



NIH PUBLIC ACCESS

Author Manuscript

Tetrahedron. Author manuscript; available in PMC 2010 June 27.

Published in final edited form as:

Tetrahedron. 2009 June 27; 65(26): 4992–5000. doi:10.1016/j.tet.2009.03.080.

Metathesis Cascade Strategies (ROM-RCM-CM): A DOS approach to Skeletally Diverse Sultams

Kyu Ok Jeon, Dinesh Rayabarapu, Alan Rolfe, Kelly Volp, Iman Omar, and Paul R. Hanson

^a Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582^b The Center for Chemical Methodologies and Library Development at the University of Kansas (KU-CMLD), 2121 Simons Drive, Structural Biology Center, West Campus, Lawrence, KS 66047, USA., phanson@ku.edu

Abstract

The development of a ring-opening metathesis/ring-closing metathesis/cross metathesis (ROM-RCM-CM) cascade strategy to the synthesis of a diverse collection of bi- and tricyclic sultams is reported. In this study, functionalized sultam scaffolds derived from intramolecular Diels-Alder (IMDA) reactions undergo metathesis cascades to yield a collection tricyclic sultams. Additional appendage based diversity was achieved by utilizing a variety of CM partners.

Keywords

cascade; sultam; RCM; DOS

1. Introduction

Diversity-oriented-synthesis (DOS) has emerged as a powerful strategy in the generation of structurally complex and skeletally diverse small molecules.ⁱ Collections of such small molecules can possess a wide range of physical and biological properties and as such are ideal for probing chemical space to identify novel lead compounds.ⁱⁱ The development of simple methodology, which allows for the generation of skeletal diversity is one of the most challenging facets of DOS. A number of efficient strategies have emerged employing skeletal rearrangement utilizing both functional-group-pairing (FGP)ⁱⁱⁱ strategies and tandem metathesis (TM) strategies.^{iv} In this regard, we envisioned an approach whereby skeletally diverse sultam scaffolds could be generated using a domino ring-opening metathesis (ROM)/ring-closing metathesis (RCM)/cross metathesis (CM) cascade sequence on a readily derived oxa-norbornenyl sultam. Recently a number of strategies employing ROM-CM strategies of norbornenes, oxa-norbornenes and aza-norbornenes derivatives have appeared.^v In particular, a number of key metathesis cascades and strategies have emerged, some in the context of DOS.^{vi} Herein is reported the application of a ROM-RCM-CM strategy for the generation of a collection of skeletally diverse sultams starting from a central norbornenyl sultam core derived from a diastereoselective intramolecular Diels-Alder (IMDA) reaction (Scheme 1).

Correspondence to: Paul R. Hanson.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Sultams (cyclic sulfonamide analogs) have emerged as important targets in drug discovery due to their potent biological activities. A number of reports have highlighted an assortment of sultams that display potent activity including inhibition of COX-2 (Ampiroxicam),^{vii}·^{viii} HIV integrase,^{ix} and cysteine protease involved in the progression of malaria.^x Recently, a number of transition metal-catalyzed approaches to sultams have come to light, including ring-closing metathesis (RCM).^{xi} Our continued interest in the development of new synthetic routes towards structurally diverse sulfur-containing small molecules^{xii} for library production has prompted the following investigation on the application of metathesis cascade processes for their construction.

2. Results and discussion

The intramolecular Diels-Alder (IMDA) reaction of both vinyl sulfonates^{xiii} and vinyl sulfonamides^{xiv} with substituted furans, pioneered by Metz and coworkers, have provided an efficient route to highly versatile intermediates rich in stereochemistry and functionality. Norbornene systems of this type, possess a strained internal double bond, and thus are attractive scaffolds for application of the aforementioned metathesis cascades. To this effect, we set about the synthesis of IMDA derived sultams **1** and **2** from commercially available starting materials.^{xiv} *c* 2-Chloroethanesulfonyl chloride was coupled with furfuryl amine to afford the corresponding sulfonamide in 86 % yield. Alkylation of the resulting sulfonamide followed by in-situ IMDA afforded the corresponding tricyclic sultams **1** and **2** in 55% and 58% yield, respectively (Scheme 2), as single diastereomers.

With scaffold **1** in hand, the application of the proposed ROM-RCM-CM cascade protocol was explored. Thus, sultam **1** was subjected to 5 mol% of (IMesH₂)(PCy₃)(Cl)₂Ru=CHPh [cat-**B**],^{xv} at 0.005 M in CH₂Cl₂ at 45 °C under argon for 3 hours, to afford homodimer **3** in 84% yield. In order to circumvent this homodimerization pathway, a cross metathesis partner was used to yield the desired product. Utilization of ethylene has been well reported in the application of ROM-RCM-CM, whereby a terminal olefin is ultimately produced.^{vi} With this in mind, sultam **1** was submitted to standard cascade conditions under an atmosphere of ethylene, in ethylene degassed solvent. As anticipated, the corresponding sultam **4** bearing a terminal olefin was afforded in 74% yield with ethylene acting as the final cross-metathesis partner. Building on this result, studies were directed toward the addition of a cross-metathesis partner to prevent dimerization and incorporate an additional point of diversity.^v When **1** was resubjected in the presence of 10 equivalents of ethyl acrylate, 10 mol% of cat-**B** in 0.005 M CH₂Cl₂ at 50 °C, the desired bridged tricyclic sultam **5** derived from ROM-RCM-CM was isolated in 65% yield (Scheme 3).

With the successful application of a ROM-RCM-CM protocol, the scope of possible cross metathesis partners was investigated. These included a variety of acrylates such as methyl acrylate and *t*-butyl acrylate affording the desired products in good yield (Table 1, entries 1–3). Surprisingly, the application of methyl vinyl ketone (MVK) did not afford the desired product. In addition to acrylates, styrene and acrylonitrile were utilized as the cross-metathesis partner. It was found that under standard reaction conditions the desired products were isolated as the sole product in good yields (Table 1, entries 4–6).

With this result in hand, application of the metathesis cascade was applied to the propargyl-substituted sultam **2**. In this case, a ring-opening metathesis/ring-closing enyne metathesis/cross-metathesis (ROM-RCEM-CM) sequence was envisioned as a means of generating skeletal diversity. Moreover, reaction of sultam **2** in the presence of ethylene would afford the desired product **11** bearing a diene motif, allowing for additional incorporation of diversity via a [4+2] cycloaddition with activated dienophiles. However, when sultam **2** was submitted to the ROM-RCEM-CM conditions none of the desired product was obtained, instead the

corresponding bicyclic tetraene **12** was isolated in good yield (75%). This result indicates that sultam **2** undergoes an intermolecular enyne metathesis with ethylene instead of the corresponding intramolecular process. Subsequent heating of **12** with maleimide afforded the corresponding [4+2] *cis*-cycloadduct **13** in 83% yield as an inseparable, 1:1 mixture of diastereomers (Scheme 5).^{xvi}

Building on these results, we investigated the synthesis of a modified sultam scaffold whereby the simple relocation of the allyl group in **1** by one carbon would allow for the generation of new tricyclic sultams **15–17** (Scheme 6). Relocation of the tethered allyl group also enhances structural diversity by yielding a new fused ring system. Thus, 2-furaldehyde was condensed with *p*-methoxy benzyl amine generating the corresponding imine, which was subsequently converted to the requisite furfuryl-substituted allyl amine by the addition of allyl magnesium bromide. Sulfonylation with 2-chloroethane sulfonyl chloride produced the corresponding vinyl sulfonamide **14**, which when heated at 100 °C for 12 h afforded the desired IMDA derived scaffold **15** in 95% as a mixture of diastereomers (~1:1).^{xvii} Addition of cat-**B** to sultam **15** in the presence of ethylene afforded the desired tricyclic sultam **16** as a single diastereoisomer via a ROM-RCM-CM cascade. Spectroscopic analysis including key ¹H NMR nOe studies determined that diastereomer **15a** selectively underwent cyclization to give the *cis*-fused tricyclic sultam **16**.

In addition to the formation of **16**, a small amount of sultam **17** resulting from ROM-CM of diastereomer **15b** with ethylene was isolated. It is proposed that in the case of diastereomer **15b**, an unfavourable steric interaction between the homoallyl substituent and the oxo-bridge, prevents proper alignment between the ruthenium alkylidene and the norbornenyl olefin, thus hindering metathesis. However, this interaction is alleviated in the case of the diastereomer **15a**, where the allyl group is oriented away from the oxygen bridge under the bicyclic ring in direct proximity of the strained norbornenyl olefin (Scheme 7). In addition to steric effects, the corresponding cyclized RCM product of **17** would have a *trans* ring junction in a bicyclo[3.3.0] ring system which under the reversible conditions of the reaction would most likely be disfavored.

During this investigation we were concurrently developing the synthesis of an IMDA-derived sultam **21** bearing additional handles and therefore probed its utility in the metathesis cascade protocol. In this regard, *N*-Boc phenylalanine was converted to the corresponding Weinreb amide and treated with lithiated furan. Subsequent reduction of the furyl ketone yielded the corresponding *N*-Boc amino alcohol **20** as a mixture of diastereoisomers (~2:1) in 64% yield over 3 steps.^{xviii} Removal of the Boc-group furnished the corresponding amino alcohol, which was taken on crude to a one-pot, sulfonylation/diastereoselective IMDA sequence to afford the desired tricyclic sultam **21**, as a single diastereoisomer in 52% yield over three steps (Scheme 8).^{xiv}

From a DOS perspective, sultam **21** represents an attractive scaffold due to a number of features, including (i) the presence of both free hydroxy (OH) and free sulfonamide (NH) groups, (ii) structural rigidity, (iii) stereochemistry and (iv) peripheral functionality. These features allow for the generation of focused libraries to probe chemical space via two approaches. One is via simple peripheral diversification and the second is via skeletal diversity utilizing the aforementioned ROM-RCM-CM cascade protocol. To this effect, chemoselective *O*-allylation of **21** yielded the desired intermediate **22**,^{xix} which when submitted to the standard ROM-RCM-CM sequence yielded the desired tricyclic sultam **23** in 90% yield (Scheme 9).

Building on this result, selective acylation of **21** yielded the corresponding sultam intermediate **24** in 92% yield. Submission to the standard metathesis cascade conditions in the presence of ethylene yielded the triene sultam **25** as the sole product via a ROM-CM process. Taken

collectively, sultams **1**, **15** and **21** are tricyclic, IMDA-derived scaffolds that upon submission to the metathesis cascade protocol generate skeletally diverse [6.6.5] or [6.5.5] fused-ring sultam systems. In addition, both pathways retain a functional handle (SO₂NH) for late stage peripheral diversification. Ultimately, selective choice of the olefin appendage in **21** allows additional skeletal diversity in the formation of either tricyclic sultam **23** or bicyclic sultam **25**, presumably due to variable olefin reactivity Types (I, II, III or IV) as defined by Grubbs affecting the site of the initial metathesis event.^{xx}

The synthesis of a sultam scaffold bearing an ester functional handle was envisioned as an alternative strategy towards the synthesis of functionalized derivatives of **1**. This goal could be achieved via incorporation of the ester moiety in the dienophile component of the IMDA protocol, as reported by Overman and coworkers.^{xxi} To this effect, furfurylamine was mesylated then subsequently allylated to yield sulfonamide **26** in 82% over 2 steps. Generation of the phosphonate, followed by Horner-Wadsworth-Emmons reaction, yielded a mixture of uncyclized sulfonamide **27** and IMDA-derived sultam **28** after purification to remove any remaining starting material. Addition of hexane to the crude mixture resulted in the sole precipitation of **28**, yielding X-ray quality crystals (Scheme 10).

It is noteworthy to mention that it was observed that in both CDCl₃ and d₄-MeOD, sultam **28** undergoes retro-IMDA to the corresponding sultam **27** over time.^{xxii} It is believed that the nature of the solvent catalyzes the retro IMDA reaction indicating the increased reactivity of the bridged tricyclic system in comparison to sultams **1** and **15**. Despite this observation, the corresponding sultam **28** underwent the metathesis cascade transformation in the presence of ethylene in CH₂Cl₂ to yield the desired tricyclic sultam **29** (Scheme 11). Formation of an additional lactone ring was achieved using iodolactonization between the ethyl ester and the terminal olefin in the presence of I₂ to afford polycyclic product **30** as a single isomer, albeit in low yield.

Conclusion

In conclusion, the synthesis of a collection of diverse bi- and tricyclic sultams has been achieved in an overall DOS approach utilizing a ROM-RCM-CM cascade strategy. A variety of functionalized, tricyclic sultams were generated as precursors for the metathesis cascade strategy. These precursors were derived from a diastereoselective IMDA reaction in good yields and selectivity. The ROM-RCM-CM proceeded in good to excellent yields generating sultams possessing both skeletal and appendage-based diversity that was controlled by elements incorporated into the sultam precursors or via the cross metathesis partner selected.

3. Experimental Section

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannulas and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH₃CN was purified by passage through the Solv-Tek purification system employing activated Al₂O₃ (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). Et₃N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO₂ obtained from Sorbent Technologies (30930M-25, Silica Gel 60A, 40–63 μm). Metathesis catalysts were provided by Materia, Inc. and used without further purification. Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively; or a Bruker Avance operating at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Melting points were obtained on a Thomas Hoover capillary

melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

6H-3a,6-Epoxy-1,2-benzisothiazole, 2,3,7,7a-tetrahydro-2-allyl, 1,1-dioxide [(±) **1**]

Into a flame dried flask under argon was added furfurylamine (1.05 mL, 11.9 mmol), Et₃N (1.66 mL, 11.9 mmol), and dry CH₂Cl₂ (20 mL). After stirring at 0 °C for 10 min, 2-chloroethanesulfonyl chloride (0.96 mL, 9.2 mmol) was added and the reaction flask stirred at rt for 2 h. The crude reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude material was dissolved in dry CH₃CN (50 mL, 0.2 M) to which K₂CO₃ (3.9 g, 32.0 mmol) was added. After stirring for 5 mins, allyl bromide (2.8 mL, 32.0 mmol) was added and the reaction mixture was stirred at 60 °C, until SM disappeared as monitored by TLC analysis. After such time, the crude reaction mixture was filtered through a pad of celite, concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to yield **1** (1.15 g, 5.0 mmol, 55%) as a white solid. Mp 98 °C; FTIR (neat): 1442, 1301, 1068, 1137 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.53 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.37 (d, *J* = 5.7 Hz, 1H), 5.88 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.30 (ddq, *J* = 24.7, 10.1, 1.3 Hz, 2H), 5.23 (dd, *J* = 4.5, 1.7 Hz, 1H), 3.84 (d, *J* = 11.3 Hz, 1H), 3.80 – 3.75 (m, 2H), 3.62 (d, *J* = 11.3 Hz, 1H), 3.18 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.61 – 2.55 (m, 1H), 1.81 (dd, *J* = 12.3, 7.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 139.5, 134.1, 132.4, 119.7, 90.5, 79.7, 60.5, 48.9, 47.6, 29.2; HRMS calculated for C₁₀H₁₃NNaO₃S (M+Na)⁺ 250.0514; found 250.0518.

6H-3a,6-Epoxy-1,2-benzisothiazole, 2,3,7,7a-tetrahydro-2-propargyl, 1,1-dioxide [(±) **2**]

Using a similar procedure as that used to produce sultam **1**, *N*-(2-furanylmethyl) ethanesulfonamide (1.0 g, 5.28 mmol), propargyl bromide (2.8 ml, 32.0 mmol) yielded **2** (68.9 mg, 3.0 mmol, 58%) as a white solid. Mp 150 °C; FTIR (neat): 3226, 1304, 1282, 1140 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.55 (dd, *J* = 1.7, 5.7 Hz, 1H), 6.42 (d, *J* = 5.7 Hz, 1H), 5.26 (dd, *J* = 4.5, 1.6 Hz, 1H), 4.10 – 4.02 (m, 2H), 3.93 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.81 (d, *J* = 11.4 Hz, 1H), 3.18 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.61 – 2.55 (m, 1H), 2.37 (t, *J* = 2.5 Hz, 1H), 1.81 (dd, *J* = 12.4, 7.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 139.5, 134.1, 90.7, 79.8, 76.8, 74.1, 60.5, 48.8, 34.7, 29.1; HRMS calculated for C₁₀H₁₁NNaO₃S (M+Na)⁺ 248.0357; found 248.0347.

Sultam (**3**)

To a flame dried flask was added dry CH₂Cl₂ (95 mL, 0.005 M), which was degassed for 30 min with argon. After such time, sultam **1** (0.1 g, 0.44 mmol) and cat-**B** (0.04 g, 0.044 mmol) were added and the reaction mixture was refluxed at 45 °C for 3 h. The crude reaction mixture concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide **3** (15.7 mg, 0.36 mmol, 84% yield) as a white solid. Mp 227 °C; FTIR (neat): 1336, 1164, 1112 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.28 (ddd, *J* = 10.1, 5.1, 2.1 Hz, 1H), 5.76 (ddd, *J* = 6.7, 3.4, 1.7 Hz, 1H), 5.55 (dt, *J* = 10.1, 2.5 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 4.19 (dt, *J* = 19.5, 2.5 Hz, 1H), 3.79 (dt, *J* = 19.6, 2.2 Hz, 1H), 3.71 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.59 (dd, *J* = 12.2, 1.9 Hz, 1H), 3.24 (dd, *J* = 12.2, 1.8 Hz, 1H), 2.71 (dddd, *J* = 14.0, 8.1, 5.8, 2.1 Hz, 1H), 2.14 – 2.06 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 134.2, 134.2, 131.2, 130.9, 124.1, 124.1, 87.6, 80.9, 80.7, 71.0, 71.0, 51.9, 50.9, 34.1, 34.1; HRMS calculated for C₁₈H₂₂N₂NaO₆S₂ (M+Na)⁺ 449.0817; found 449.0816.

General Procedure A for ROM-RCM-CM metathesis cascade

To a flame dried flask was added dry CH₂Cl₂ (0.005 M), which was degassed for 30 min with argon. To this was added, sultam (1 eq.), cat-**B** (10 mol%) and CM partner (10 eq.). The reaction mixture was refluxed at 45 °C for 3 h. The crude reaction mixture was concentrated under

reduced pressure and purified by flash chromatography (1:1 hexane: EtOAc) to afford the desired compound.

Sultam [(±) 4]

According to general procedure **A**, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) was added to ethylene degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **4** [50 mg, 0.22 mmol, 74%] as a yellow solid. Mp 91 °C; FTIR (neat): 2925, 1350, 1338, 1166 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.28 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.80 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.57 – 5.48 (m, 1H), 5.33 – 5.25 (m, 1H), 5.19 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.82 (dd, *J* = 14.6, 6.9 Hz, 1H), 4.18 (dt, *J* = 19.5, 2.4 Hz, 1H), 3.76 (dt, *J* = 19.5, 2.2 Hz, 1H), 3.70 (ddd, *J* = 10.9, 6.0, 1.9 Hz, 1H), 3.59 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.23 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.68 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 2.09 (ddd, *J* = 14.1, 10.9, 7.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 135.6, 133.5, 123.0, 116.4, 86.6, 81.4, 70.2, 51.1, 50.0, 33.0; HRMS calculated for C₁₀H₁₃NNaO₃S (M+Na)⁺ 250.0514; found 250.0507.

Sultam [(±) 5]

According to general procedure **A**, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and ethyl acrylate (3.2 mL, 30 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **5** [58 mg, 0.19 mmol, 65%] as a pale yellow solid. Mp 232 °C; FTIR (neat): 1716, 1350, 1269, 1167 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.85 (dd, *J* = 15.6, 5.0 Hz, 1H), 6.30 (d, *J* = 10.1 Hz, 1H), 6.04 (d, *J* = 15.6 Hz, 1H), 5.57 (d, *J* = 10.1 Hz, 1H), 5.02 (dd, *J* = 6.7, 13.4 Hz, 1H), 4.24 – 4.16 (m, 3H), 3.82 – 3.75 (m, 1H), 3.75 – 3.69 (m, 1H), 3.62 – 3.56 (m, 1H), 3.30 – 3.25 (m, 1H), 2.83 – 2.74 (m, 1H), 2.21 – 2.12 (m, 1H), 1.32 – 1.27 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 165.9, 144.7, 134.0, 124.2, 121.7, 88.0, 80.0, 70.5, 60.8, 52.1, 51.0, 33.5, 14.2; HRMS calculated for C₁₃H₁₇NNaO₅S (M+Na)⁺ 322.0725; found 322.0698.

Sultam [(±) 6]

According to general procedure **A**, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and methyl acrylate (2.7 mL, 30 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **6** [48 mg, 0.16 mmol, 56%] as a pale yellow solid. Mp 144 °C; FTIR (neat): 1722, 1350, 1340, 1167 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.86 (d, *J* = 13.8 Hz, 1H), 6.30 (d, *J* = 8.0 Hz, 1H), 6.05 (d, *J* = 15.3 Hz, 1H), 5.56 (d, *J* = 7.9 Hz, 1H), 5.02 (s, 1H), 4.19 (d, *J* = 19.2 Hz, 1H), 3.85 – 3.53 (m, 6H), 3.28 (d, *J* = 11.6 Hz, 1H), 2.78 (s, 1H), 2.16 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 166.3, 145.0, 133.9, 124.2, 121.2, 88.0, 80.0, 70.5, 52.1, 51.9, 50.9, 33.5; HRMS calculated for C₁₂H₁₅NNaO₅S (M+Na)⁺ 308.0569; found 308.0562.

Sultam [(±) 7]

According to general procedure **A**, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and *t*-butyl acrylate (4.3 mL, 30 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **7** [76 mg, 0.23 mmol, 78%] as a yellow oil. FTIR (neat): 2978, 1711, 1352, 1314, 1165 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.77 (dd, *J* = 15.6, 5.0 Hz, 1H), 6.34 (d, *J* = 10.2 Hz, 1H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.59 (d, *J* = 10.3 Hz, 1H), 5.03 (s, 1H), 4.23 (d, *J* = 19.6 Hz, 1H), 3.87 – 3.71 (m, 2H), 3.62 (d, *J* = 12.5 Hz, 1H), 3.30 (d, *J* = 12.2 Hz, 1H), 2.80 (s, 1H), 2.19 (ddd, *J* = 14.0, 10.8, 6.6 Hz, 1H), 1.51 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 165.1, 143.4, 134.1, 124.2, 123.6, 88.0, 81.0, 80.1, 76.8, 70.6, 52.1, 50.9, 33.5, 31.0, 28.1; HRMS calculated for C₁₅H₂₁NNaO₅S (M+Na)⁺ 350.1038; found 350.1030.

Sultam [(±) 8]

According to general procedure **A**, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and styrene (3.4 mL, 30 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **8** [73 mg, 0.24 mmol, 81%] as a brown liquid. FTIR (neat): 1348, 1338, 1164, 1132, 968, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.39 (dd, *J* = 5.0, 3.4 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.28 (dt, *J* = 4.7, 1.9 Hz, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.34 (dq, *J* = 10.1, 2.1 Hz, 1H), 6.15 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.56 (dt, *J* = 10.1, 2.5 Hz, 1H), 5.01 (q, *J* = 7.2 Hz, 1H), 4.22 (dt, *J* = 19.5, 2.5 Hz, 1H), 3.84 – 3.74 (m, 2H), 3.66 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.28 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.78 (ddd, *J* = 13.9, 8.0, 5.7 Hz, 1H), 2.21 (ddd, *J* = 14.2, 11.1, 7.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 135.9, 134.4, 132.8, 128.9, 128.3, 127.3, 126.7, 124.0, 87.5, 82.2, 71.3, 51.9, 51.0, 34.4; HRMS calculated for C₁₆H₁₇NNaO₃S (M+Na)⁺ 326.0827; found 326.0795.

Sultam [(±) 9]

According to general procedure, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and 4-bromostyrene (3.9 mL, 30 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **9** [87 mg, 0.23 mmol, 80%] as a white solid. Mp 140 °C; FTIR (neat): 1487, 1350, 1338, 1164, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 7.48 – 7.43 (m, 2H), 7.25 (dt, *J* = 9.0, 2.2 Hz, 2H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.33 (dq, *J* = 10.1, 2.1 Hz, 1H), 6.14 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.57 (dt, *J* = 10.1, 2.5 Hz, 1H), 4.99 (q, *J* = 7.1 Hz, 1H), 4.22 (dt, *J* = 19.5, 2.5 Hz, 1H), 3.84 – 3.73 (m, 2H), 3.65 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.28 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.77 (ddd, *J* = 13.9, 8.0, 5.7 Hz, 1H), 2.19 (ddd, *J* = 11.4, 11.1, 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 134.8, 134.3, 131.8, 131.5, 128.2, 128.1, 124.1, 122.1, 87.6, 81.9, 71.2, 51.9, 51.0, 34.3; HRMS calculated for C₁₆H₁₆BrNNaO₃S (M+Na)⁺ 403.9932; found 403.9619.

Sultam [(±) 10]

According to general procedure **A**, **1** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) and acrylonitrile (1.9 mL, 30 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **10** [50 mg, 0.20 mmol, 67%] as a white solid. Mp 170 °C; FTIR (neat): 1338, 1164, 1114 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.67 (dd, *J* = 16.2, 4.3 Hz, 1H), 6.28 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.67 (dd, *J* = 1.9, 16.2 Hz, 1H), 5.60 (dt, *J* = 10.1, 2.5 Hz, 1H), 5.03 – 4.96 (m, 1H), 4.21 (dt, *J* = 19.6, 2.5 Hz, 1H), 3.80 (dt, *J* = 19.6, 2.2 Hz, 1H), 3.72 (ddd, *J* = 10.8, 6.4, 1.9 Hz, 1H), 3.58 (dd, *J* = 2.0, 12.3 Hz, 1H), 3.29 (dd, *J* = 2.0, 12.3 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.16 (ddd, *J* = 14.1, 10.9, 6.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 149.9, 132.3, 123.5, 115.4, 99.4, 87.1, 78.4, 69.1, 50.9, 49.9, 32.2; HRMS calculated for C₁₁H₁₂N₂NaO₃S (M+Na)⁺ 275.0466; found 275.0468.

Sultam [(±) 12]

According to general procedure **A**, **2** (80 mg, 0.3 mmol, cat-**B** (30 mg, 0.03 mmol) was added to argon degassed, dry CH₂Cl₂ (85 mL, 0.005 M) to yield (±) **12** [63 mg, 0.23 mmol, 75%] as a brown liquid. FTIR (neat): 2927, 1597, 1311, 1150, 931 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.36 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.99 (dd, *J* = 17.0, 10.6 Hz, 1H), 5.81 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.57 – 5.44 (m, 2H), 5.33 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.28 – 5.16 (m, 5H), 4.71 – 4.65 (m, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.53 (d, *J* = 8.6 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.28 (d, *J* = 10.9 Hz, 1H), 3.10 (d, *J* = 10.9 Hz, 1H), 2.70 (dd, *J* = 5.0, 13.7 Hz, 1H), 2.00 (ddd, *J* = 8.7, 10.8, 13.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 139.4, 137.3, 136.2, 136.0, 119.9, 118.1, 116.4, 115.7, 85.7, 81.8, 66.6, 56.7, 44.7, 35.1; HRMS calculated for C₁₄H₁₉NNaO₃S(M+Na)⁺ 304.0983; found 304.0947.

Sultam [(±) 13]

To a flame dried flask containing dry toluene (0.5 mL) was added diene **12** (30 mg, 0.1 mmol) and *N*-phenylmaleimide (0.23 g, 0.13 mmol). The reaction was heated at 85 °C for 24 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (3:2 hexane:EtOAc) to yield **13** (38 mg, 8.3×10^{-5} mol, 83% yield) as a yellow oil. FTIR (neat): 1709, 1498, 1383, 1309, 1147 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.43 (dd, $J = 8.0, 16.5$ Hz, 2H), 7.36 (dd, $J = 7.5, 15.2$ Hz, 1H), 7.32 – 7.27 (m, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 5.94 (td, $J = 10.8, 16.7$ Hz, 2H), 5.80 (dddd, $J = 6.8, 10.4, 13.4, 17.0$ Hz, 1H), 5.56 – 5.47 (m, 1H), 5.37 (dd, $J = 17.2, 22.0$ Hz, 1H), 5.28 – 5.13 (m, 2H), 4.79 – 4.71 (m, 1H), 3.81 (d, $J = 14.1$ Hz, 1H), 3.52 (d, $J = 8$ Hz, 1H), 3.42 – 3.22 (m, 3H), 3.16 (dd, $J = 5.5, 10.8$ Hz, 1H), 3.06 (dd, $J = 3.0, 10.8$ Hz, 1H), 2.76 – 2.64 (m, 3H), 2.47 – 2.32 (m, 2H), 2.00 (ddd, $J = 7.7, 14.1, 17.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 178.8, 178.7, 178.4 (2), 137.3, 137.2, 136.3, 136.2, 134.4, 134.0, 131.9 (2), 129.1, 129.0, 128.6, 128.5, 126.4 (2), 125.7, 125.6, 118.2, 117.8, 116.6, 116.5, 86.0, 85.7, 82.2, 81.7, 66.7 (2), 57.9, 57.0, 49.5, 49.2, 39.4, 39.0, 38.9 (2), 34.9, 34.8, 25.6 (2), 24.3, 24.1; HRMS calculated for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{NaO}_5\text{S}$ ($\text{M} + \text{Na}$) $^+$ 477.1460; found 477.1436.

Sultam [(±) 15]

To a flame dried flask under argon was added furfural (1.72 mL, 20.8 mmol), 4-methoxybenzylamine (2.7 mL, 20.8 mmol), MgSO_4 (3.0 g) and dry CH_2Cl_2 (20 mL). After stirring at RT for 6 h, the crude reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was dissolved in THF (20 mL) to which was added allyl magnesium bromide (5.57 mL, 11.15 mmol). The reaction mixture was stirred for 5 h. after which time NH_4Cl (sat. aq., 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4×20 mL) and the combined organic layer was dried (MgSO_4). The crude reaction mixture **14** (1.2 g) was solvated in dry toluene (5 mL) and heated at reflux for 12 h. After such time the crude reaction mixture concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to provide the desired compound (95% yield) as a yellow liquid. FTIR (neat): 1612, 1514, 1301, 1247, 1137 cm^{-1} ; [Mixture of Diastereoisomers (1:1)] ^1H NMR (500 MHz, CDCl_3) δ ppm 7.37 (d, $J = 8.6$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 1H), 6.95 – 6.81 (m, 4H), 6.52 (dd, $J = 5.8, 1.7$ Hz 1H), 6.47 – 6.38 (m, 3H), 6.18 (d, $J = 5.7$ Hz, 1H), 5.93 – 5.78 (m, 1H), 5.74 – 5.58 (m, 1H), 5.28 (dd, $J = 4.5, 1.5$ Hz 1H), 5.22 – 5.14 (m, 2H), 5.09 – 4.97 (m, 2H), 4.51 (d, $J = 15.7$ Hz, 1H), 4.41 (d, $J = 15.3$ Hz, 1H), 4.28 (dd, $J = 15.5, 8.7$ Hz 2H), 3.81 (dd, $J = 8.9, 5.6$ Hz, 6H), 3.72 (t, $J = 5.3$ Hz, 1H), 3.24 (dd, $J = 7.9, 3.2$ Hz, 1H), 3.13 (dd, $J = 7.8, 3.3$ Hz, 1H), 2.74 – 2.59 (m, 1H), 2.56 – 2.48 (m, 1H), 2.45 (t, $J = 7.2$ Hz, 1H), 1.80 (td, $J = 12.4, 7.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 159.3, 159.2, 139.7, 137.9, 135.3, 132.9, 132.6, 132.1, 130.0, 129.9, 127.6, 127.3, 119.4, 118.9, 114.1, 114.1, 94.5, 92.2, 79.4, 78.8, 60.4, 59.7, 58.6, 58.4, 55.3, 55.3, 46.6, 46.0, 34.6, 33.8, 30.1, 29.5; HRMS calculated for $\text{C}_{18}\text{H}_{21}\text{NNaO}_4\text{S}$ ($\text{M} + \text{Na}$) $^+$ 370.1089; found 370.1075.

Sultam [(±) 16]

According to general procedure **A**, **15** (0.06 g, 0.17 mmol), cat-**B** (0.015 g, 0.017 mmol) in ethylene degassed CH_2Cl_2 (35 mL). The crude reaction was purified by flash chromatography (2:1 hexane:EtOAc) to provide **16** (32 mg, 54%) and **17** (10 mg, 16%). FTIR (neat): 1612, 1514, 1305, 1249, 1149 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.42 – 7.22 (m, 2H), 7.11 – 6.74 (m, 2H), 6.10 – 5.87 (m, 1H), 5.80 (ddd, $J = 17.1, 10.4, 6.6$ Hz, 1H), 5.72 (dt, $J = 5.7, 2.2$ Hz, 1H), 5.30 (dt, $J = 17.2, 1.2$ Hz, 1H), 5.23 – 5.15 (m, 1H), 4.52 – 4.38 (m, 2H), 4.05 (d, $J = 14.4$ Hz, 1H), 3.82 (d, $J = 5.2$ Hz, 3H), 3.64 – 3.54 (m, 2H), 2.75 (ddd, $J = 13.8, 5.5, 2.0$ Hz, 1H), 2.64 – 2.43 (m, 2H), 2.12 (dt, $J = 13.8, 9.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 159.5, 135.9, 135.1, 130.4, 130.2, 126.8, 118.0, 114.1, 97.3, 80.1, 64.6, 63.8, 55.3, 45.4, 35.5, 35.2; HRMS calculated for $\text{C}_{18}\text{H}_{21}\text{NNaO}_4\text{S}$ ($\text{M} + \text{Na}$) $^+$ 370.1089; found 370.1087.

Sultam [(±) 17]

FTIR (neat): 1514, 1303, 1247, 1145 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.31 (d, $J = 8.7$ Hz, 2H), 6.90 – 6.85 (m, 2H), 5.97 – 5.81 (m, 2H), 5.72 (dddd, $J = 11.7, 9.5, 7.5, 6.4$ Hz, 1H), 5.56 – 5.48 (m, 1H), 5.39 (ddd, $J = 12.5, 4.3, 3.1$ Hz, 2H), 5.27 – 5.20 (m, 1H), 5.00 – 4.92 (m, 2H), 4.76 (dd, $J = 11.0, 5.9$ Hz, 1H), 4.42 (d, $J = 15.8$ Hz, 1H), 4.10 (d, $J = 15.8, 1\text{H}$), 3.84 – 3.78 (s, 3H), 3.55 (d, $J = 8.4$ Hz, 1H), 3.38 (dd, $J = 7.4, 5.2$ Hz, 1H), 2.75 (ddd, $J = 13.6, 5.1, 0.9$ Hz, 1H), 2.47 – 2.38 (m, 1H), 2.34 – 2.26 (m, 1H), 2.02 (ddd, $J = 13.6, 10.8, 8.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 159.5, 139.1, 136.8, 129.8, 118.1, 118.1, 117.1, 114.3, 88.5, 82.4, 66.9, 66.1, 55.7, 46.0, 35.1, 32.5; HRMS calculated for $\text{C}_{20}\text{H}_{25}\text{NNaO}_4\text{S}$ ($\text{M}+\text{Na}$) $^+$ 398.1402; found 398.1401.

Sultam [(±) 18]

According to general procedure **A**, **15** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), ethyl acrylate (3.0 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield (\pm) **18** [61 mg, 0.147 mmol, 49%] as a yellow oil. FTIR (neat): 1718, 1514, 1303, 1149 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.28 – 7.24 (m, 2H), 6.90 – 6.82 (m, 3H), 6.01 (ddd, $J = 9.7, 7.9, 1.9$ Hz, 2H), 5.71 (dt, $J = 2.2, 5.7$ Hz, 1H), 4.65 – 4.60 (m, 1H), 4.46 (d, $J = 14.4$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.04 (d, $J = 14.4$ Hz, 1H), 3.81 (s, 3H), 3.63 (dd, $J = 9.7, 1.9$ Hz, 1H), 3.59 (dd, $J = 7.2, 3.7$ Hz, 1H), 2.63 – 2.44 (m, 3H), 2.14 (dt, $J = 13.8, 9.9$ Hz, 1H), 1.28 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 165.9, 159.5, 144.1, 135.4, 130.2, 130.1, 126.7, 122.2, 114.2, 97.8, 76.8, 64.6, 63.6, 60.7, 55.3, 45.5, 35.3, 35.2, 14.2; HRMS calculated for $\text{C}_{21}\text{H}_{25}\text{NNaO}_6\text{S}$ ($\text{M}+\text{Na}$) $^+$ 442.1300; found 442.1283.

Sultam [(±) 19]

According to general procedure **A**, **15** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), *t*-butyl acrylate (4.3 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield (\pm) **19** [69 mg, 0.156 mmol, 52%] as a yellow oil. FTIR (neat): 2978, 1710, 1514, 1308, 1151 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ ppm 7.27 – 7.23 (m, 2H), 6.90 – 6.85 (m, 2H), 6.74 (dd, $J = 15.7, 5.3$ Hz, 1H), 6.01 – 5.98 (m, 1H), 5.94 (dd, $J = 15.7, 1.4$ Hz, 1H), 5.71 (dt, $J = 5.7, 2.2$ Hz, 1H), 4.59 (dd, $J = 7.3, 2.7$ Hz, 1H), 4.46 (d, $J = 14.4$ Hz, 1H), 4.03 (d, $J = 14.4$ Hz, 1H), 3.81 (s, 3H), 3.62 (dd, $J = 19.7, 1.9$ Hz, 1H), 3.57 (dd, $J = 7.2, 3.8$ Hz, 1H), 2.80 (ddd, $J = 13.8, 5.8, 2.0$ Hz, 1H), 2.60 – 2.46 (m, 1H), 2.13 (dt, $J = 13.8, 9.9$ Hz, 1H), 1.87 – 1.82 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ ppm 165.2, 159.5, 142.9, 135.4, 130.2, 130.1, 126.7, 124.1, 114.2, 97.7, 80.8, 76.8, 64.6, 63.6, 55.3, 45.4, 35.2, 35.2, 28.1; HRMS calculated for $\text{C}_{23}\text{H}_{29}\text{NNaO}_6\text{S}$ ($\text{M}+\text{Na}$) $^+$ 470.1613; found 470.1601.

***tert*-Butyl (2S)-1-(furan-2-yl)-1-hydroxy-3-phenylpropan-2-ylcarbamate (20)**

To a stirring suspension of imidazole (12.8 g, 188 mmol) in CH_2Cl_2 (40 mL) was added a solution of $\text{PhOP}(\text{O})\text{Cl}_2$ (5.61 mL, 37.7 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h, the reaction was cooled to 0 °C and a solution of Boc-phenylalanine (10.0 g, 37.7 mmol) in CH_2Cl_2 (28 mL) was added and the reaction mixture stirred for 1 h. After such time, Weinreb amine (3.68 g, 37.7 mmol) was added and the reaction stirred at rt for 14 h. The reaction was quenched with citric acid (2M aq., 80 mL), the organic layer washed with NaHCO_3 (1M aq., 80 mL) and brine (80 mL). The organic layer was dried (MgSO_4), filtered and concentrated under reduced pressure to generate the desired intermediate as a clear oil (crude NMR analysis).

A portion of the crude (6.59 g, 25.3 mmol) in THF (84.5 mL) was cooled to –40 °C was stirred for 30 min. In a separate round bottom flask, a solution of furan (4.6 mL, 63.3 mmol) in THF (110 mL) was cooled to –78 °C to which $^n\text{BuLi}$ (26.3 mL) was added slowly and upon completion, was stirred for 30 min. After such time, this solution was added slowly to the crude mixture at –40 °C and the reaction mixture was subsequently stirred for an additional 6 h. After

such time the reaction was quenched with NH_4Cl (sat. aq., 80 mL) and the reaction mixture warmed to RT. The aqueous layer was extracted with EtOAc (3×120 mL) and the combined organic layers were dried (MgSO_4), filtered and concentrated under reduced pressure to give the desired intermediate as a clear oil (crude NMR analysis). A portion of the crude (1.0 g) in THF (12 mL)/MeOH (1.5 mL) was cooled to 0°C and after stirring for 15 min, NaBH_4 (0.14 g, 3.8 mmol) was added and reaction stirred for 2 h at 0°C . After such time the reaction was warmed to RT, diluted with EtOAc (10 mL) followed by HCl (10% aq., 10 mL). After stirring for 15 min, the organic layer was washed with HCl (10% aq., 10 mL), H_2O (10 mL), NaHCO_3 (sat. aq., 10 mL) and brine (10 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated under reduced pressure to yield the desired intermediate as a white solid. Mp $144\text{--}146^\circ\text{C}$; FTIR (neat) 1716, 1454, 1292, 1172, 1132 cm^{-1} ; [Major Isomer] ^1H NMR (500 MHz, CDCl_3) δ 7.48 – 7.43 (m, 1H), 7.34 – 7.17 (m, 5H), 6.38 – 6.29 (m, 2H), 4.80 (d, $J = 19.2$ Hz, 1H), 4.70 – 4.78 (m, 1H), 4.27 (br s, 1H), 3.55 (br s, 1H), 2.80 (d, $J = 6.3$ Hz, 2H), 1.35 (s, 9H). [Minor Isomer] ^1H NMR (500 MHz, CDCl_3) δ 7.39 (s, 1H), 7.16 – 7.35 (m, 5H), 6.43 – 6.38 (m, 2H), 4.89 (s, 1H), 4.75 (s, 1H), 4.14 (s, 1H), 3.08 (s, 1H), 2.88 – 2.99 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.6, 154.6, 154.0, 142.3, 142.0, 137.9, 137.6, 129.3, 129.3, 128.5, 128.5, 126.5, 126.5, 110.3, 107.8, 106.8, 80.0, 79.7, 77.3, 77.0, 76.7, 70.1, 68.7, 56.5, 55.4, 37.6, 36.6, 28.3; HRMS calculated for $\text{C}_{18}\text{H}_{23}\text{NO}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 340.1525; found 340.1520 (TOF MS ES^+).

7H-4a,7-Epoxy-2H-1,2-benzothiazin-4-ol, 3,4,8,8a-tetrahydro-3-(phenylmethyl)-, 1,1-dioxide, (3S,4R) (21)

Carbamate **20** (2.0 g, 6.3 mmol) was dissolved in CH_2Cl_2 (32 mL), cooled to 0°C and after stirring for 15 min TFA (1.95 mL, 25.2 mmol) was added cautiously. After stirring at RT for 3 h, the reaction was cooled to 0°C and NaOH (10% aq., 35 mL) was added. The reaction was diluted with CH_2Cl_2 (32 mL), the aqueous layer extracted with CH_2Cl_2 (2×30 mL) and the combined organic dried (MgSO_4), filtered and concentrated under reduced pressure to afford the desired carbamate intermediate as a white solid. The crude product (1.78 g) was dissolved in EtOH (40 mL) and NaOH (1M aq., 40 mL) was added. After stirring at reflux for 14 h, the organic solvent was removed under reduced pressure. The resulting aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried (MgSO_4), filtered and concentrated under reduced pressure to produce the desired amino alcohol intermediate as a yellow oil. The crude material was dissolved in CH_2Cl_2 (11.7 mL), to which was added Et_3N (1.58 mL, 91 mmol) and the reaction was cooled to 0°C . After stirring for 10 mins, 2-chloroethanesulfonyl chloride (0.52 mL, 4.89 mmol) was added drop wise over 5 min. The reaction mixture was warmed to RT and stirred for 12 hours. After which time the crude mixture was concentrated and purified by flash chromatography (1:2 hexane:EtOAc) to yield (1.0 g, 3.2 mmol, 52%) of **21** as a white solid. FTIR (neat) 3480, 3350, 2358, 1448, 1305, 1139 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.19 (m, 3H), 6.55 (dd, $J = 5.7, 1.5$ Hz, 1H), 6.34 (d, $J = 5.7$ Hz, 1H), 5.19 (dd, $J = 4.7, 1.5$ Hz, 1H), 4.64 (d, $J = 10.6$ Hz, 1H), 4.07 (dd, $J = 16.4, 9.7$ Hz 1H), 3.90 (s, 1H), 3.21 (dd, $J = 7.9, 3.2$ Hz 1H), 3.10 (dd, $J = 13.9, 6.6$ Hz, 1H), 2.92 (dd, $J = 13.8, 8.9$ Hz, 1H), 2.61 – 2.52 (m, 1H), 2.35 (s, 1H), 1.77 (dd, $J = 12.2, 7.9$ Hz 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.1, 136.1, 133.4, 129.1, 129.0, 127.2, 91.2, 79.5, 64.2, 56.2, 55.6, 37.0, 28.8.; HRMS calculated for $\text{C}_{15}\text{H}_{17}\text{NO}_4\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ 330.0776; found 330.2017 (TOF MS ES^+).

Sultam [22]

Into a 1 dram vial was added **21** (85 mg, 0.27 mmol), DMF (0.6 mL, 0.46 M), Cs_2CO_3 (0.18 g, 0.55 mmol) and allyl bromide (25 μL , 0.30 mmol). The reaction was heated at 50°C and stirred for 4 h after which time the crude mixture was filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (1:2 hexane:EtOAc) to yield (86 mg, 2.48 mmol, 92%) of **22** as a yellow oil. FTIR (neat) 3386, 3249, 2358, 1336,

1315, 1152 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.30 (m, 2H), 7.25 (dd, $J = 7.2, 5.2$ Hz 3H), 6.57 (dt, $J = 5.6, 2.8$ Hz 1H), 6.27 (d, $J = 5.7, 1\text{H}$), 6.04 – 5.94 (m, 1H), 5.33 (ddq, $J = 20.2, 10.4, 1.4$ Hz 2H), 5.21 (dd, $J = 4.7, 1.6$ Hz 1H), 4.71 (d, $J = 12.1$ Hz, 1H), 4.31 (dt, $J = 5.5, 1.4$ Hz, 2H), 4.14 (dddd, $J = 12.1, 8.3, 7.1, 1.0$ Hz, 1H), 3.64 (s, 1H), 3.20 (dd, $J = 7.9, 3.3$ Hz, 1H), 3.11 (dd, $J = 14.3, 7.1$ Hz, 1H), 2.90 (dd, $J = 14.3, 8.5$ Hz, 1H), 2.60 (ddd, $J = 12.2, 4.6, 3.4$ Hz, 1H), 1.78 (dd, $J = 12.1, 7.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.3, 136.5, 133.6, 133.4, 129.1, 129.0, 127.1, 118.2, 91.0, 79.5, 74.9, 72.5, 56.7, 56.1, 37.4, 29.0; HRMS calculated for $\text{C}_{18}\text{H}_{21}\text{NO}_5\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ 370.1089; found 370.1087 (TOF MS ES^+).

Sultam [23]

According to general procedure **A**, sultam **22** (20 mg) underwent ROM-RCM-CM with ethylene to yield **23** (18 mg, 90%) as a clear oil. FTIR (neat): 3481, 2975, 1724 1445, 1308, 1139 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25 – 7.17 (m, 3H), 7.14 (ddd, $J = 9.5, 6.6, 3.4$ Hz, 2H), 6.46 (d, $J = 5.7$ Hz, 1H), 6.37 (dd, $J = 5.7, 1.6$ Hz, 1H), 5.75 (dddd, $J = 17.2, 10.0, 7.6, 5.7$ Hz, 1H), 5.16 (ddd, $J = 13.6, 11.0, 1.1$ Hz, 2H), 5.02 (dd, $J = 4.6, 1.6$ Hz, 1H), 4.03 – 3.90 (m, 3H), 3.80 – 3.70 (m, 2H), 3.25 – 3.16 (m, 2H), 3.01 (dd, $J = 13.4, 5.1$ Hz 1H), 2.18 (dt, $J = 12.7, 4.4$ Hz, 1H), 1.87 (dd, $J = 12.7, 8.5$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 137.9, 137.3, 135.3, 134.9, 129.4, 128.6, 126.7, 118.6, 91.6, 78.4, 64.2, 62.9, 57.3, 53.6, 37.1, 30.8; HRMS calculated for $\text{C}_{18}\text{H}_{21}\text{NO}_4\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ 370.1089; found 370.1087 (TOF MS ES^+).

Sultam [24]

To a stirring solution of sultam **21** (50 mg, 0.16 mmol), Et_3N (45 μL , 0.32 mmol), and CH_2Cl_2 (0.35 mL) in a 1 dram vial was added was added acryloyl chloride (17 μL , 0.21 mmol). After stirring for 4 h at RT, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc) to yield (53 mg, 0.14 mmol, 92%) of **24** as a yellow oil. FTIR (neat): 3470, 2980, 1726 1452, 1300, 1140 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.22 (m, 3H), 7.17 (dd, $J = 6.6, 5.0$ Hz, 2H), 6.62 (dd, $J = 17.3, 1.0$ Hz 1H), 6.54 (dd, $J = 5.8, 1.6$ Hz, 1H), 6.27 (dd, $J = 17.3, 10.4$ Hz, 1H), 6.06 (dd, $J = 10.4, 1.0$ Hz, 1H), 5.95 (d, $J = 5.8$ Hz, 1H), 5.48 (d, $J = 19.2$ Hz, 1H), 5.22 (dd, $J = 4.7, 1.6$ Hz 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 4.21 (dtd, $J = 11.6, 7.3, 1.0$ Hz, 1H), 3.19 (dd, $J = 7.9, 3.2$ Hz, 1H), 2.84 (qd, $J = 14.3, 7.3$ Hz, 2H), 2.67 – 2.57 (m, 1H), 1.79 (dd, $J = 12.2, 7.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.9, 137.2, 135.3, 134.9, 129.4, 128.6, 126.7, 118.6, 91.6, 78.4, 64.2, 62.9, 57.3, 53.6, 37.1, 30.8; HRMS calculated for $\text{C}_{18}\text{H}_{19}\text{NO}_5\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ 384.0882; found 384.0886 (TOF MS ES^+).

Sultam [25]

According to general procedure **A**, sultam **24** (18 mg) underwent ROM-RCM-CM with ethylene to yield **25** (16 mg, 85%) as a clear oil. FTIR (neat): 3480, 2982, 1726 1448, 1305, 1139 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.23 (t, $J = 7.3$ Hz, 2H), 7.16 (dd, $J = 15.3, 7.9$ Hz, 1H), 7.11 (d, $J = 7.1$ Hz, 2H), 6.43 (dd, $J = 17.2, 0.9$ Hz, 1H), 6.08 (dd, $J = 17.2, 10.4$ Hz 1H), 5.91 (dd, $J = 10.4, 0.9$ Hz, 1H), 5.77 – 5.69 (m, 1H), 5.66 (dd, $J = 17.4, 10.8$ Hz, 1H), 5.26 (d, $J = 17.4$ Hz, 1H), 5.19 (dd, $J = 13.9, 7.4$ Hz, 2H), 5.09 (d, $J = 10.2$ Hz, 1H), 5.07 (s, 1H), 4.93 (dd, $J = 16.2, 7.8$ Hz, 1H), 4.36 (d, $J = 12.1$ Hz, 1H), 4.27 – 4.19 (m, 1H), 3.63 (d, $J = 6.6$ Hz, 1H), 2.73 – 2.60 (m, 3H), 2.03 (ddd, $J = 14.0, 9.5, 6.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.2, 138.9, 138.3, 135.6, 133.2, 129.1, 128.7, 127.0, 127.0, 118.2, 118.1, 87.1, 81.4, 77.3, 61.8, 54.7, 37.5, 32.8; HRMS calculated for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ 412.1195; found 412.1190 (TOF MS ES^+).

***N*-Allyl-*N*-(furan-2-ylmethyl)methanesulfonamide (**26**)**

xxiii Into a flame dried flask under argon was added methanesulfonyl chloride (2.03 mL, 26.2 mmol), Et₃N (4.4 mL, 31.6 mmol) and dry CH₂Cl₂ (70 mL). After cooling down to 0 °C, furfurylamine (2.32 mL, 26.1 mmol) was added and the reaction flask stirred at room temperature for 5 h. After such time, the crude reaction mixture was washed with water and the organic layer dried (MgSO₄), filtered and concentrated under reduced pressure to yield a yellow oil. The crude material was subsequently dissolved in CH₃CN (100 mL), to which K₂CO₃ (7.27 g, 52.6 mmol) and allyl bromide (3.0 mL, 34.6 mmol) was added. After stirring at 60 °C for 12 h, the crude reaction mixture was filtered through a pad of celite and washed with CH₂Cl₂. The crude mixture was concentrated under reduced pressure and purified by flash chromatography (4:1 hexane:EtOAc) to provide (5.35 g, 24.8 mmol, 95 % yield) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.43 – 7.40 (m, 1H), 6.36 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.31 (d, *J* = 3.2 Hz, 1H), 5.78 (ddt, *J* = 16.4, 10.1, 6.3 Hz, 1H), 5.30 (ddd, *J* = 10.9, 8.7, 1.3 Hz 2H), 4.42 (s, 2H), 3.82 (d, *J* = 6.2 Hz, 2H), 2.79 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 149.7, 142.9, 132.6, 119.4, 110.5, 110.0, 49.3, 42.5, 39.4; HRMS calculated for C₉H₁₃NNaO₃S (M+Na)⁺ 238.0514; found 238.0510.

Sultam [(±) **28]**

To a flame dried flask was added, **26** (2 g, 9.29 mmol), diethyl chlorophosphate (1.6 mL, 11.1 mmol) and THF (40 mL). The reaction mixture was cooled to –78 °C and after stirring for 15 mins, LHMDS (1.0 M solution in THF) was added. The resulting solution was warmed to 0 °C and maintained for 2 h. To another flame dried flask, ethyl glyoxalate (3.7 mL, 18.7 mmol) and THF (40 mL) were added at –78 °C. After stirring for 15 min, this solution was added to the anionic solution containing **26** via cannula. The resulting solution was stirred at –78 °C for 7 h and then warmed to rt and stirred for an additional for 18 h. After such time, NH₄Cl (sat. aq., 25 mL) was added and the mixture was extracted with CH₂Cl₂ (4 × 25 mL). The organic layer was dried (MgSO₄), filtrated, concentrated under reduced pressure and purified by flash chromatography (7:1 hexane:EtOAc) to provide the mixture of Diels-Alder product **28** and precursor **27** product. Addition of hexane and Et₂O followed by cooling at 0 °C, resulted in crystallization of the desired product **28** as a white solid (1.55g, 5.2 mmol, 56%). FTIR (neat): 2983, 1736, 1301, 1141, 1020 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.51 (d, *J* = 5.7 Hz, 1H), 6.48 (dd, *J* = 5.7, 1.5 Hz, 1H), 5.88 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.40 (dd, *J* = 4.7, 1.4 Hz 1H), 5.34 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.1, 1.0 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.84 (dd, *J* = 9.9, 5.9 Hz, 2H), 3.81 – 3.77 (m, 2H), 3.62 (d, *J* = 11.5 Hz, 1H), 3.55 (d, *J* = 3.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 168.8, 137.4, 135.6, 132.2, 119.9, 91.8, 81.0, 63.4, 61.8, 48.8, 48.3, 47.7, 14.2; HRMS calculated for C₁₃H₁₇NNaO₅S (M+Na)⁺ 322.0725; found 322.0721.

Sultam [(±) **29]**

To a flame dried flask was added dry CH₂Cl₂ (50 mL, 0.005 M), which was degassed with ethylene 30 min. After such time, sultam **28** (0.1 g, 0.33 mmol) and cat-**B** (0.03 g, 0.033 mmol) were added and the reaction was refluxed at 40 °C for 1 h under ethylene (1 atm). After cooling to rt, the crude reaction mixture concentrated under reduced pressure and purified flash chromatography (6:1 hexane:EtOAc) to yield **29** (58 mg, 1.94 mmol, 59% yield) as a grey solid. Mp 155 °C; FTIR (neat): 2978, 1732, 1340, 1194, 999 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.34 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.73 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.58 (dt, *J* = 2.5, 10.1, 1H), 5.39 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.27 (dt, *J* = 10.4, 1.1 Hz 1H), 5.08 (dd, *J* = 8.2, 7.4 Hz, 1H), 4.21 (ddd, *J* = 6.7, 5.7, 1.9 Hz 1H), 4.18 – 4.12 (m, 3H), 3.82 – 3.75 (m, 2H), 3.57 (dd, *J* = 12.3, 2.0 Hz 1H), 3.31 (dd, *J* = 12.3, 2.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 168.9, 134.3, 132.7, 124.1, 119.3, 87.2, 84.2, 72.2, 61.8, 52.7, 51.0, 50.9, 14.1; HRMS calculated for C₁₃H₁₇NNaO₅S (M+Na)⁺ 322.0725; found 322.0716.

Sultam [(±) 30]

Into a flame dried flask under argon sultam **29** (862 mg, 2.88 mmol), CH₃CN (11.5 mL, 0.25 M), and I₂ (730 mg, 2.88 mmol) were added. The resulting solution was stirred at RT for 24 h. The reaction was quenched with aqueous NaHCO₃ and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layer was dried (MgSO₄) and was filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (6:1 hexane:EtOAc) to provide 78 mg (25% yield) of the desired compound. FTIR (neat): 2961, 1778, 1354, 1159, 1111 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ ppm 6.26 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.61 (dt, *J* = 10.1, 2.5 Hz, 1H), 4.85 (d, *J* = 6.6 Hz, 1H), 4.66 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.24 (dt, *J* = 19.7, 2.5 Hz, 1H), 3.99 (dd, *J* = 6.6, 3.5 Hz, 1H), 3.87 – 3.82 (m, 2H), 3.59 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.43 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.30 (dd, *J* = 11.1, 6.9 Hz, 1H), 3.29 (dd, *J* = 12.5, 1.9 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ ppm 173.5, 132.0, 125.0, 89.4, 85.0, 81.2, 73.1, 50.9, 49.0, 3.6. HRMS calculated for C₁₁H₁₂INNaO₅S (M+Na)⁺ 419.9379; found 419.9344.

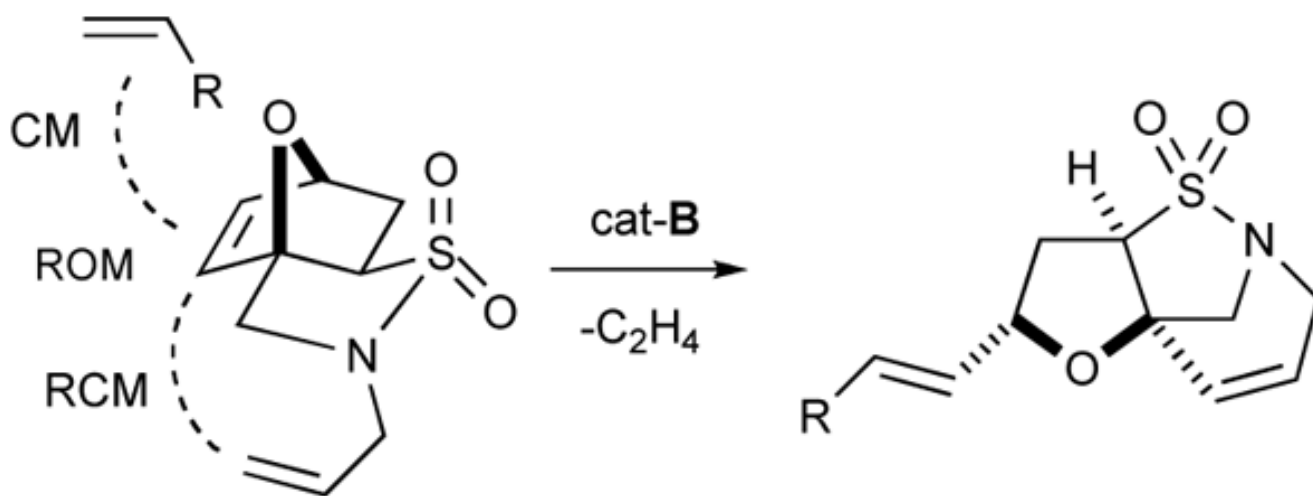
Acknowledgments

This work was generously supported by funds provided by the Center for Chemical Methodologies and Library Development at the University of Kansas (KU-CMLD) [P50 GM069663], Pilot Scale Libraries Program (P41 GM076302) and NIH COBRE award P20 RR015563 with additional funds from the State of Kansas. The authors thank the Umaer Basha Research fellowship for student support (I.O.) and Materia, Inc. for supplying catalyst and helpful discussion. The authors also thank Sarah Neuenswander for assistance with NMR measurements, and Dr. Victor Day for crystal structure data.

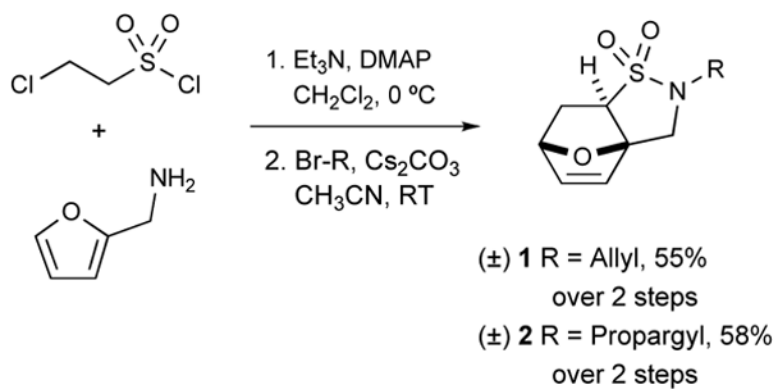
Literature Cited

- [i]. (a) Schreiber SL. *Science* 2000;287:1964–1969. [PubMed: 10720315] (b) Burke MD, Schreiber SL. *Angew Chem Int Ed* 2004;43:46–58. (c) Spandl RJ, Bender A, Spring DR. *Org Biomol Chem* 2008;6:1149–1158. [PubMed: 18362950] (d) Comer E, Rohan E, Deng L, Porco JA Jr. *Org Lett* 2007;9:2123–2126. [PubMed: 17472394] (e) Spring AR. *Org Biomol Chem* 2003;1:3867–3870. [PubMed: 14664374] (f) Shun S, Acquilano DE, Arumugasamy J, Beeler AB, Eastwood EL, Giguere JR, Lan P, Lei X, Min GK, Yeager AR, Zhou Y, Panek JS, Snyder JK, Schaus SE, Porco JA Jr. *Org Lett* 2005;7:2751–2754. [PubMed: 15957938] (g) Mitchell JM, Shaw JT. *Angew Chem Int Ed* 2006;45:1722–1726.
- [ii]. (a) Ko SK, Jang HJ, Kim E, Park SB. *Chem Commun* 2006:2962–2964. (b) Wyatt EE, Fergus S, Galloway WRJD, Bender A, Fox DJ, Plowwright AT, Jessiman AS, Welch M, Spring DR. *Chem Commun* 2006:3296–3298. (c) Thomas GL, Spandl RJ, Glandsdorp FG, Welch M, Bender A, Cockfield J, Lindsay JA, Bryant C, Brown DFJ, Loiseleur O, Rudyk H, Ladlow M, Spring DR. *Angew Chem Int Ed* 2008;47:2808–2812.
- [iii]. Functional group pairing (FGP) (a) Comer E, Rohan E, Deng L, Porco JA Jr. *Org Lett* 2007;9:2123–2126. [PubMed: 17472394] (b) Nielsen TE, Schreiber SL. *Angew Chem Int Ed* 2008;47:48–56. (c) Zhou A, Rayabarapu D, Hanson PR. *Org Lett* 2009;11:531–534. [PubMed: 19115841]
- [iv]. Tandem metathesis [TM] (a) Carreras J, Avenzoza A, Busto JH, Peregrina JM. *J Org Chem* 2009;74:1736–1739. [PubMed: 19133729] (b) Deiters A, Martin SF. *Chem Rev* 2004;104:2199–2238. [PubMed: 15137789] (c) Hoveyda AH, Zhugralin AR. *Nature* 2007;450:243–251. [PubMed: 17994091]
- [v]. (a) Schneider MF, Blechert S. *Angew Chem Int Ed Engl* 1996;35:411–412. (b) Morgan JP, Morrill C, Grubbs RH. *Org Lett* 2002;4:67–70. [PubMed: 11772092] (c) Cortez GA, Baxter CA, Schrock RR, Hoveyda AH. *Angew Chem Int Ed* 2007;46:4534–4538. (d) Ishikura M, Hasunuma M, Yanada K. *Heterocycles* 2005;65:2587–2592.
- [vi]. (a) Morton D, Leach S, Cordier C, Warriner S, Nielson A. *Angew Chem Int Ed Engl* 2009;48:104–109. [PubMed: 19016294] (b) Lee D, Sello JK, Schreiber SL. *Org Lett* 2000;2:709–712. [PubMed: 10814416] (c) Oikawa M, Ikoma M, Sasaki M. *Tetrahedron Lett* 2005;46:5863–5866. (d) Maechling S, Norman SE, McKendrick JE, Basra S, Köppner K, Blechert S. *Tetrahedron Lett* 2006;47:189–192. (e) Groaz E, Banti D, North M. *Eur J Org Chem* 2007:3727–3745. (f) Stragies

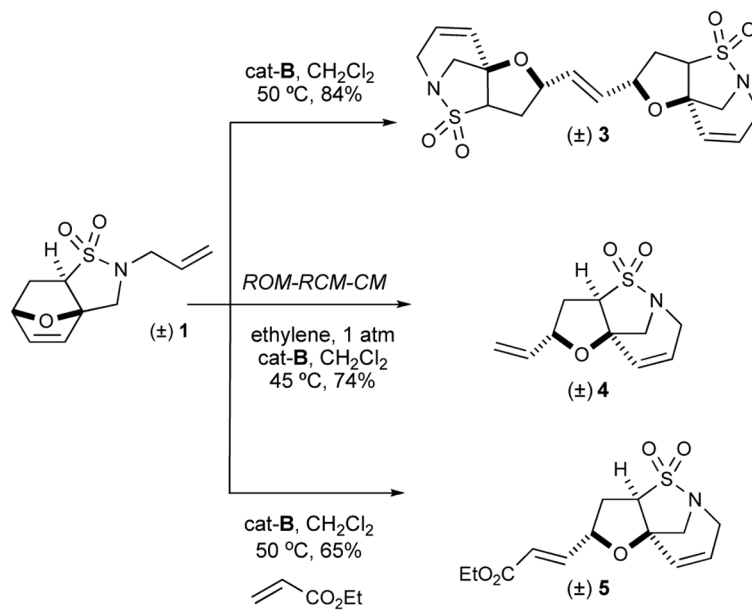
- R, Blechert S. *Synlett* 1998:169–170. (g) Arjona O, Csáký AG, Leon V, Medel R, Plumet J. *Tetrahedron Lett* 2004;45:565–567. (h) Spandl RJ, Rudyk H, Spring DR. *Chem Commun* 2008:3001–3003. (i) Chandler CL, Phillips AJ. *Org Lett* 2005;16:3493–3495. [PubMed: 16048325] (j) Wasilke JC, Obrey SJ, Baker RT, Bazan GC. *Chem Rev* 2005;105:1001–1020. [PubMed: 15755083] (k) Ikoma M, Oikawa M, Gill MB, Swanson GT, Sakai R, Shimamoto K, Sasaki M. *Eur J Org Chem* 2008:5215–5220.
- [vii]. Levy L. *Drugs Future* 1992;17:451–454.
- [viii]. Rabasseda X, Hopkins SL. *Drugs Today* 1994;30:557–563.
- [ix]. Zhuang L, Wai JS, Embrey MW, Fisher TE, Egbertson MS, Payne LS, Guare JP Jr, Vacca JP, Hazuda DJ, Felock PJ, Wolfe AL, Stillmock KA, Witmer MV, Moyer G, Schleif WA, Gabryelski LJ, Leonard YM, Lynch JJ Jr, Michelson SR, Young SDJ. *Med Chem* 2003;46:453–456.
- [x]. Valente C, Guedes RC, Moreira R, Iley J, Gut J, Rosental PJ. *Bioorg Med Chem Lett* 2006;16:4115–4119. [PubMed: 16697641]
- [xi]. (a) Hanson PR, Probst DA, Robinson RE, Yau M. *Tetrahedron Lett* 1999;40:4761–4764. (b) Wanner J, Harned AM, Probst DA, Poon KWC, Klein TA, Snelgrove KA, Hanson PR. *Tetrahedron Lett* 2002;43:917–921. (c) Long DD, Termin AP. *Tetrahedron Lett* 2000;41:6743–6747. (d) Brown RCD, Castro JL, Moriggi JD. *Tetrahedron Lett* 2000;41:3681–3685. (e) Moriggi JM, Brown LJ, Castro JL, Brown RCD. *Org Biomol Chem* 2004;2:835–844. [PubMed: 15007411] (f) Freitag D, Schwab P, Metz P. *Tetrahedron Lett* 2004;45:3589–3592. (g) Karsch S, Freitag D, Schwab P, Metz P. *Synthesis* 2004;10:1696–1712. (h) Jiménez-Hopkins M, Hanson PR. *Org Lett* 2008;10:2951–2954. [PubMed: 18553974]
- [xii]. (a) Rolfe A, Young K, Hanson PR. *Eur J Org Chem* 2008:5254–5262. (b) Zhou A, Hanson PR. *Org Lett* 2008;10:2951–2954. [PubMed: 18553974]
- [xiii]. (a) Metz P, Stölting J, Läge M, Krebs B. *Angew Chem Int Ed Engl* 1994;33:2195–2198. (b) Metz P, Meiners U, Fröhlich R, Grehl M. *J Org Chem* 1994;59:3687–3689. (c) Bovenschulte E, Metz P, Henkel G. *Angew Chem Int Ed Engl* 1989;28:202–203.
- [xiv]. (a) Rogatchov VO, Bernsmann H, Schwab P, Fröhlich R, Wibbeling B, Metz P. *Tetrahedron Lett* 2002;43:4753–4756. (b) Metz P, Send D, Fröhlich R, Wibbeling B. *Synlett* 1996:741–742. (c) Rogachev VO, Metz P. *ARKIVOC* 2007;5:167–190.
- [xv]. Cat-B: Scholl M, Ding S, Lee CW, Grubbs RH. *Org Lett* 1999;1:953–956. [PubMed: 10823227] It should be noted, that we did not use the Grubbs first generation catalyst $(PCy_3)_2(Cl)_2Ru=CHPh$ [Cat-A] in this study. (a) Schwab P, Grubbs RH, Ziller JW. *J Am Chem Soc* 1996;118:100–110. (b) Schwab P, France MB, Ziller JW, Grubbs RH. *Angew Chem, Int Ed Engl* 1995;34:2039–2041.
- [xvi]. The 1:1 ratio of diastereomers was indistinguishable by 1H . However, ^{13}C NMR spectroscopy was able to distinguish both as reported in the supplementary information.
- [xvii]. Diastereomeric ratio of 1.43:1.0 was determined by 1H NMR analysis of crude 15.
- [xviii]. Previous results by both Hoffman and Howell have demonstrated higher selectivity with a series of serine-derived amino ketones. (a) Hoffman RV, Tao J. *J Org Chem* 1998;63:3979–3985. (b) So RC, Izmirian DP, Richardson SK, Guerrero RL, Howell AR. *J Org Chem* 2004;69:3233–3235. This selectivity could be increased up to ~ 4:1 using low temperature (-78 °C), however the yield of the reaction was reduced. [PubMed: 15104474]
- [xix]. Ikoma M, Oikawa M, Sasaki M. *Eur J Org Chem* 2009:72–84.
- [xx]. Chatterlee A, Choi TL, Sanders DP, Grubbs RH. *J Am Chem Soc* 2003;125:11360–11370. [PubMed: 16220959]
- [xxi]. Brosius AD, Overman LE, Schwink L. *J Am Chem Soc* 1999;121:700–709.
- [xxii]. Quantitatively it was found that after 2 h, a 3:1 ratio of 28:27 was observed. However, when the same NMR sample was analyzed after 4 and then 12 h, a mixture of 2:1 of 28:27 was observed as in the 1H NMR.
- [xxiii]. McNelis BJ, Starr JT, Dang H. *J Heterocyclic Chem* 1998;35:1509–1513.



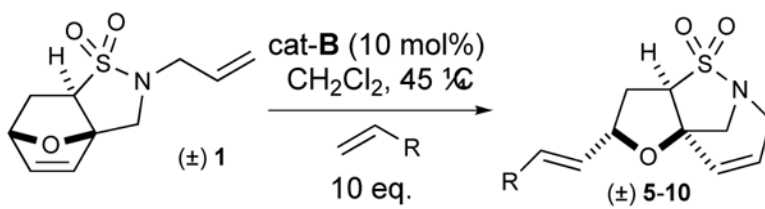
Scheme 1.

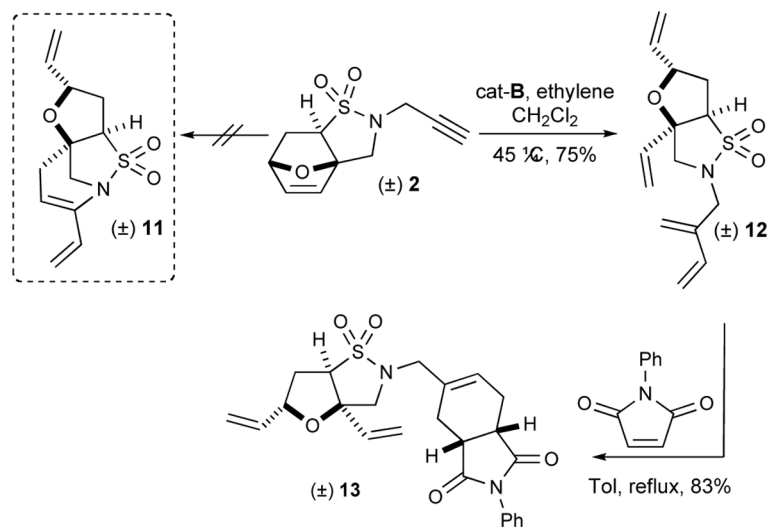


Scheme 2.

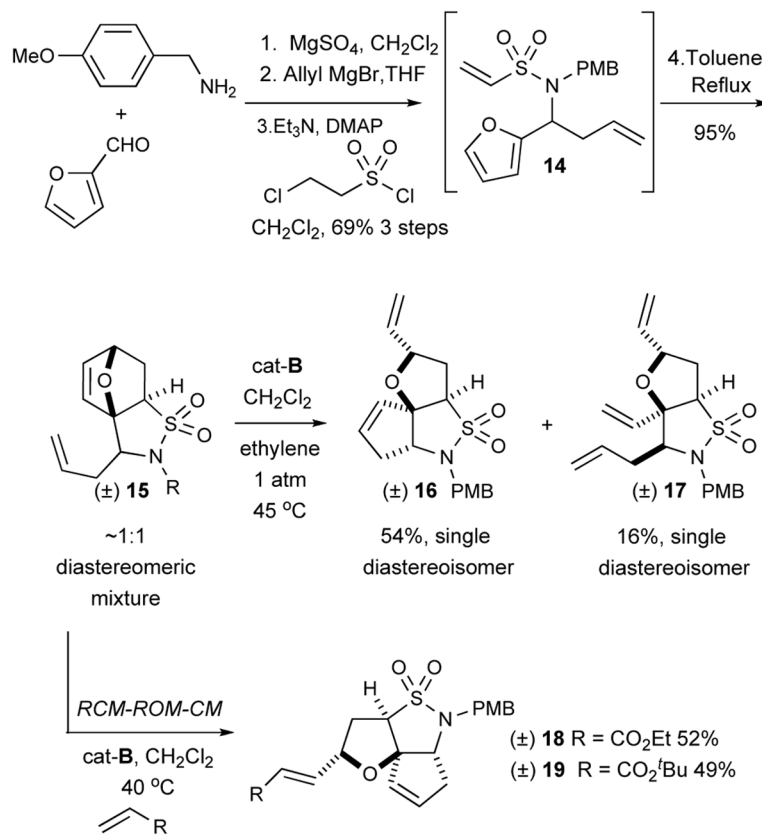


Scheme 3.

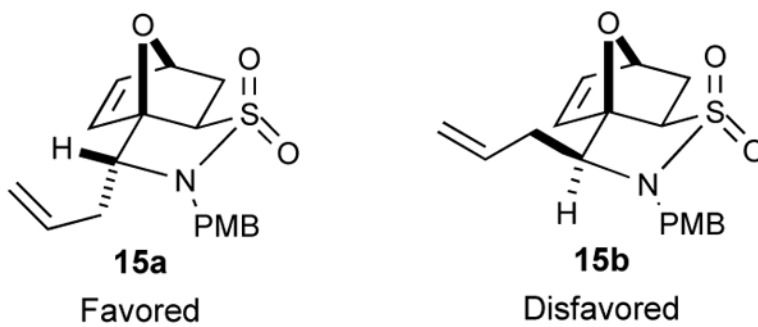




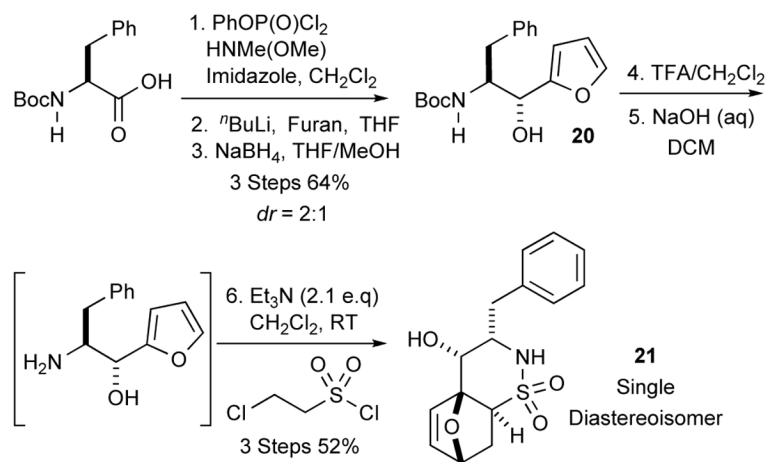
Scheme 5.



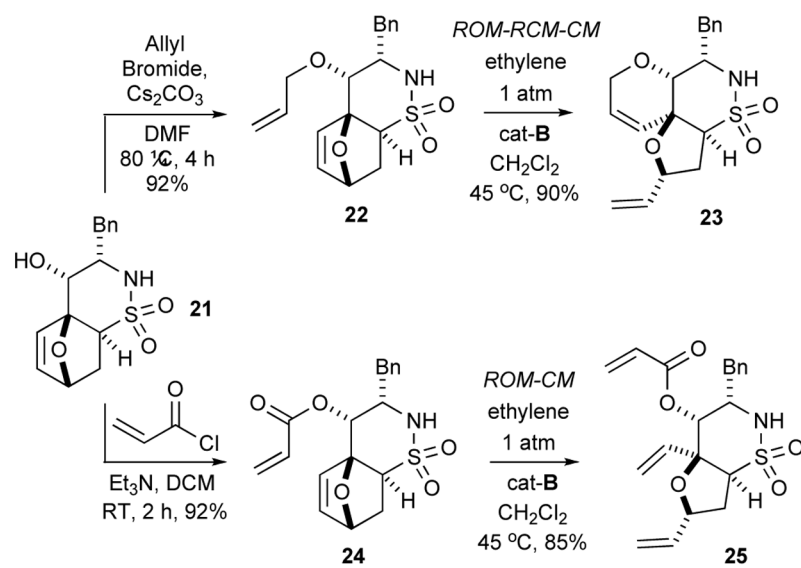
Scheme 6.



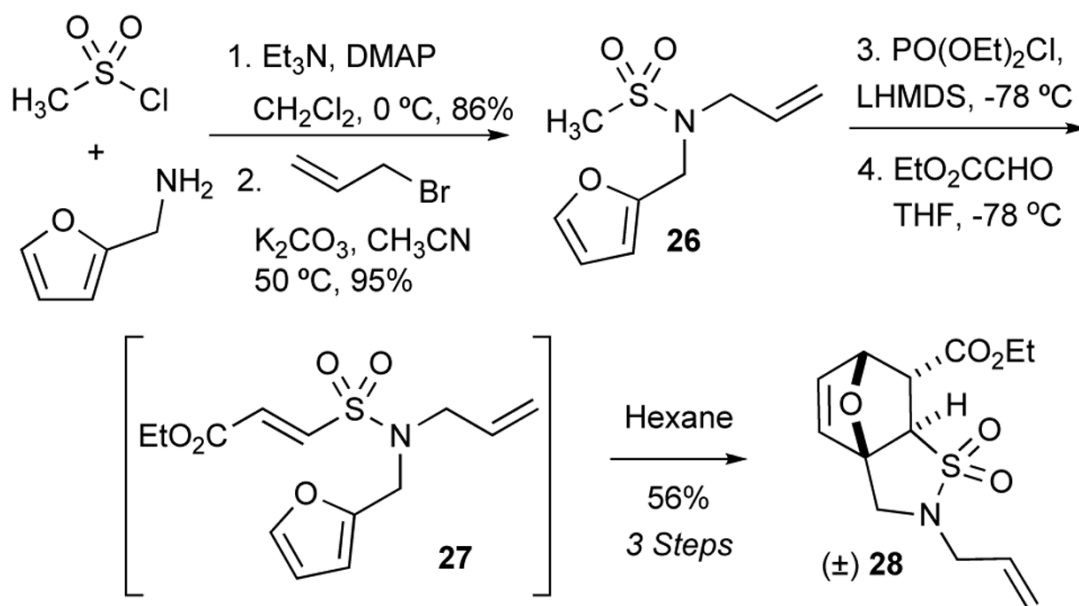
Scheme 7.



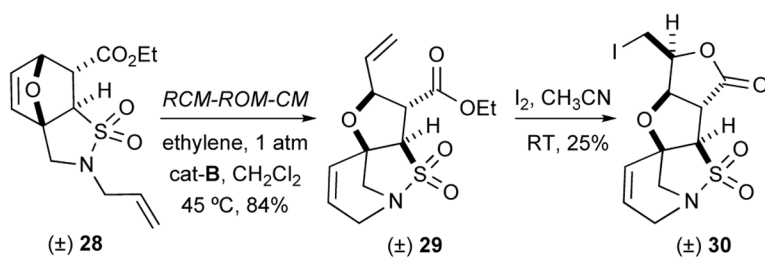
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

Table 1

entry	R
1	CO ₂ Et
2	CO ₂ Me

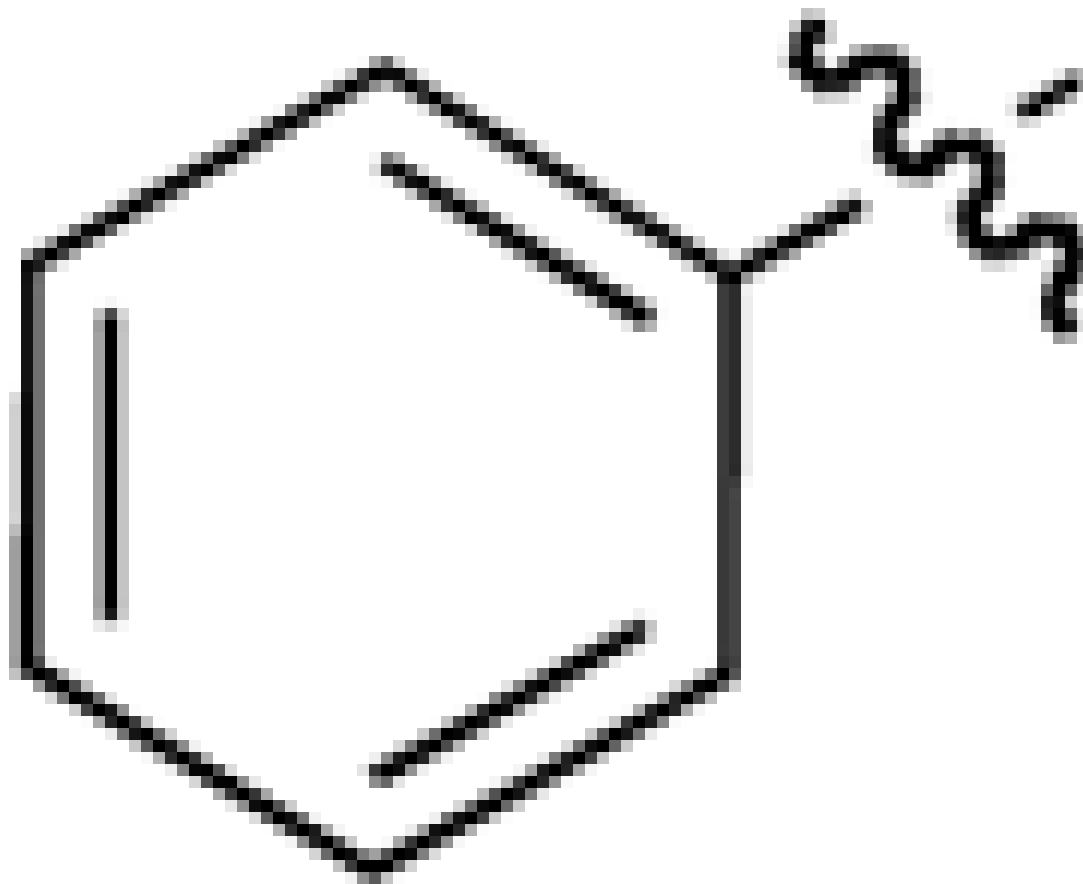
Me

entry	R
3	CO ₂ ^t Bu

tBu

entry**R**

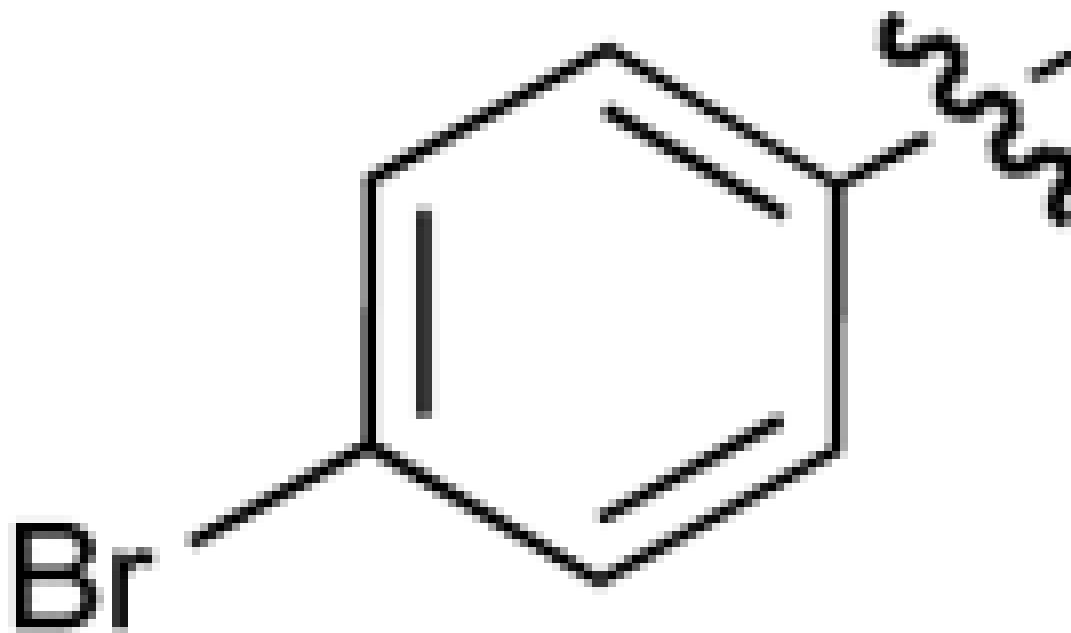
4



entry

R

5



Br

entry	R
6	CN
