (dt, *J* = 7.5, 1.8 Hz, 1H), 6.84 (ddd, *J* = 15.8, 7.8, 5.1 Hz, 1H), 5.87 (dt, *J* = 15.8, 1.5 Hz, 1H), 4.41 (dddd, *J* = 18.4, 9.0, 6.4, 1.5 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.09 (d, *J* = 10.3 Hz, 1H), 3.54 (s, 3H), 2.15 – 2.06 (m, 1H), 1.29 – 1.23 (m, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.91 (dd, *J* = 9.0, 3.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 171.0, 165.7, 144.4, 139.2, 135.4, 133.8, 133.1, 127.6, 123.1, 120.3, 65.5, 60.4, 51.7, 46.5, 28.9, 19.8, 19.3, 14.2; HRMS calculated for C₁₈H₂₄BrNNaO₆S (M+Na)⁺ 484.0405; found 484.0379.

(*S*)-methyl-2-(2-bromo-*N*-(but-3-enyl)phenylsulfonamido) propanoate (3a)—Into a flame-dried flask under argon was added **1** (7.82 mmol), amino ester/amine (7.82 mmol) and CH₂Cl₂ (20 mL). Et₃N (16.4 mmol) was added and the reaction flask stirred at RT for 2 h. The

crude reaction mixture was filtered and concentrated under reduced pressure. A portion of the crude (2.56 g 7.64 mmol) was added to a flame-dried flask under argon (2.56 g 7.64 mmol), to which was added PPh₃ (2.21 g, 8.45 mmol) and dry CH₂Cl₂ (40 mL). After stirring for 5 mins, 3-buten-1-ol (0.72 mL, 8.45 mmol) was added followed by drop wise addition of diisopropyl azodicarboxylate (DIAD) (1.71 mL, 8.45 mmol) at RT. The reaction mixture was stirred for 3 h, after which time the crude mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 EtOAc: Hexane) to provide **3a** (2.34 g, 79% yield) as a white solid. FTIR (neat): 3064, 2950, 1795, 1448, 1434, 1342, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.15 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.71 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H), 7.37 (td, *J* = 7.6, 1.7 Hz, 1H), 5.62 (ddt, *J* = 17.2, 10.5, 7.7 Hz, 1H), 4.96 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.94 (dq, *J* = 11.8, 1.7 Hz, 1H), 4.82 (q, *J* = 7.4 Hz, 1H), 3.63 (s, 3H), 3.57 – 3.47 (m, 1H), 3.17 (ddd, *J* = 15.3, 9.3, 7.2, 1H), 2.28 – 2.21 (m, 2H), 1.50 (d, *J* = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.06, 135.44, 134.40, 133.47, 132.16, 127.50, 116.92, 55.43, 52.29, 45.14, 34.69, 16.48; HRMS calculated for C₁₄H₁₈BrNNaO₄S (M+Na)⁺ 398.0038; found 398.0045.

(S)-methyl 2-(2-bromo-N-(but-3-enyl)phenylsulfonamido)-4-methylpentanoate (3b)—Using a similar procedure as that used to produce sultam **3a**, sultam **3b** was produced in 69%. FTIR (neat): 3064, 2955, 1795, 1448, 1434, 1336, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.14 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.45 (td, *J* = 7.7, 1.3 Hz, 1H), 7.38 (td, *J* = 7.6, 1.7 Hz, 2H), 5.72 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.04 (dddd, *J* = 16.0, 1.5, 1.5, 1.5 Hz, 1H), 5.03 (m, 1H), 4.56 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.59 – 3.51 (m, 1H) 3.54 (s, 3H), 3.32 (ddd, *J* = 16.0, 11.0, 5.2 Hz, 1H), 2.57 – 2.48 (m, 1H), 2.34 – 2.25 (m, 1H), 1.78 – 1.69 (m, 2H), 1.65 – 1.56 (m, 1H), 0.93 (dd, *J* = 17.1, 6.2 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 171.7, 139.2, 135.5, 134.7, 133.4, 132.4, 127.5, 120.4, 117.0, 58.3, 52.1, 45.8, 39.4, 35.5, 24.5, 22.6, 21.7; HRMS calculated for C₁₇H₂₄BrNNaO₄S (M+Na)⁺ 440.0507; found 440.0500.

Methyl-2-(2-bromo-N-(but-3-enyl)phenylsulfonamido) acetate (3c)—Using a similar procedure as that used to produce sultam **3a**, sultam **3c** was produced in 87%. FTIR (neat): 2951, 1753, 1340, 1161, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 (td, *J* = 7.5, 1.7 Hz, 1H), 5.59 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.01 (ddd, *J* = 11.0, 6.6, 5.5 Hz, 2H), 4.28 (s, 2H), 3.71 (s, 3H), 3.57 – 3.38 (m, 2H), 2.34 – 2.11 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 169.5, 139.3, 135.5, 134.1, 133.6, 132.2, 127.5, 120.5, 117.5, 52.3, 48.5, 47.6, 32.0. HRMS calculated for C₁₃H₁₆BrNNaO₄S (M+Na)⁺ 383.9881; found 383.9882.

N-Benzyl-2-bromo-N-(but-3-enyl)benzenesulfonamide (3d)—Using a similar procedure as that used to produce sultam **3a**, sultam **3d** was produced in 67%. FTIR (neat): 3064, 2927, 1641, 1448, 1434, 1332, 1124 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.9 Hz, 1H), 7.34 – 7.26 (m, 5H), 5.56 – 5.47 (m, 1H), 4.94 – 4.92 (m, 1H), 4.90 (t, *J* = 1.3 Hz, 1H), 4.57 (s, 2H), 3.26 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.16 – 2.10 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 139.47, 135.90, 135.53, 134.30, 133.49, 132.34, 128.63, 128.26, 127.80, 127.51, 120.52, 117.13, 77.25, 77.00, 76.75, 51.26, 46.01, 31.90; HRMS calculated for C₁₇H₁₈BrNNaO₂S (M+Na)⁺ 402.0140; found 402.0139.

(S)-methyl 3-(N-allyl-2-bromophenylsulfonamido)-5-methyl-2-oxohexanoate (4)—Using a similar procedure as that used to produce sultam **2**, sultam **4** was produced as a clear oil in 85% yield. [α]_D²⁰ - 42.8 (c 3.38, CH₂Cl₂), colorless oil FTIR (neat): 2966, 1740, 1340, 1163, 748 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 8.01-7.28 (aromatic H, 4H), 5.80 (m, 1H), 5.06 (d, *J* = 17.2 Hz, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 4.49 (dd, *J* = 6.4, 3.9 Hz, 1H), 4.10 (dd, *J* = 16.4, 8.0 Hz, 1H), 3.93 (d, *J* = 10.4 Hz, 1H), 3.40 (s, 3H), 2.10 (m, 1H), 0.94 (d, *J* =

6.6 Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 170.7, 139.4, 135.5, 135.3, 133.6, 132.8, 127.5, 120.1, 117.3, 65.5, 51.3, 48.6, 28.5, 19.5, 18.8; HRMS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{20}\text{BrNO}_4\text{SNa}$ 412.0194 ($\text{M}+\text{Na}$) $^+$, found 412.0181.

Sultam (5)—Into a microwave vial was added sulfonamide **4** (1.77 g, 4.30 mmol), Pd(OAc) $_2$ (0.43 mmol, 96 mg), PPh_3 (0.86 mmol, 225 mg), CH_3CN (17 mL) and Et_3N (1.8 mL, 12.9 mmol). After stirring for 5 min., the reaction was run in the microwave at 100 °C for 1 h. After 1 h, the reaction mixture was cooled to RT and filtered through a small Celite pad and thoroughly washed with CH_2Cl_2 . The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane:EtOAc) to provide a 1.24 g (89%) of a mixture of compounds **5/6/7** [1:0.14:0.74 based on ^1H -NMR] as a yellow oil. FTIR (neat): 2964, 1740, 1340, 1170, 748 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 8.06-7.41 (aromatic H, 4H), 5.78 (s, 1H), 5.25 (s, 1H), 4.67 (d, $J = 6.7$ Hz, 1H), 4.49 (d, $J = 6.8$ Hz, 1H), 4.11 (d, $J = 10.6$ Hz, 1H), 3.25 (s, 3H), 1.68 (m, 1H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.06 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 170.2, 136.0, 134.3, 133.5, 131.1, 127.6, 125.3, 120.4, 113.8, 64.3, 51.4, 47.9, 27.9, 19.2, 18.8; HRMS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{19}\text{NO}_4\text{SNa}$ 332.0932 ($\text{M}+\text{Na}$) $^+$, found 332.0936.

Intramolecular Heck reaction to sultam 8—To the alkylated sulfonamide **2** was added Pd(OAc) $_2$ (12.5 mg, 0.056 mmol), PPh_3 (29 mg, 0.11 mmol) and Et_3N (0.23 mL, 1.68 mmol) and the reaction mixture was heated at 70 °C for overnight. After 12 h the reaction mixture was cooled to room temperature and filtered through a small Celite pad and thoroughly washed with CH_2Cl_2 . The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 Hexane:EtOAc) to provide **8** (67% yield) as a yellow oil. $[\alpha]^{25} = -12.1$; (c 0.05, CHCl_3); FTIR (neat): 2968, 1739, 1332, 1199, 1117, 1026 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ ppm 7.94 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.68 – 7.58 (m, 1H), 7.51 (ddd, $J = 8.0, 6.4, 2.5$ Hz, 2H), 6.96 (s, 1H), 4.56 (d, $J = 10.4$ Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 3.59 (s, 2H), 2.24 (ddt, $J = 13.3, 10.4, 6.7$ Hz, 1H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm 170.7, 170.6, 132.5, 132.1, 131.4, 128.1, 127.8, 124.0, 122.1, 113.5, 62.5, 61.2, 52.5, 36.6, 29.9, 19.1, 18.6, 14.1; HRMS calculated for $\text{C}_{18}\text{H}_{23}\text{NO}_6\text{SNa}$ ($\text{M}+\text{Na}$) $^+$ 404.1144; found 404.1146.

(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-5-methylene- α -(2-methylpropyl)-, methyl ester, 1,1-dioxide (9b)—Into a microwave vial was added sulfonamide **3b** (1.8 g, 4.30 mmol), Pd(OAc) $_2$ (0.43 mmol, 96 mg), PPh_3 (0.86 mmol, 225 mg), CH_3CN (17 mL) and Et_3N (1.8 mL, 12.9 mmol). After stirring for 5 min., the reaction was run in the microwave at 100 °C for 1 h. After 1 h, the reaction mixture was cooled to RT and filtered through a small Celite pad and thoroughly washed with CH_2Cl_2 . The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane:EtOAc) to provide 1.29 g (89%) of the title compound **9b** as a yellow oil. $[\alpha]^{25} = -35.4$; (c 7.30, CHCl_3); colorless liquid. FTIR (neat): 2954, 2869, 1741, 1467, 1153 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ ppm 8.46 (dd, $J = 7.8, 1.1$ Hz, 1H), 8.03 (td, $J = 7.5, 1.3$ Hz, 1H), 7.97 – 7.89 (m, 2H), 5.86 (d, $J = 0.7$ Hz, 1H), 5.82 (d, $J = 1.2$ Hz, 1H), 5.23 (dd, $J = 9.4, 6.0$ Hz, 1H), 4.32 (ddd, $J = 13.0, 8.2, 4.6$ Hz, 1H), 4.19 (dt, $J = 10.7, 5.1$ Hz, 1H), 3.92 (s, 3H), 3.22 – 2.96 (m, 2H), 2.19 (dq, $J = 17.1, 8.7$ Hz, 2H), 2.04 (ddd, $J = 13.6, 6.7, 6.5$ Hz, 1H), 1.44 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm 171.4, 147.0, 139.7, 139.7, 132.2, 129.9, 127.2, 126.1, 119.0, 57.5, 51.7, 45.0, 38.1, 35.0, 24.3, 22.8, 21.3; HRMS calculated for $\text{C}_{17}\text{H}_{23}\text{NNaO}_4\text{S}$ ($\text{M}+\text{Na}$) $^+$ 360.1245; found 360.1224.

(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro- α -methyl-5-methylene-, methyl ester, 1,1-dioxide (9a)—Using a similar procedure as that used to produce sultam **9b**, sultam **9a** was produced in 72%. $[\alpha]^{25} = -34.0$; (c 3.45, CHCl_3); colorless liquid. FTIR

(neat): 2951, 1750, 1365, 1170, 1158 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ ppm 7.88 (dd, $J = 7.9, 1.1$ Hz, 1H); 7.46 (td, $J = 7.6, 1.3$ Hz, 1H), 7.36 (td, $J = 7.7, 1.5$ Hz, 2H), 5.29 (s, 1H), 5.26 (s, 1H), 4.69 (q, $J = 7.3$ Hz, 1H), 3.70 (t, $J = 4.3$ Hz, 2H), 3.46 (s, 3H), 2.52 (ddd, $J = 14.4, 6.2, 5.9$ Hz, 2H), 1.33 (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 171.7, 147.0, 139.8, 139.7, 132.2, 130.1, 127.3, 126.2, 119.3, 55.1, 52.0, 45.5, 35.5, 16.1; HRMS calculated for $\text{C}_{14}\text{H}_{17}\text{NNaO}_4\text{S}$ ($\text{M}+\text{Na}$) $^+$ 318.0776; found 318.0780 (FAB).

(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-5-methylene-, methyl ester, 1,1-dioxide (9c)—Using a similar procedure as that used to produce sultam **9b**, sultam **9c** was produced in 70%. FTIR (neat) 2952, 1755, 1417, 1128, 860 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ ppm 7.92 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.52 (td, $J = 7.5, 1.4$ Hz, 1H), 7.44–7.35 (m, 2H), 5.36 (d, $J = 0.9$ Hz, 1H), 5.28 (d, $J = 1.2$ Hz, 1H), 3.83 (s, 4H), 3.70 (s, 3H), 2.58 (t, $J = 4.0$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm 168.9, 146.8, 140.2, 137.7, 132.8, 130.5, 127.5, 127.5, 119.7, 52.2, 50.5, 48.8, 32.6; HRMS calculated for $\text{C}_{13}\text{H}_{15}\text{NNaO}_4\text{S}$ ($\text{M}+\text{Na}$) $^+$ 304.0619; found 304.0613.

1,2-Benzothiazepine, 2,3,4,5-tetrahydro-5-methylene -2-(phenylmethyl)-, 1,1-dioxide (9d)—Using a similar procedure as that used to produce sultam **9b**, sultam **9d** was produced in 62%. FTIR (neat): 2943, 1352, 1336, 1163, 727 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ ppm 8.05 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.56 (td, $J = 7.5, 1.4$ Hz, 1H), 7.45 (ddd, $J = 16.2, 7.6, 1.3$ Hz, 2H), 7.38–7.29 (m, 5H), 5.38 (d, $J = 0.7$ Hz, 1H), 5.31 (t, $J = 2.0$ Hz, 1H), 4.18 (s, 2H), 3.60 (s, 2H), 2.55 (t, $J = 5.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 147.1, 140.6, 137.4, 135.7, 132.8, 130.6, 128.6, 128.3, 128.2, 128.2, 127.9, 127.6, 119.7, 50.0, 47.6, 31.5; HRMS calculated for $\text{C}_{17}\text{H}_{17}\text{NNaO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 322.0878; found 322.0865.

(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro- α -(2-methylpropyl))-5-oxo-, methyl ester, 1,1-dioxide (10b)—To a round bottom flask were added **9b** (1.88 g 5.57 mmol), Sudan(III) (1 mg) and CH_2Cl_2 (50 mL). The reaction mixture was cooled down to -78°C and O_3 was bubbled into the solution for 15 min. After such time, Me_2S (5 mL) was added drop wise upon disappearance of the pink color of the crude reaction mixture. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (4:1 hexanes:EtOAc) to provide 82% yield of the desired product (**10c**) as a colorless oil. $[\alpha]_D^{25} = 8.7$; (c 1.39, CHCl_3); FTIR (neat): 2956, 1741, 1693, 1342, 1203, 1172, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 8.00 (ddd, $J = 7.0, 4.4, 2.5$ Hz, 1H), 7.90 (ddd, $J = 8.8, 4.8, 2.2$ Hz, 1H), 7.65–7.62 (ddd, $J = 5.0, 2.4, 2.1$ Hz, 2H), 4.78 (dd, $J = 8.3, 7.3$ Hz, 1H), 3.75–3.50 (m, 2H), 3.49–3.36 (m, 3H), 3.18 (dt, $J = 13.9, 5.0$ Hz, 1H), 1.81–1.57 (m, 4H), 1.02 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 198.9, 171.1, 140.8, 135.6, 132.4, 132.0, 129.4, 126.3, 58.9, 52.0, 42.3, 39.9, 38.0, 24.5, 23.1, 21.0; HRMS calculated for $\text{C}_{16}\text{H}_{21}\text{NNaO}_5\text{S}$ ($\text{M}+\text{Na}$) $^+$ 362.1038; found 362.1047.

(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro- α -methyl-5-oxo-, methyl ester, 1,1-dioxide (10a)—Using a similar procedure as that used to produce sultam **10b**, sultam **10a** was produced in 84% yield as a colorless oil. $[\alpha]_D^{25} = 30.5$; (c 0.67, CHCl_3); FTIR (neat): 2935, 1693, 1589, 1315, 1280, 1153 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ ppm 7.99 (ddd, $J = 8.8, 4.8, 2.4$ Hz, 1H), 7.87 (ddd, $J = 9.2, 4.8, 2.4$ Hz, 1H), 7.66 (ddd, $J = 8.8, 4.4, 2.0$ Hz, 2H), 4.81 (q, $J = 7.2$ Hz, 1H), 3.50 (s, 3H), 3.45–3.64 (m, 3H), 3.24 (ddd, $J = 10.8, 6.4, 4.4$ Hz, 1H), 1.45 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 199.1, 171.1, 140.7, 135.7, 132.4, 132.0, 129.4, 126.2, 56.2, 52.2, 42.3, 40.0, 16.0; HRMS calculated for $\text{C}_{13}\text{H}_{15}\text{NNaO}_5\text{S}$ ($\text{M}+\text{Na}$) $^+$ 320.0569; found 320.0570.

1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-5-oxo-, methyl ester, 1,1-dioxide (10c)—Using a similar procedure as that used to produce sultam **10b**, sultam **10c**

was produced in 78 % yield as a colorless oil. FTIR (neat) 2954, 1751, 1693, 1342, 1163, 769 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.95 (ddd, $J = 9.0, 5.6, 3.2$ Hz, 1H), 7.83 (ddd, $J = 9.0, 6.4, 3.0$ Hz, 1H), 7.68 (ddd, $J = 10.0, 5.7, 3.3$ Hz, 2H), 4.11 (s, 2H), 3.66 (s, 3H), 3.62 (t, $J = 6.0$ Hz, 2H), 3.34 (t, $J = 6.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 199.8, 168.8, 138.8, 136.0, 132.7, 132.0, 129.5, 126.3, 52.3, 51.2, 45.3, 41.7; HRMS calculated for $\text{C}_{12}\text{H}_{13}\text{NNaO}_5\text{S}$ ($\text{M}+\text{Na}$) $^+$ 306.0412; found 306.0425.

1,2-Benzothiazepin-5-(2H)-one, 3,4-dihydro-2-(phenylmethyl)-, 1,1-dioxide (10d)

—Using a similar procedure as that used to produce sultam **10b**, sultam **10d** was produced in 78% yield as a colorless oil. FTIR (neat): 2956, 1693, 1512, 1340, 1160 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 8.06 (ddd, $J = 8.8, 5.6, 3.6$ Hz, 1H), 7.83 – 7.60 (m, 3H), 7.49 – 7.24 (m, 5H), 4.30 (s, 2H), 3.49 (t, $J = 6.0$ Hz, 2H), 3.14 (t, $J = 6.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 200.6, 137.5, 137.2, 135.0, 132.9, 131.7, 129.3, 128.8, 128.3, 128.2, 127.2, 52.5, 43.5, 41.2; HRMS calculated for $\text{C}_{16}\text{H}_{15}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$ 324.0670; found 324.0667 (FAB).

Sultam (11)—Using a similar procedure as that used to produce sultam **8**, sultam **4** was produced and carried through crude using a similar procedure as that used to produce sultam **10**, to yield **11** (39% over 2 steps) as a clear oil. FTIR (neat): 2964, 1739, 1469, 1340, 1170 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ ppm 8.05 (d, $J = 7.3$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.78 – 7.66 (m, 2H), 4.70 (d, $J = 18.8$ Hz, 1H), 4.39 (d, $J = 18.9$ Hz, 1H), 4.22 (d, $J = 10.0$ Hz, 1H), 3.20 (s, 3H), 2.28 – 2.03 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 4H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 188.4, 170.3, 140.1, 134.2, 132.9, 129.9, 128.1, 123.4, 65.3, 54.0, 51.6, 28.4, 19.1, 19.1; HRMS calculated for $\text{C}_{14}\text{H}_{17}\text{NNaO}_5\text{S}$ ($\text{M}+\text{Na}$) $^+$ 334.0725; found 334.0737.

N-Benzyl-2-bromo-N-methylbenzenesulfonamide 12a—Into a flame-dried flask under argon was added sulfonyl chloride **1** (1.0 g, 3.9 mmol), aniline (0.36 mL, 3.9 mmol), dry CH_2Cl_2 (39 mL, 0.1M) and pyridine (1.58 mL, 1.95 mmol). After stirring at RT for 2 h the crude reaction mixture was filtered, washed with water (2×20 mL), dried with MgSO_4 and concentrated under reduced pressure. A portion of the crude material (1.0 g, 0.32 mmol) was added to a flame-dried flask followed by the addition of CH_3I (1.0 mL, 1.61 mmol), K_2CO_3 (2.22 g, 1.61 mmol) and dry CH_3CN (12 mL, 0.1 M) were added and reaction mixture was stirred at RT, until the starting material disappeared as monitored by TLC. The crude reaction mixture was filtered through a pad of celite and washed with CH_2Cl_2 . The mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide **12a** (88% yield) as a clear oil; FTIR (neat): 1493, 13339, 1157, 741, 565 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.83 (dd, $J = 7.1, 2.0$ Hz, 1H), 7.66 (dd, $J = 7.0, 2.0$ Hz, 1H), 7.36 – 7.07 (m, 7H), 3.37 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 141.0, 138.2, 135.8, 133.9, 133.1, 129.4, 127.6, 127.6, 127.2, 120.7, 39.7; HRMS calculated for $\text{C}_{13}\text{H}_{12}\text{BrNNaO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 347.9670; found 347.9636.

N-benzyl-2-bromo-N-ethylbenzenesulfonamide 12b—Using a similar procedure as that used to produce sultam **12a**, sultam **12b** was produced as a yellow oil in 85% yield. FTIR (neat): 2974, 1490, 1336, 1174, 741, 696 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.77 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.65 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.33 – 7.08 (m, 7H), 3.86 (q, $J = 7.1$ Hz, 2H), 1.09 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 138.8, 138.3, 135.6, 133.7, 133.1, 129.7, 129.4, 128.2, 127.5, 120.6, 47.7, 14.9; HRMS calculated for $\text{C}_{14}\text{H}_{14}\text{BrNNaO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 361.9827; found 361.9830.

Intramolecular C-arylation to 6H-dibenzo[c,e][1,2] thiazine, 6-methyl-, 5,5-dioxide 13a—To **12a** was added $\text{Pd}(\text{OAc})_2$ (3.02 mg, 0.0135 mmol.), PPh_3 (7.08 mg, 0.027 mmol), Cs_2CO_3 (131 mg, 0.405 mmol) and toluene (4 mL). The crude reaction mixture was heated at 110 °C for 12–24 h, until the SM was consumed, as indicated by TLC. After 24 h the

reaction mixture was cooled to RT and filtered through a small Celite pad and thoroughly washed with CH₂Cl₂. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane:EtOAc) to afford the desired product **13a** in 83% yield as a yellow oil. FTIR (neat): 1477, 1327, 1174, 754 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.03 (td, *J* = 6.5, 1.4 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.72 (td, *J* = 7.5, 1.4 Hz, 1H), 7.58 (td, *J* = 7.7, 1.1 Hz, 1H), 7.52 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1H), 7.38 – 7.29 (m, 2H), 3.46 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 139.4, 134.1, 132.4, 132.3, 130.4, 128.2, 125.5, 125.4, 124.6, 123.9, 122.4, 119.3, 32.7; HRMS calculated for C₁₃H₁₁NNaO₂S (M + Na)⁺ 268.0408; found 268.0430.

6H-dibenzo[c,e][1,2] thiazine, 6-ethyl-, 5,5-dioxide 13b—Using a similar procedure as that used to produce sultam **13a**, sultam **13a** was produced in 77% as a yellow oil. FTIR (neat): 1635, 1336, 1166, 1095, 977 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.03-7.95 (m, 3H), 7.71 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.57 (td, *J* = 7.7, 1.1 Hz, 1H), 7.50 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H), 7.40 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.37 (td, *J* = 7.6, 1.1 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 140.9, 139.4, 134.8, 133.5, 133.3, 130.2, 129.9, 129.5, 129.0, 128.5, 128.3, 127.5, 56.1, 39.0; HRMS calculated for C₁₄H₁₃NNaO₂S (M+Na)⁺ 282.0565; found 282.0553.

2-Bromo-N-(4-methoxybenzyl)-N-methylbenzene-sulfonamide (14b)—Into a flame-dried flask under argon was added 2-bromobenzenesulfonyl chloride (150 mg, 0.58 mmol), methylamine (1.76 mmol), and dry CH₂Cl₂ (6 mL). Et₃N (0.11 mL, 0.76 mmol) and DMAP (5 mg, 0.1 mmol) were added and the reaction flask stirred at RT for 2 hrs. The crude reaction mixture was filtered and washed with water. The mixture was dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide the corresponding *N*-methyl sulfonamide in 98% yield as a yellow solid. To the 2-bromo-*N*-methylbenzene-sulfonamide (0.56 mmol) in dry CH₃CN (6 mL, 0.1 M) was added Cs₂CO₃ (294 mg, 1.165 mmol). *p*-Methoxy benzyl bromide (0.66 mmol) was added and the reaction mixture was stirred at 60 °C, until the SM disappeared as monitored by TLC. The crude reaction mixture was filtered through a pad of Celite, washed with CH₂Cl₂, concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide 2-bromo-*N*-(4-methoxybenzyl)-*N*-methylbenzene-sulfonamide **14b** in 88% yield. ¹H NMR (500 MHz, CDCl₃) δ 8.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 (td, *J* = 7.6, 1.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.1, 2.2 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 2.76 (s, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 159.8, 135.6, 133.6, 132.4, 129.6, 127.5, 120.5, 113.6, 113.2, 55.20, 54.04, 33.94; HRMS calculated for C₁₅H₁₆BrNNaO₃S (M+Na)⁺ 391.9932; found 398.9906

N-benzyl-2-bromo-N-methylbenzenesulfonamide 14a—Using a similar procedure as that used to produce sultam **14b**, sultam **14a** was produced as a yellow oil in 71% yield. FTIR (neat): 3062, 2912, 1795, 1446, 1434, 1332, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (td, *J* = 7.6, 1.8 Hz, 1H), 7.36 – 7.34 (m, 1H), 7.33 – 7.32 (m, 2H), 7.31 (d, *J* = 1.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 4.44 (s, 2H), 2.75 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 138.4, 135.8, 135.7, 133.6, 132.4, 128.7, 128.2, 127.8, 127.6, 120.3, 77.2, 77.0, 76.7, 54.1, 33.9; HRMS calculated for C₁₄H₁₄BrNNaO₂S (M+Na)⁺ 361.9827; found 361.9843

N,N-dibenzyl-2-bromobenzenesulfonamide 14c—Using a similar procedure as that used to produce sultam **14b**, sultam **14a** was produced as a white solid in 96% yield. Mp: 110 °C; FTIR (neat): 1332, 1159, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.48 – 8.09 (m, 1H), 8.09 – 7.65 (m, 1H), 7.58 – 7.16 (m, 8H), 7.16 – 6.91 (m, 4H), 4.42 (s, 4H); ¹³C NMR

(126 MHz, CDCl₃) δ ppm 139.7, 135.6, 135.4, 133.6, 132.5, 128.6, 128.6, 127.8, 127.6, 120.8, 50.2; HRMS calculated for C₂₀H₁₈BrNNaO₂S (M+Na)⁺ 452.0170; found 452.0238.

Dibenzo[d,f][1,2]thiazepine, 6,7-dihydro-6-methyl-, 5,5-dioxide 15a—Using a similar procedure as that used to produce sultam **13a**, sultam **15a** was produced in 85% as a yellow oil. FTIR (neat): 1635, 1336, 1166, 1095, 977 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.01 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.73 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.57 (td, *J* = 7.7, 1.3 Hz, 1H), 7.54–7.42 (m, 4H), 3.78 (s, 2H), 2.89 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 140.9, 139.4, 134.8, 133.5, 133.3, 130.2, 129.9, 129.5, 129.0, 128.5, 128.3, 127.5, 56.1, 39.0; HRMS calculated for C₁₄H₁₃NNaO₂S (M+Na)⁺ 282.0565; found 282.0553.

Sultam 15b—Using a similar procedure as that used to produce sultam **13a**, sultam **15b** was produced in 56% yield as a yellow oil. FTIR (neat): 3335, 1636, 1340, 1120, 967 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.00 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.3 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.56 (td, *J* = 7.7, 1.3 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.93 (dd, *J* = 2.7, 8.3 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 2H), 2.85 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 160.2, 142.1, 139.3, 134.7, 133.3, 131.4, 128.4, 127.5, 125.6, 114.6, 113.7, 55.5, 55.3, 38.9; HRMS calculated for C₁₅H₁₅NNaO₃S (M+Na)⁺ 312.0670; found 312.0652.

Sultam 15c—Using a similar procedure as that used to produce sultam **13a**, sultam **15c** was produced in 95% yield as a yellow oil. FTIR (neat): 3058, 3028, 1446, 1334, 1168, 912, 746 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.07 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H), 7.58 (ddd, *J* = 10.5, 8.7, 4.4 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.57 (td, *J* = 7.6, 1.1 Hz, 1H), 7.42 (d, *J* = 7.1 Hz, 2H), 7.40–7.34 (m, 3H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 4.45 (s, 2H), 3.70 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 135.8, 133.6, 133.2, 130.1, 129.9, 129.4, 129.0, 128.7, 128.6, 128.5, 128.3, 127.9, 127.0, 55.0, 52.7; HRMS calculated for C₂₀H₁₇NNaO₂S (M+Na)⁺ 358.0878; found 358.0868.

(S)-2-Bromo-N-(but-3-enyl)-N-(1-hydroxy-3-phenylpropan-2-yl) benzenesulfonamide (16)—A flame-dried flask was charged with the homo allylated sulfonamide (0.917g, 2.027mmol) and Et₂O (4 mL) and cooled to 0 °C. LiAlH₄ (81 mg, 2.128 mmol) was added portion-wise to the reaction mixture over 10 min after which the reaction was allowed to warm to RT and stirred for 1 h. The reaction was quenched using the Fieser work up procedure. The organic layer was extracted with Et₂O (5 mL × 2), dried (Na₂SO₄), concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to afford the alcohol in 95% yield. FTIR (neat): 3527, 3028, 1446, 1326, 1124, 919, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.83–7.79 (m, 2H), 7.58–7.54 (m, 1H), 7.50–7.45 (m, 1H), 7.24–7.16 (m, 2H), 7.02–6.98 (m, 1H), 5.78 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.12 (dd, *J* = 3.1, 1.5 Hz, 1H), 5.09 (td, *J* = 3.3, 1.9 Hz, 1H), 5.07 (s, 1H), 4.03–3.97 (m, 1H), 3.60 (t, *J* = 6.1 Hz, 1H), 3.41 (dt, *J* = 8.3, 7.3 Hz, 1H), 3.31–3.23 (m, 1H), 2.70 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.61 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.47 (dt, *J* = 14.5, 7.2 Hz, 1H), 1.97 (t, *J* = 5.9, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 140.5, 137.4, 134.9, 132.6, 129.1, 128.9, 128.6, 127.2, 126.7, 117.4, 77.3, 77.2, 77.0, 76.8, 62.2, 62.1, 44.3, 36.3, 35.4. HRMS calculated for C₁₉H₂₂NBrNaO₃S (M+Na)⁺ 446.0401; found 446.0402.

Procedure for intramolecular O-arylation reaction 17—To sulfonamide **16** (0.301 g, 0.70 mmol) was added CuI (0.117 mmol, 22 mg), ethylene glycol (0.26 mL, 4.702 mmol), Cs₂CO₃ (1.53 g, 4.70 mmol) and DMF (3 mL) under Ar. The crude mixture was heated at 120 °C for 12–24 h, till the SM is consumed, as indicated on TLC. After 24 h the reaction mixture was cooled to RT, filtered through a small Celite pad, thoroughly washed with CH₂Cl₂,

concentrated under reduced pressure and purified using flash chromatography (4:1 hexane:EtOAc) to provide **19** in 49% yield as a yellow oil. $[\alpha]_D^{25} = -56.7$; (c 2.39, CHCl₃); FTIR (neat): 3064, 1593, 1440, 1218, 1153, 1008, 918 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.83 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.36 (dddd, *J* = 19.4, 17.4, 12.1, 4.5 Hz, 6H), 7.17 – 7.11 (m, 1H), 7.03 – 6.97 (m, 1H), 5.56 (dddd, *J* = 16.3, 13.6, 9.5, 6.8 Hz, 1H), 4.94 (s, 1H), 4.91 (dd, *J* = 3.7, 2.1 Hz, 1H), 4.78 (t, *J* = 12.0 Hz, 1H), 4.34 (dd, *J* = 13.2, 4.6 Hz, 1H), 3.86 (s, 1H), 3.21 (dd, *J* = 13.7, 7.9 Hz, 1H), 3.06 (t, *J* = 7.7 Hz, 2H), 2.91 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.96 (dt, *J* = 14.1, 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 155.5, 137.6, 134.4, 133.4, 132.1, 129.5, 129.4, 128.8, 128.7, 126.8, 123.2, 121.3, 117.0, 73.8, 64.6, 51.4, 37.3, 32.9; FT-IR (neat): 3064, 1593, 1440, 1218, 1153, 1008, 918 cm⁻¹; HRMS calculated for C₁₉H₂₁NNaO₃S (M+Na)⁺ 366.1140; found 366.1136.

N,4-dimethyl-2 ((trimethylsilyl)ethynyl)benzene-sulfonamide 20—To a stirring solution of tosyl chloride (1.0 g, 5.24 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added Et₃N (2.2 mL) and methylamine (0.23 mL, 5.24 mmol). After stirring for 2 h, the reaction was quenched with H₂O (10 mL), the organic layer removed and the aqueous layer extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were washed with sat. brine (10 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to give the desired sulfonamide as a pale yellow solid. A portion of this crude (0.8 g, 4.31 mmol) in Et₂O (43 mL) was cooled to -78 °C and stirred for 15 mins. After such time *n*-BuLi (1.0 M, 4.31 mmol) was added drop wise to the crude mixture and the reaction was stirred for an additional 15 mins. Elemental I₂ (0.65g, 5.17 mmol) was added to the reaction mixture and after 15 mins was warmed to RT and stirred for 2 h. The reaction was quenched with aqueous sat. NH₄Cl (10 mL), extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with aqueous sat. Na₂SO₃ (10 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford sulfonamide **19** as pale yellow solid. To a portion of crude material (500 mg, 1.6 mmol) in DMF (8.2 mL) was added PdCl₂(PPh₃)₂ (33.8 mg, 0.048 mmol), PPh₃ (51 mg, 0.192 mmol), CuI (8.8 mg, 0.08 mmol) and Et₃N (0.67 mL, 4.818 mmol). After the addition of TMS acetylene (0.68 mL, 4.818 mmol), the reaction was heated to 80 °C and stirred for 14 h after which time the crude mixture was cooled to RT and concentrated under reduced pressure. The crude material was purified using flash chromatography (1:1 hexane:EtOAc) to provided **20** in 46% yield over 3 steps as a yellow oil. FTIR (neat): 2359, 1731, 1330, 1315, 1174, 1141, 846 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.72 (d, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 1.1, 0.5 Hz, 1H), 7.09 – 7.05 (m, 1H), 2.40 (d, *J* = 5.5 Hz, 3H), 2.21 (s, 3H), 0.11 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 142.9, 137.2, 135.0, 129.6, 129.6, 120.0, 103.1, 101.5, 29.4, 21.1; HRMS calculated for C₁₃H₁₉NNaO₂SSi (M+Na)⁺ 304.0803; found 304.0806.

Sultam 22—To a flame-dried Rb- flask charged with **20** (0.5 g, 0.177 mmol) was added CH₃CN (2.0 mL) and K₂CO₃ (0.7 g, 0.523 mmol) and the reaction mixture was stirred at 60 °C for 2 h. After such time, the crude reaction mixture was filtered through a silica pad, concentrated under pressure and purified by flash chromatography (4:1 hexane:EtOAc) to provide **22** in 67% yield as a yellow oil. FTIR: (neat) 2358, 2341, 1298, 1140, 790 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.39 (m, 1H), 7.31 (dd, *J* = 8.0, 0.7 Hz, 1H), 4.89 (d, *J* = 2.8 Hz, 1H), 4.35 (d, *J* = 2.8 Hz, 1H), 3.05 (s, 3H), 2.41 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 144.0, 138.9, 131.3, 130.6, 129.4, 121.5, 120.7, 84.2, 25.8, 21.8; HRMS calculated for C₁₀H₁₁NNaO₂S (M+Na)⁺ 232.0408; found 232.0392.

Sultam 23—To a flame-dried Rb-flask charged with **21** (45 mg, 0.14 mmol) and toluene (5 mL) was added Co₂(CO)₈ (52 mg, 0.15 mmol). The reaction mixture was heated at 90 °C for 2h, concentrated and the crude product was purified by column chromatography (1:1 hexanes:EtOAc) furnishing the tricyclic product in 67% yield as a yellow oil. FTIR (neat): 2948, 1780, 1323, 1147, 1122, 946, 906 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.03 (s,

1H), 7.81 (d, $J = 8.2$ Hz, 1H), 7.30 – 7.23 (m, 1H), 7.20 (s, 1H), 4.57 (d, $J = 14.4$ Hz, 1H), 3.46 – 3.33 (m, 1H), 3.29 (dd, $J = 14.4, 1.3$ Hz, 1H), 2.83 (s, 3H), 2.77 – 2.62 (m, 1H), 2.44 (s, 3H), 2.33 (dd, $J = 17.6, 1.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 206.0, 164.4, 143.7, 143.1, 142.0, 130.4, 130.0, 129.9, 129.2, 60.4, 43.6, 40.3, 39.0, 21.4; HRMS calculated for $\text{C}_{14}\text{H}_{15}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$ 300.0670; found 300.0677.

(Z)-Methyl 2-(2-benzyl-3-benzisothiazoline-1-ylidene)-acetate 25—Into a 1 dram vial was added *N*-benzyl-2-idobenzenesulfonamide (50 mg, 0.13 mmol), Et_3N (37 μL , 0.26 mmol), Bu_4NCl (50 mg, 0.13 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (2 mol%, 2.8 mg, 0.0027 mmol) and dry DMF (0.98 mL). After stirring for 5 min at RT, methyl propiolate (33 μL , 0.40 mmol) was added and the reaction vial was placed immediately into a preheated reaction block. The reaction was stirred at 110 $^\circ\text{C}$ for 14 hours after which time the reaction was cooled and concentrated under reduced pressure. The crude product was purified using flash chromatography (8:1 hexane:EtOAc) to yield **25** as a yellow oil (31.6 mg, 76%, 0.096 mmol). FTIR (neat) 2362, 1730, 1291, 1172 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.26 (dd, $J = 17.2, 1.3$ Hz, 1H), 7.92–7.83 (m, 1H), 7.73–7.63 (m, 2H), 7.38–7.21 (m, 3H), 5.25 (s, 1H), 4.79 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) 166.1, 143.1, 133.9, 133.7, 132.8, 132.1, 129.6, 129.0, 128.1, 127.3, 126.9, 121.1, 96.1, 53.6, 44.4; HRMS calculated for $\text{C}_{17}\text{H}_{15}\text{NO}_4\text{SNa}$ ($\text{M}+\text{Na}$) $^+$ 352.0619 found 352.0593 (TOF MS EI $^+$).

Sultam 26—Into a flame-dried round bottom flask was added benzothiazepeneone **10e** (0.1 g, 0.33 mmol), benzaldehyde (0.5 mL, 0.49 mmol) and EtOH (2 mL). To this mixture was added KOH (0.48 mmol) and the reaction mixture was heated at 50 $^\circ\text{C}$ for 4 h. After such time, the crude mixture was filtered and recrystallized from EtOH to produce **26** (80% yield) as a white solid. Mp 171 $^\circ\text{C}$; FTIR (neat): 3060, 1676, 1607 1172, 958 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.94 (s, 1H), 7.91 (m, 2H), 7.73 – 7.65 (m, 2H), 7.36 – 7.24 (m, 7H), 7.19 (m, 2H), 7.09 (t, $J = 7.5$ Hz, 1H), 4.24 (s, 2H), 3.52 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 192.1, 143.3, 136.9, 134.8, 134.6, 134.0, 133.4, 132.7, 130.8, 130.7, 129.9, 129.7, 129.5, 128.8, 128.6, 128.4, 126.3, 55.9, 47.8; HRMS calculated for $\text{C}_{23}\text{H}_{19}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$ 412.0984; found 412.0983.

Sultam 27—To a flame dried round bottom flask was added benzothiazepeneone (0.1 g, 0.33 mmol) and benzaldehyde (0.5 mL, 0.49 mmol) was dissolved in EtOH (2 mL). The reaction mixture was treated with KOH (0.48 mmol) and heated at 50 $^\circ\text{C}$ for 4 h. The crude product was filtered and recrystallized from EtOH producing the desired aldol product in 80% yield. To a flame-dried screw cap vial, aldol product (0.1 mmol) and ethyl vinyl ether (0.30 mmol) were heated at 70 $^\circ\text{C}$ in neat condition for overnight. The TLC analysis indicated that the reaction was complete and the crude product was purified by column chromatography (2:1 hexanes:EtOAc) to afford desired hetero-Diels-Alder product in 62% yield as a yellow oil. FTIR (neat): 2974, 1336, 1296, 1168, 1081 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.95 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.56 (td, $J = 7.7, 1.3$ Hz, 1H), 7.44 (td, $J = 7.7, 1.2$ Hz, 1H), 7.35 – 7.29 (m, 2H), 7.29 – 7.17 (m, 3H), 7.06 – 7.01 (m, 3H), 6.77 (d, $J = 7.1$ Hz, 2H), 5.20 (t, $J = 3.0$ Hz, 1H), 4.13 (d, $J = 14.6$ Hz, 1H), 3.95 (dq, $J = 9.5, 7.1$ Hz, 1H), 3.82 (d, $J = 14.6$ Hz, 1H), 3.66 (dq, $J = 9.5, 7.1$ Hz, 1H), 3.51 (t, $J = 8.2$ Hz, 1H), 3.08 (d, $J = 13.8$ Hz, 1H), 2.93 (d, $J = 13.7$ Hz, 1H), 2.20 – 2.04 (m, 2H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 147.3, 142.3, 136.9, 135.7, 134.4, 132.4, 129.3, 128.8, 128.6, 128.6, 128.4, 127.8, 127.3, 127.0, 126.9, 111.3, 97.0, 64.3, 54.0, 48.9, 39.4, 36.0, 15.3; HRMS calculated for $\text{C}_{27}\text{H}_{27}\text{NNaO}_4\text{S}$ ($\text{M}+\text{Na}$) $^+$ 484.1558; found 484.1534.

Sultam 28—To a solution of aldol **26** (0.1 g, 0.25 mmol) in EtOH (3 mL) was added phenyl hydrazine (0.1 mL, 1.0 mmol) and a drop of sulfuric acid. The reaction mixture was stirred at RT overnight. The product was obtained after concentration of the solution, filtration and

recrystallization from hexanes to afford **28** in 74% yield as a yellow oil. FTIR (neat): 1593, 1493, 1336, 1163, 1139, 746 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 8.08 – 7.91 (m, 2H), 7.54 (td, $J = 7.6$, 1.3 Hz, 1H), 7.43 (td, $J = 7.6$, 1.3 Hz, 1H), 7.32 – 7.17 (m, 6H), 7.16 – 7.00 (m, 6H), 6.95 (d, $J = 7.8$ Hz, 2H), 6.77 (t, $J = 7.3$ Hz, 1H), 4.69 (d, $J = 7.0$ Hz, 1H), 4.37 (d, $J = 13.6$ Hz, 1H), 3.97 – 3.74 (m, 2H), 3.61 (s, 1H), 3.36 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 145.8, 143.7, 140.6, 138.3, 135.0, 132.6, 130.8, 130.5, 129.5, 129.0, 128.8, 128.8, 128.5, 128.3, 128.2, 125.3, 120.4, 113.7, 76.8, 69.6, 54.4, 48.7. HRMS calculated for $\text{C}_{29}\text{H}_{25}\text{N}_3\text{NaO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 502.1565; found 502.1560.

Sultam 29—To a solution of aldol product **26** (50 mg, 0.128 mmol) in EtOH (3 mL), was added malononitrile (9.3 mg, 0.14 mmol) and a drop of piperidine. The reaction mixture was stirred at RT for overnight, after which time the crude reaction mixture was concentrated and the crude product was purified by column chromatography (4:1 hexanes:EtOAc) furnishing the desired product **29** in 68% yield as a clear oil. FTIR (neat): 2974, 1650, 1512, 1336, 1168, 1081, 767 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 8.10 (dd, $J = 7.8$, 1.3 Hz, 1H), 8.02 (dd, $J = 8.1$, 1.0 Hz, 1H), 7.68 (td, $J = 1.4$, 7.8 Hz, 1H), 7.54 (td, $J = 7.7$, 1.1 Hz, 1H), 7.36 – 7.27 (m, 3H), 7.22 – 7.12 (m, 5H), 6.92 – 6.84 (m, 2H), 4.65 (s, 2H), 4.02 (d, $J = 14.1$ Hz, 1H), 3.86 (s, 1H), 3.80 (d, $J = 17.8$ Hz, 1H), 3.53 (d, $J = 14.1$ Hz, 1H), 3.45 (d, $J = 17.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 158.7, 141.9, 140.3, 137.4, 134.5, 132.9, 129.2, 129.1, 128.8, 128.7, 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 118.9, 116.40, 76.8, 60.4, 52.4, 48.2, 42.8.; HRMS calculated for $\text{C}_{26}\text{H}_{21}\text{N}_3\text{NaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$ 478.1201; found 478.1211.

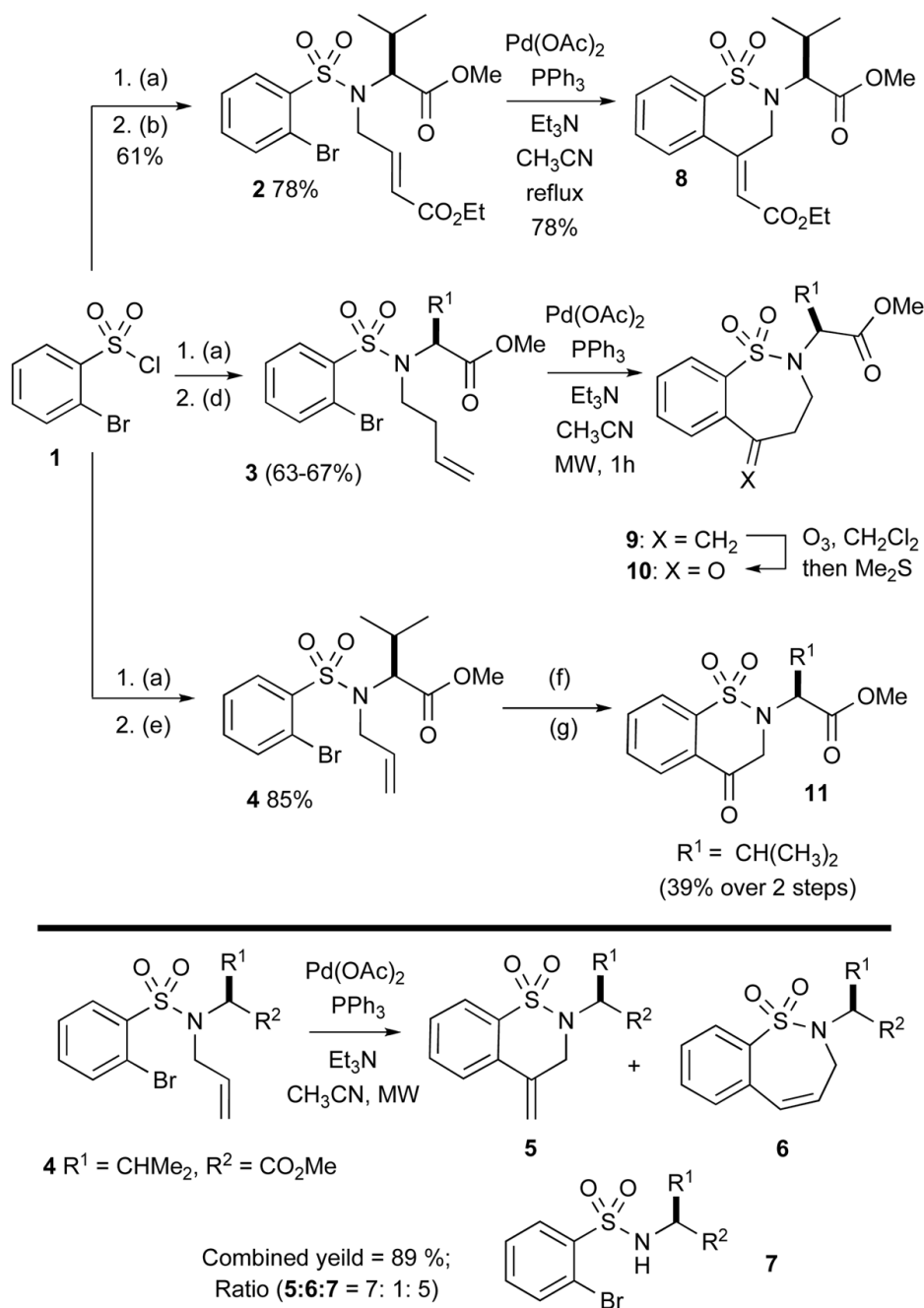
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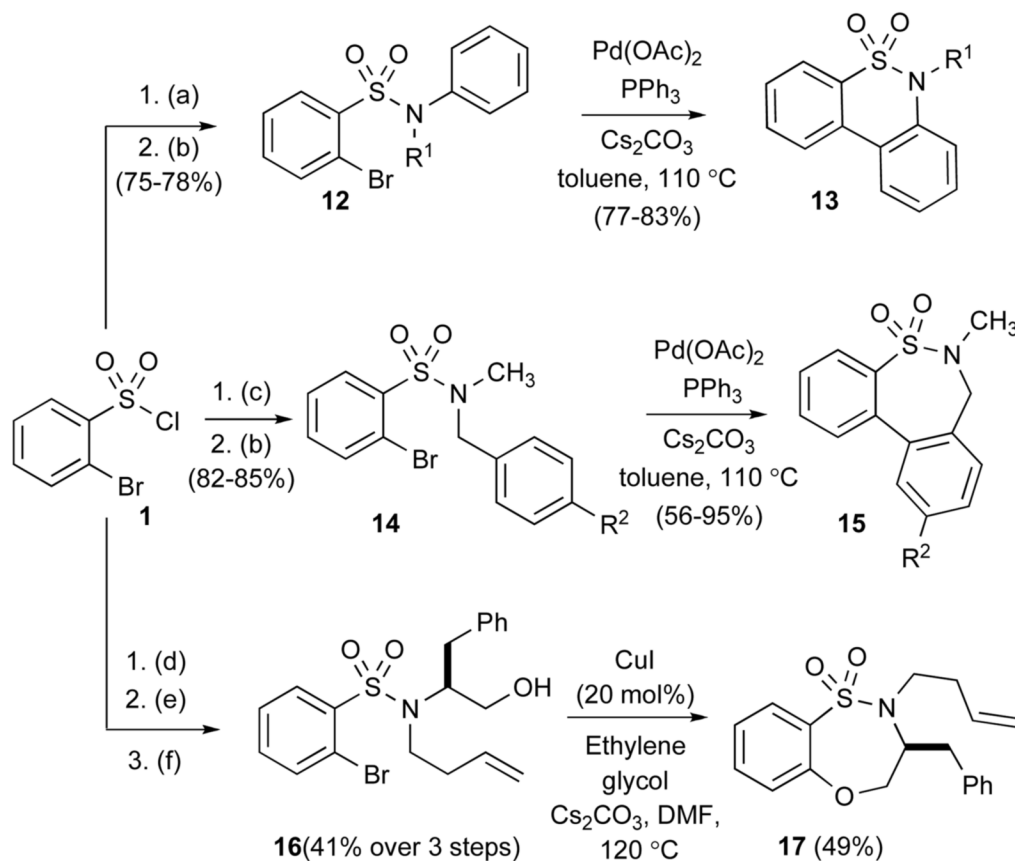
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- (xviii). Sultam 5 could not be separated from by-products and isolated for characterization. The crude reaction mixture was taken through crude and subjected to ozonolysis to afford sultam 11.
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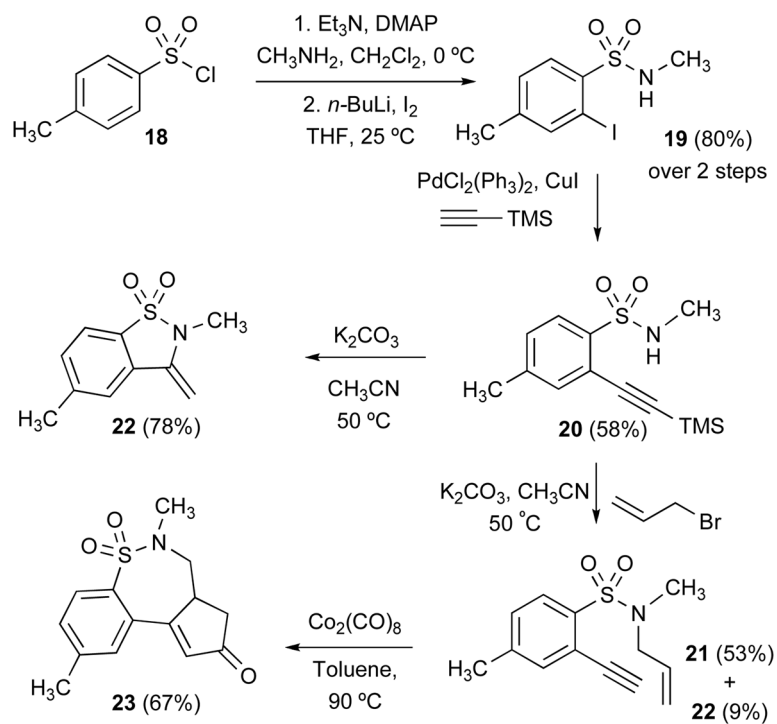
**Scheme 1.****Intramolecular Heck**

(a) Amino ester, Et₃N, DMAP, CH₂Cl₂; (b) Ethyl 4-bromocrotonate, K₂CO₃, CH₃CN, 60 °C;
 (c) Amino ester, Et₃N, DMAP, CH₂Cl₂; (d) 4-Buten-1-ol, DIAD, PPh₃, CH₂Cl₂, RT; (e) Allyl
 bromide, K₂CO₃, CH₃CN, RT; (f) Pd(OAc)₂, PPh₃, Et₃N, CH₃CN. (g) O₃, CH₂Cl₂, -78 °C
 then Me₂S.

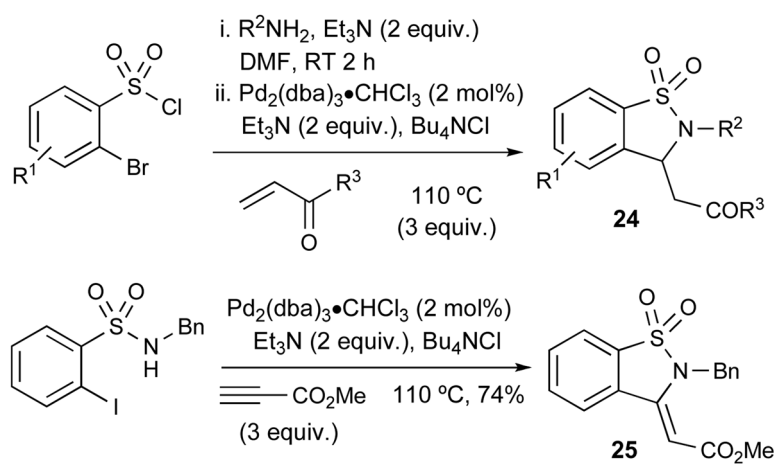
**Scheme 2.**

C- and O-arylation reactions.

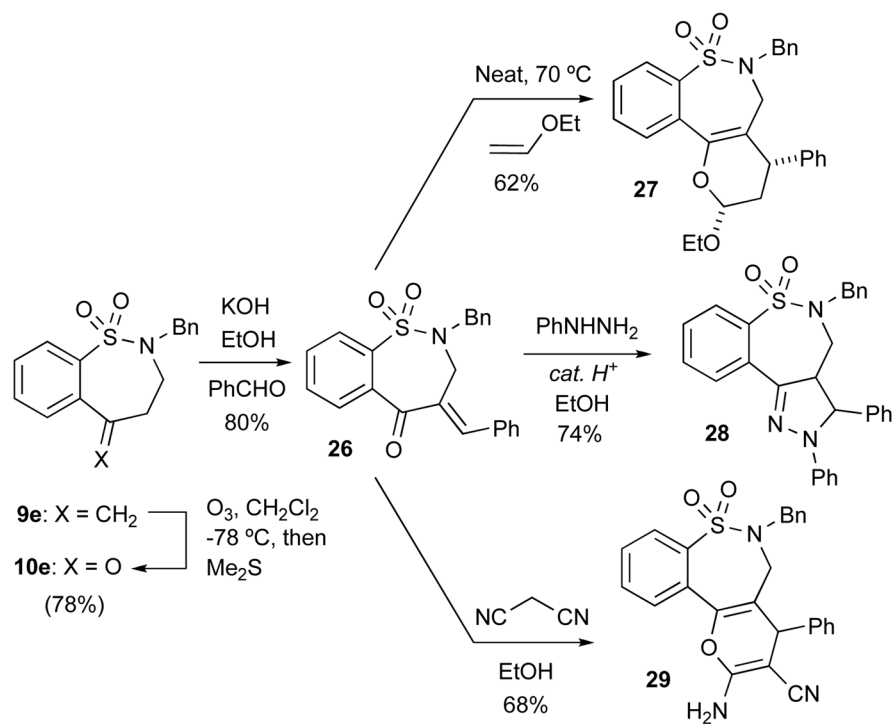
(a) Aniline, pyridine, CH_2Cl_2 ; (b) Methyl iodide or ethyl iodide, K_2CO_3 , CH_3CN , 50 °C; (c) benzyl amine, Et_3N , DMAP, CH_2Cl_2 ; (d) phenyl alanine methyl ester, Et_3N , DMAP, CH_2Cl_2 ; (e) DIAD, PPh_3 , 4-buten-1-ol (f) LiAlH_4 , THF, 0 °C to rt.



Scheme 3.
Sonogashira-PK and -IHA Strategies.

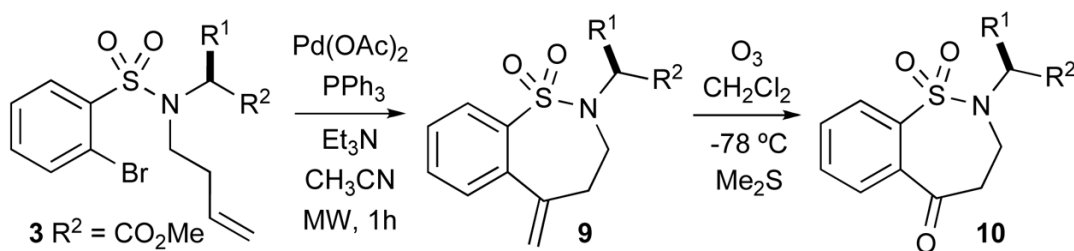


Scheme 4.
Domino aza-Michael-Heck Strategy



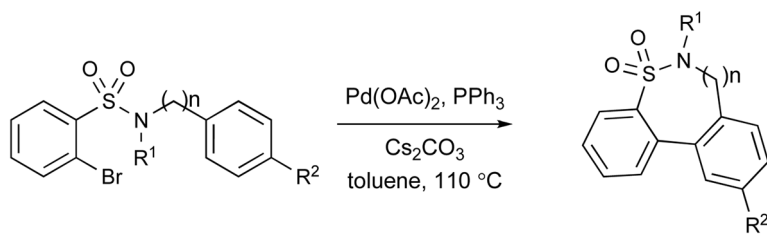
Scheme 5.
Reagent-Based DOS Approach

Table 1

Pd(0)-catalyzed Heck cyclizations of substrate **3**.^a

| entry | SM | product | 9 yield ^b % | 10 yield ^c % |
|-------|-----------|--|-------------------------------|--------------------------------|
| 1 | 3a | R ¹ = CH ₃ | 9a (72) | 10a (84) |
| 3 | 3b | R ¹ = CH ₂ CHMe ₂ | 9b (91) | 10b (82) |
| 4 | 3c | R ¹ = H | 9c (70) | 10c (78) |
| 5 | 3d | R ¹ = H, R ² = C ₆ H ₅ | 9d (62) | 10d (78) |

^a Isolated yields^b Heck conditions: substrate (1.00 mmol), Pd(OAc)₂ (0.1 mmol; 10.0 mol %), PPh₃ (0.2 mmol) in CH₃CN (0.25 M) at 100 °C for 1 h under microwave.^c O₃, -78 °C, CH₂Cl₂, then Me₂S.

Table 2Pd(0)-catalyzed C-arylation of substrates **12** and **14**.^a

| entry | SM | product | yield ^b (%) |
|-------|------------|--|------------------------|
| 1 | 12a | $n = 0, R^1 = \text{Me}, R^2 = \text{H}$ | 13a (83) |
| 2 | 12b | $n = 0, R^1 = \text{Et}, R^2 = \text{H}$ | 13b (77) |
| 3 | 14a | $n = 1, R^1 = \text{Me}, R^2 = \text{H}$ | 15a (85) |
| 4 | 14b | $n = 1, R^1 = \text{Me}, R^2 = \text{OMe}$ | 15b (56) |
| 5 | 14c | $n = 1, R^1 = \text{Bn}, R^2 = \text{H}$ | 15c (95) |

^a Isolated yields^b conditions: substrate (1.0 mmol), Pd(OAc)₂ (0.1 mmol; 10.0 mol %), PPh₃ (0.2 mmol), Cs₂CO₃ (2.0 mmol) in toluene (4.0 mL) at 110 °C in sealed tube for 12–24 h.