Supporting Information

Correction to: "One-Pot Double Annulation Strategy for the Synthesis of Unusual Fused Bis-Heterocycles"

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General Remarks

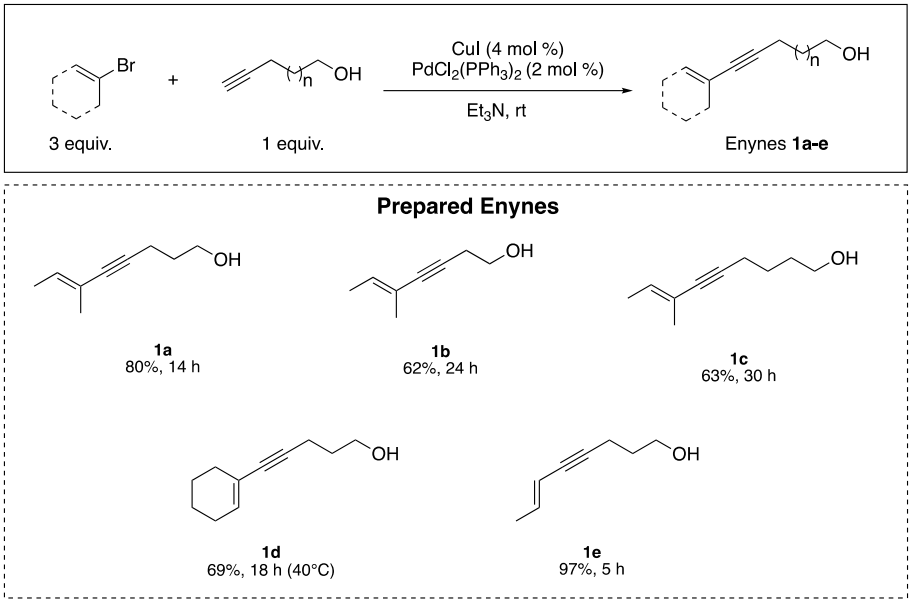
All reactions were carried out under an argon atmosphere in flame-dried glassware with magnetic stirring unless otherwise noted. Syringe needles used to dispense solvent were not flame-dried. Reagents were used as obtained from commercial suppliers without further purification. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (DCM), 1,2-dichloroethane (DCE), and toluene (PhMe) were purchased from Fisher and dispensed using the Glass Contour solvent purification system. Hydrocarbon-stabilized (ChromAR®) chloroform ($CHCl_3$) was purchased from Macron Fine Chemicals and was dried for at least 24 hours over activated 4 Å molecular sieves before use in any reactions. Both 4 Å molecular sieves used for drying solvent, and 5 Å molecular sieves used as desiccants in certain reactions were purchased from Aldrich, stored in an oven and activated under high vacuum prior to use. Celite 545 was purchased from EMD. ACS grade hexanes, pentane and DCM were used for column chromatography. Thin-layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 glass-supported plates from EMD, and visualization was performed with a UV lamp followed by staining with *p*-anisaldehyde solution followed by heating. Column chromatography was carried out on EM Science silica gel (60 Å pore size, 230-400 mesh). Preparatory thin-layer chromatography (prep-TLC) was carried out using Analtech Uniplate F254 Prep-20x20 cm TLC plates. High-performance liquid chromatography (HPLC) was performed using Prominence-i LC 2030 Plus with a chiral stationary phase column (Chiralpak AD-H, Daicel Corp, 0.46 cm x 0.15 cm). Deuterated chloroform was purchased from Cambridge Isotope Laboratories.

^{1}H NMR spectra of all starting materials were recorded at room temperature on a 500 MHz Bruker Avance spectrometer or a 400 MHz Bruker Avance spectrometer. For the exception of cyclization products azepines **3o-t**, all ^{1}H spectra acquired for cyclization/annulation products were acquired at 55°C in $CDCl_3$. Chemical shifts are given in parts per million (ppm) referenced to solvent residual proton resonance (δ = 7.26 for $CHCl_3$). NMR data are reported as: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dq = doublet of quartets, td = triplet of doublets), coupling constants (*J*) given in Hz, and integration. In cases where two stereoisomers are present, all chemical shifts from the major stereoisomer are listed and resonances corresponding

to the minor isomer are listed "(minor)." ^{13}C NMR spectra were recorded at room temperature for all starting materials on a 125 MHz Bruker Avance spectrometer with proton decoupling. For the exception of cyclization products azepines **3o-t**, all ^{13}C spectra acquired for cyclization/annulation products were acquired at 55°C in $CDCl_3$. Chemical shifts are given in parts per million (ppm) from referenced to solvent carbon resonance (δ = 77.16 for $CHCl_3$). In cases where two stereoisomers/rotamers are present, chemical shifts from the minor isomer are reported followed by "(minor)." High resolution mass spectra (HRMS) were measured at the University of Rochester Mass Spectrometry Resource Lab. X-ray crystallography data were collected by the X-ray Crystallographic Facility of the University of Rochester, Rochester, NY 14627 (USA). X-ray crystallography data were collected by the X-ray Crystallographic Facility of the University of Rochester, Rochester, NY 14627 (USA)

Experimental Details

General method A for Sonogashira reaction to Enynes 1a-e:

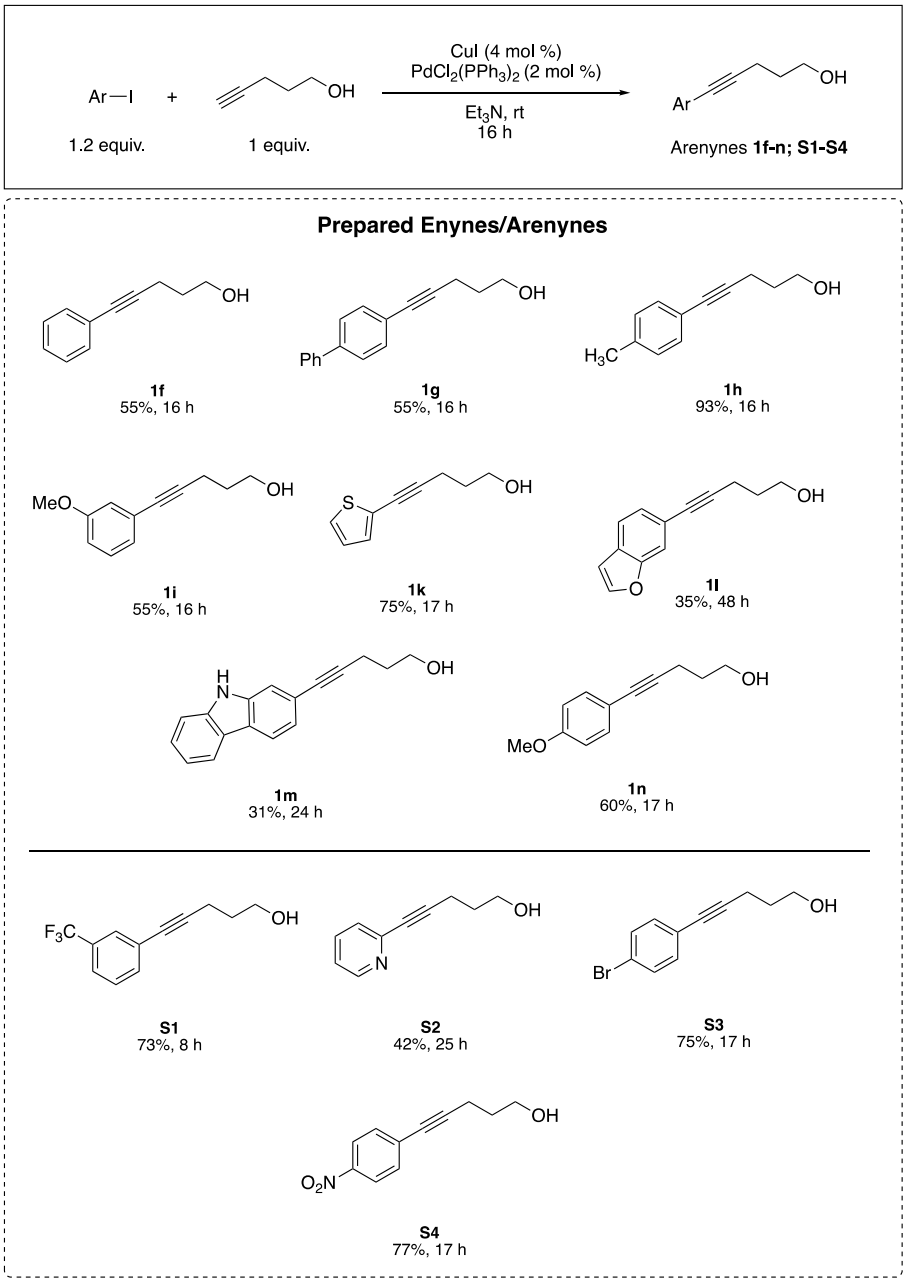


Scheme S1. Sonogashira reaction scope of prepared enynes **1a-e**.

A round-bottom flask was charged with a stir-bar and purged with argon multiple times. Triethylamine (adjusted so that the limiting reagent alkyne reaches a concentration of 0.2 M) was added and the solvent was degassed by sparging with argon through a long needle. $Pd(PPh_3)_2Cl_2$ (0.02 equiv.), copper iodide (0.04 equiv.) and vinyl bromide (3 equiv.) were added successively, while still degassing. After 10 min of continued degassing, alkynyl alcohol (1 equiv.) was added dropwise. Degassing was ceased and the reaction was carried out at rt (unless otherwise mentioned) until consumption of starting material was observed by TLC, upon which an amount of Et_2O (equal to the initial volume of triethylamine) was added. The reaction was filtered over Celite 545. The filtrate was transferred to a separating funnel and washed repeatedly (typically twice) with 1 M aq. HCl, until the obtained aqueous layer was roughly pH 1 and all triethylamine was removed from the organic layer. The remaining organic layer was then washed with a saturated aqueous solution of $NaHCO_3$ and water, and the organic layer was then dried with $MgSO_4$ and filtered. The filtrate was concentrated and purified by column chromatography (typically eluting Hexanes/DCM) to obtain pure enyne starting materials.

Enynes **1a-e** are literature compounds and their spectroscopic matches that of what has been reported in the literature.[1]

General Method B for Sonogashira Reaction to Arenynes 1f-n, S1-S4:



Scheme S2. Sonogashira reaction for the synthesis of arenynes **1f-m** and **S1-S4**.

A round-bottom flask was charged with a stir-bar and purged with argon multiple times. $PdCl_2(PPh_3)_2$ (0.02 equiv.) and copper(I) iodide (0.04 equiv.) were added to the flask followed by reagent-grade triethylamine (Et_3N) to reach a concentration of 0.2 M with respect to the limiting reagent. 3-iodoanisole (1.2 equiv.) was introduced to the stirring solution via syringe, and the mixture was degassed by sparging with argon through a long needle. After ten minutes of degassing, 4-pentyn-1-ol (1 equiv) was added dropwise, and the mixture immediately became cloudy with precipitate. Degassing was ceased, and the reaction was carried out at ambient temperature (unless otherwise indicated) until consumption of starting material was observed by TLC by staining with *p*-anisaldehyde, upon which an amount of Et_2O (equal to the initial volume of triethylamine) was added. The reaction was filtered over Celite 545,

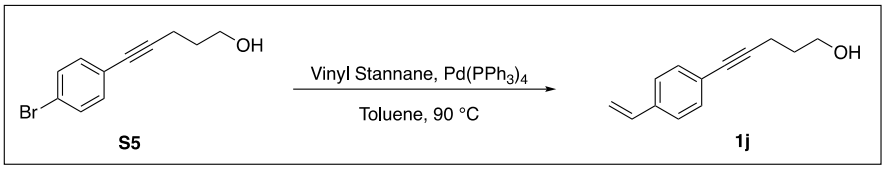
and the celite pad was washed with excess Et_2O. The filtrate was transferred to a separatory funnel along with copious amounts of ice and washed with 2 M aq. HCl to remove Et_3N. Once the aqueous layer reached a pH of approximately 1, the remaining organic layer was washed with a saturated aqueous solution of $NaHCO_3$ followed by water, and the organic layer was then dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to obtain pure arenynes **1f-n** and **S1-S4**. It is essential to note that hexanes/EtOAc were insufficient in removing residual palladium impurities from the reaction mixture after column chromatography. Copious amounts of Hexanes/DCM should be first washed through the column in order to remove these contaminants before increasing the polarity of the column eluent to 100% DCM.

Arenyne starting materials **1f**[2], **1g**[3], **1h**[4], **1i**[2], **1n**[5], **1k**[5], **S1**[2], **S2**[6], **S3**[7], **S4**[8] were all prepared by the listed procedure and their spectroscopic data matches that of the literature.

Arenyne 1l: A yellow-orange oil (35 mg) was obtained in 35% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.77 (s, 1H), 3.88 (t, *J* = 6.0 Hz, 2H), 2.66 (t, *J* = 6.7 Hz, 2H), 2.00 – 1.88 (m, 2H), 1.77 (s (broad), 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 145.3, 127.9, 127.5, 122.9, 121.2, 108.1, 107.0, 94.4, 75.8, 62.0, 31.5, 16.5. **HRMS** Calculated for $C_{13}H_{12}O_2$ ($[M+H]^+$): m/z 201.0916, found: 201.0911

Arenyne 1m: Isolated as a white solid (151 mg) in 31% yield, m.p. 166 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.7 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.44 – 7.39 (m, 2H), 7.31 – 7.18 (m, 2H), 3.93 – 3.83 (m, 2H), 2.60 (t, *J* = 6.9 Hz, 2H), 1.97 – 1.86 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.4, 126.4, 126.4, 123.4, 123.2, 120.9, 120.6, 120.3, 119.9, 113.8, 110.8, 97.3, 89.0, 82.3, 62.1, 31.6, 16.3. **HRMS** Calculated for $C_{17}H_{15}NO$ ($[M+H]^+$): m/z 250.1232, found: 250.1227

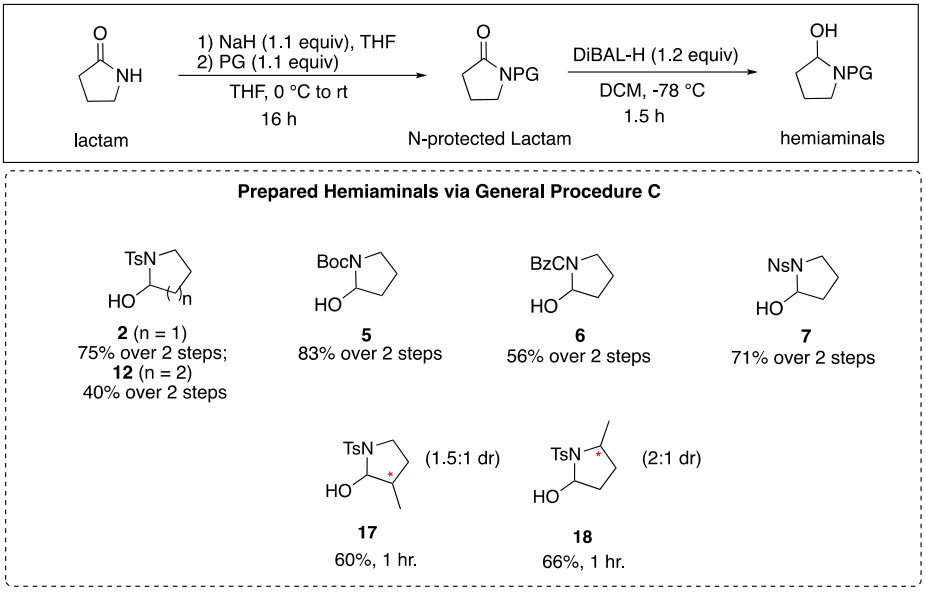
Synthesis of Arenyne 1j[9]



Scheme S3. Synthesis of arenyne **1j** via Stille coupling of **S5** with vinylstannane.

S5 (4 mmol, 1 equiv) and $Pd(PPh_3)_4$ (0.12 mmol, 3 mol%) were introduced to a flamed-dried pressure tube charged with a magnetic stir bar and capped with a rubber septum. Following the addition of the solids, the headspace was purged with argon 3 times (~15 min). Under the inert atmosphere, anhydrous toluene (5 mL) was subsequently added and allowed to stir for 15 minutes. Next, tributyl(vinyl)stannane (5.2 mmol, 1.3 equiv) was added dropwise via syringe and the mixture was stirred at 90 °C for 18 h. After cooling, the mixture was filtered through Celite while eluting with Et_2O and evaporated under reduced pressure. The residue was then treated with 1 M HCl soln and EtOAc. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, filtered and then concentrated. The crude product was purified by column chromatography a step gradient of 100% Hexanes/DCM to 100% DCM/Hexanes to obtain **1j** as a brownish yellow oil (350mg, 54% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 6.68 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.74 (d, *J* = 17.5 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 3.82 (t, *J* = 6.1 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.90 – 1.83 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.0, 136.4, 131.8, 126.2, 123.2, 114.5, 90.1, 81.3, 62.0, 31.5, 16.2. **HRMS** Calculated for $C_{13}H_{14}O$ ($[M+H]^+$): m/z 187.1123, found: 187.1127

General Procedure C for the Synthesis of Hemiaminals 2, 5-7, 12, 17, and 18



Scheme S4. Synthesis of hemiaminals via General Procedure C.

General Protection Method: At 0 °C, neat lactam (1 equiv) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 1.1 equiv) in dry THF (adjusted such that the limiting reactant reaches a concentration of 0.2 M in THF). After 1 h of stirring at 0 °C, the protecting group (TsCl Boc_2O, CBz-Cl, NsCl) (1.1 equiv) in THF (equal volume to the original THF volume) was added dropwise. The reaction was then allowed to warm to rt and stirred until completion as observed by TLC analysis (typically overnight, 16 h) Upon consumption of the lactam starting material, sat. aq. NH_4Cl (equal volume to the combined THF volume) was added, the mixture was transferred to a separatory funnel and extracted twice with EtOAc (both extractions equal to the volume of aqueous layer). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography using 60% Hexanes/EtOAc as the lead eluent or recrystallization in 9:1 Hexanes/EtOAc to afford pure protected lactam.

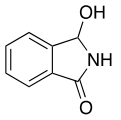
General DiBAL-H reduction method: To a flame-dried round bottom flask charged with a magnetic stir and protected lactam was added DCM (adjusted such that the limiting reactant reaches a concentration of 0.25M) and cooled to -78 °C. Following, a freshly prepared 1M solution of DiBAL-H in toluene (1.2 equiv) was added dropwise to and the reaction was stirred at -78 °C until completion was observed by TLC analysis (typically a couple of hours). Upon completion the reaction was cooled to 0 °C and few milliliters of water are added to quench the reaction (hydrogen gas evolves quite violently!). A 10% w/v aq. solution of Rochelle's salt (equal to the original volume of DCM) is added to the quenched stirring reaction and is allowed to stir further for 5 min. The reaction was transferred to a separatory funnel and the milky aqueous layer was extracted twice with DCM (both extractions equal to the volume of aqueous layer). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography using 60% Hexanes/EtOAc or recrystallized from EtOAc (refluxed to supersaturation) at -20 °C to yield an off-white crystalline product.

Hemiaminals **2**[10], **12**[11]**, 5**[12], **6**[13], and **7**[14]**,17**[15], **18**[16], were prepared by General Procedure C and their spectroscopic data matched that previously reported in the literature.

Synthesis of Hemiaminals 14-16, 19-21:

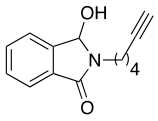
14

Preparation of hemiaminal **14**: To solution of **2** (1 mmol) in CH_3OH (5 mL) was added *p*-toluenesulfonic acid (0.5 mmol) and left to stir at room temperature for 24 hours and monitored by TLC analysis. Upon consumption of starting material, the reaction was quenched with aqueous $NaHCO_3$ and extracted with DCM and dried with $MgSO_4$, filtered and concentrated to afford the crude product. The crude was purified via column chromatography 80% Hexane/EtOAc to afford the product as a clear oil (204 mg) in 80% yield. Characterization data match that which was previously reported. [17]



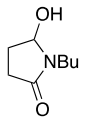
15

Preparation of hemiaminal **15**: 1.0 mmol of phthalimides was stirred at 0 °C in MeOH (5 mL) and THF (10 mL) for 10 min. NaBH4 (1.0 mmol) was added slowly over 5–10 min, the mixture was stirred at 0 °C until the N-substituted phthalimides disappeared (monitored by TLC). The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated in vacuo to afford a white solid (104 mg) in 70% yield. Characterization data match that which was previously reported.[18]



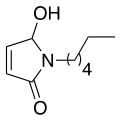
16

Preparation of hemiaminal **16**: In a round bottom flask charged with a magnetic stir bar, 6-chlorohex-1-yne (4.5 mmol) was dissolved in 20 mL of DMF. Subsequently, 1.2 equivalents of phthalimide (5.4 mmol) was added in one portion followed by 1.5 equivalents (6.75 mmol) of K_2CO_3, and 0.2 equivalents (0.9 mmol) of potassium iodide. The yellowish suspension was heated at 70°C for 24 hours. The reaction was then cooled to room temperature and then cooled to room temperature. 70 mL of H_2O was introduced to the reaction and extracted with Et_2O (4 x 70 mL). The combined organics were then washed with brine (3 x 70 mL) to remove the DMF. Combined organics were dried over anhydrous $MgSO_4$, filtered and then concentrated to afford crude *N*-(5-Hexynyl)phthalimide which was used directly for the next step. Reduction of *N*-(5-Hexynyl)phthalimide (1.0 mmol) was carried out using an identical procedure for the synthesis of hemiaminal **15**, affording **16** as a white solid (179 mg) in 78% yield over 2 steps (m.p. 95-96°C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.46 (m, 3H), 7.39 (t, *J* = 7.4 Hz, 1H), 5.71 (d, *J* = 11.4 Hz, 1H), 4.34 – 4.08 (m, 1H), 3.53 – 3.35 (m, 1H), 3.34 – 3.15 (m, 1H), 2.18 (t, *J* = 5.6 Hz, 2H), 1.92 (s, 1H), 1.78 – 1.58 (m, 2H), 1.56 – 1.41 (m, 2H). **^{13}C NMR** (101 MHz, $CHCl_3$) δ 167.5, 143.9, 132.2, 131.3, 129.6, 123.2, 123.0, 83.9, 81.5, 68.8 – 68.3 (m), 38.3, 27.2, 25.6, 18.0. **HRMS** Calculated for $C_{14}H_{15}NO_2$ ($[M+H]^+$): m/z 230.1181, found: 230.1183



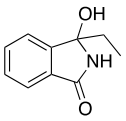
19

Preparation of hemiaminal **19**: In a round bottom flask charged with a magnetic stir bar, bromobutane (4.5 mmol) was dissolved in 20 mL of acetone. Subsequently, 1.2 equivalents of succinimide (5.4 mmol) was added in one portion followed by 1.5 equivalents (6.75 mmol) of K_2CO_3, and 0.2 equivalents (0.9 mmol) of potassium iodide. The yellowish suspension was heated at 50 °C for 24 hours. The reaction was then cooled to room temperature and then cooled to room temperature. 70 mL of H_2O was introduced to the reaction and extracted with Et_2O (4 x 70 mL). The combined organics were then washed with brine (3 x 70 mL) to remove the DMF. Combined organics were dried over anhydrous $MgSO_4$, filtered and then concentrated to afford crude *N*-butylsuccinimide which was used directly for the next step. Reduction of *N*-butylsuccinimide with $NaBH_4$ using the identical procedure for the synthesis of hemiaminal **15**, affording **19** as a clear oil (118 mg, 75% yield over 2 steps). Characterization data match that which was previously reported.[19]



20

Preparation of hemiaminal **20**: To a solution of Hexan-1-ol (1 mmol) in 8 mL THF was added PPh_3 (1.1 mmol), 1*H*-Pyrrole-2,5-dione (1.1 mmol), and diisopropyl azidodicarboxylate (DIAD) (1.2 mmol). The reaction mixture was left to stir at room temperature until consumption of starting material was observed by TLC (10 hours). Solvent was removed via rotatory evaporator and then partial re-dissolved in a 1:1 mixture of hexanes to diethyl ether. The suspension was then filtrated through a short Celite plug and the collected filtrate was concentrated and purified by column chromatography using 80% Hex/EtOAc as the lead eluent to afford 1-hexyl-1*H*-Pyrrole-2,5-dione which was then reduced with $NaBH_4$ using the identical procedure for the synthesis of **15**, affording **20** as a clear oil (97 mg, 53% yield over 2 steps). Characterization data matched that which was previously reported. [20]

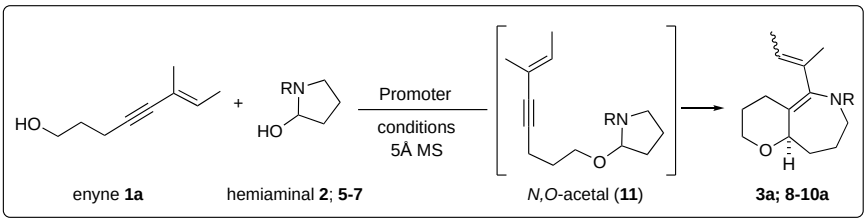


21

Preparation of hemiaminal **21**: To a flame-dried flask containing a magnetic stir bar was added phthalimide (1 mmol) followed by dry Et_2O and left to stir at room temperature for 10 minutes. Next, the flask was cooled to 0 °C and 1.2 mL (1.2 mmol) of 1M ethyl magnesium bromide (in THF) was added dropwise over 10 minutes. The reaction was monitored by TLC analysis and upon the observed consumption of starting material, the reaction was quenched with NH_4Cl, washed with brine, dried with $MgSO_4$ filtered and concentrated to afford the crude product which was then purified by column chromatography using 50% Hex/EtOAc as the lead eluent to afford **21** as a white crystalline solid (90 mg, 51% yield). Characterization data match that which was previously reported.[21]

Full Optimization Series for Double Annulation Strategy:

Table S1. Full optimization series of the cyclization method with enyne **1a** toward bicyclic scaffolds.



Entry	1a equiv	R (hemiaminal)	Promoter (equiv)	Solvent (0.1M)	Time / Temp (°C)	Result (*E*/*Z*)
1	1.75	Ts (**2**)	Tf_2NH (0.25)	$CHCl_3$	1 h / -20	82% **3a** (>19:1) 14% **11**
2	1.2	Ts **(2)**	Tf_2NH (1.0)	$CHCl_3$	1 h / -20	91% **3a** (10:1)
3	1.2	Ts **(2)**	Tf_2NH (0.25)	$CHCl_3$	1 h / -20	94% **3a** (>19:1)
4	1.2	Ts **(2)**	TfOH (0.25)	$CHCl_3$	6 h / -20	No reactivity
5	1.2	Ts **(2)**	TfOH (0.25)	$CHCl_3$	1 h / 0	>95% deprotection of **11**
6	1.2	Ts **(2)**	Tf_2NH (1.0)	DCM	75 min / -20	95% **3a** (>19:1)
7	1.2	Ts **(2)**	Tf_2NH (0.25)	DCM	75 min / -20	97% **3a** (>19:1)
8	1.2	Ts **(2)**	Tf_2NH (0.25)	THF	5 h / -20	94% **11**
9	1.2	Ts **(2)**	Tf_2NH (0.25)	Et_2O	5 h / -20	44% **3a** (10:1) 50% **11**
10	1.2	Ts **(2)**	Tf_2NH (0.25)	MTBE	5 h / -20	33% **3a** (5:1) 66% **11**
11	1.2	Ts **(2)**	Tf_2NH (0.25)	$CyCH_3$	5 h / -20	trace **3a** 86% **11**
12	1.2	Ts **(2)**	Tf_2NH (1.0)	Toluene	5 h / -20	94% **11**
13	1.2	Boc **(5)**	Tf_2NH (1.0)	DCM	1 h / -20	(N/A) **8a**[a]
14	1.2	CBz **(6)**	Tf_2NH (1.0)	DCM	1 h / -20	30% **9a** (>19:1)
15	1.2	Ns **(7)**	Tf_2NH (1.0)	DCM	10 h / -20	35% **10a** (>19:1)

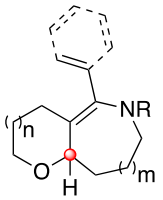
[a] Decomposition under reaction conditions

3a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a clear oil was obtained in 97% yield (70 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.48 (q, *J* = 6.7 Hz, 1H), 4.19 (d, *J* = 9.8 Hz, 1H), 4.03 (d, *J* = 13.2 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.51 – 3.39 (m, 1H), 2.99 (t (broad), *J* = 10.5 Hz, 1H), 2.41 (s, 3H), 2.34 – 2.23 (m, 2H), 2.12 – 2.01 (m, 1H), 1.99 – 1.77 (m, 3H), 1.60 (dd, *J* = 12.3, 5.6 Hz, 2H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 3H). **^{13}C NMR** ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 139.0, 136.7, 131.0, 129.2, 129.1, 127.4, 127.3, 79.1, 64.4, 51.7, 29.3, 27.3, 25.4, 23.3, 21.6, 14.4, 13.6. **HRMS** Calculated for $C_{20}H_{27}NO_3S$ ($[M+H]^+$): m/z 362.1790, found: 362.1789

9a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a clear oil in 30% yield (20 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, *J* = 29.0 Hz, 5H), 5.53 – 5.36 (m, 1H), 5.20 – 5.09 (m, 1H), 5.11 – 5.02 (m, 1H), 4.13 – 4.01 (m, 1H), 3.93 (t (broad), *J* = 8.6 Hz, 1H), 3.56 – 3.44 (m, 1H), 2.41 (s (broad), 1H), 2.32 – 2.19 (m, 1H), 1.92 – 1.75 (m, *J* = 12.0 Hz, 3H), 1.60 (s, 7H), 1.45 (s, 1H), 1.29 (s, 1H). **^{13}C NMR** (101 MHz, $CHCl_3$) δ 154.9, 139.4, 138.1, 136.8, 132.8, 132.0, 128.2, 127.7, 125.1, 78.9, 66.7, 64.6, 49.2, 29.7, 29.1, 25.0, 23.8, 15.0, 14.0. **HRMS** Calculated for $C_{21}H_{25}NO_2$ ($[M+H]^+$): m/z 324.1964, found: 324.1964

10a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a clear oil in 35% yield (27 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 5.50 (q, *J* = 6.2 Hz, 1H), 4.23 (d, *J* = 9.4 Hz, 1H), 4.01 (s (broad) , 1H), 3.93 (dd, *J* = 11.0, 8.4 Hz, 1H), 3.52 – 3.39 (m, 1H), 3.06 (s (broad), 1H), 2.32 – 2.20 (m, 2H), 2.16 – 1.79 (m, 4H), 1.71 – 1.56 (m, 2H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.18 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 147.7, 138.5, 136.0, 130.9, 128.6, 128.3, 123.8, 78.9, 64.8, 52.4, 30.8 (s (minor)), 29.8, 27.2, 25.6, 24.2, 14.6, 13.4. **HRMS** Calculated for $C_{19}H_{24}N_2O_5S$ ($[M+H]^+$): m/z 393.1484, found: 393.1484

General Procedure D for the Preparation of Azepines (3) and Azocines (13) – 1 mmol scale:



A round-bottom flask was charged with oven-dried 5 Å molecular sieves (0.3 g / mmol of limiting reactant, 0.372g) and stir-bar and was heated under vacuum for roughly one minute by heat gun to fully activate the molecular sieves. After cooling to room temperature, the flask was purged with argon three times and briefly opened and charged successively with hemiaminal **2** (1.24 mmol, 1 equiv, 0.3g), and arenynes/enyne **1a** (1.49 mmol, 1.2 equiv, 0.21g). Dry dichloromethane (adjusted such that limiting reactant reached a concentration of 0.1 M, 12.4 mL) was added through a needle and the reaction was cooled in a cryo-cooled acetone bath to -20°C. Anhydrous bis-trifluoromethanesulfonimide (0.25 equiv, 87mg) was added while limiting its exposure to moisture (bis-trifluoromethanesulfonimide that appears deliquescent, not free-flowing, or self-adhesive typically results in longer reaction times and/or poorer yields) was added quickly and a slow color change was observed. The starting hemiaminal is typically consumed almost instantly, forming the *N,O*-acetal **11**, which is much less polar than both starting materials (Rf values are 0.7-0.9 in 60% Hex/EtOAc and typically matches the color of enyne/arenyne **1** when stained with *p*-Anisaldehyde). The reaction was carried out at -20°C until consumption of the mixed *N,O*-acetal **11** was observed by TLC furnishing **3** (typically a slightly more polar spot, Rf = 0.6-0.7), upon which anhydrous $NaHCO_3$ (5 equiv.) was added as a solid. The suspension was filtered over a silica plug, eluting with Et_2O. The crude-containing filtrate was concentrated and purified by column chromatography or prep-TLC using 60% Hex/EtOAc as the lead eluent to obtain pure **3** or **13**.

Azepines **3** and azocines **13** possess a characteristic signal at ~77-80 ppm in ^{13}C NMR corresponding the bridgehead methine (labeled with red sphere). Furthermore, it must be noted that the isolated bicycles undergo rapid conformational changes at room temperature and the rapid equilibration of conformational isomers is exemplified in the ^{1}H NMR spectra as indistinct (blobby) multiplets. As shown in Figure S1, better resolved spectra were obtained with spectra acquisitions at 55°C in $CDCl_3$ (below).

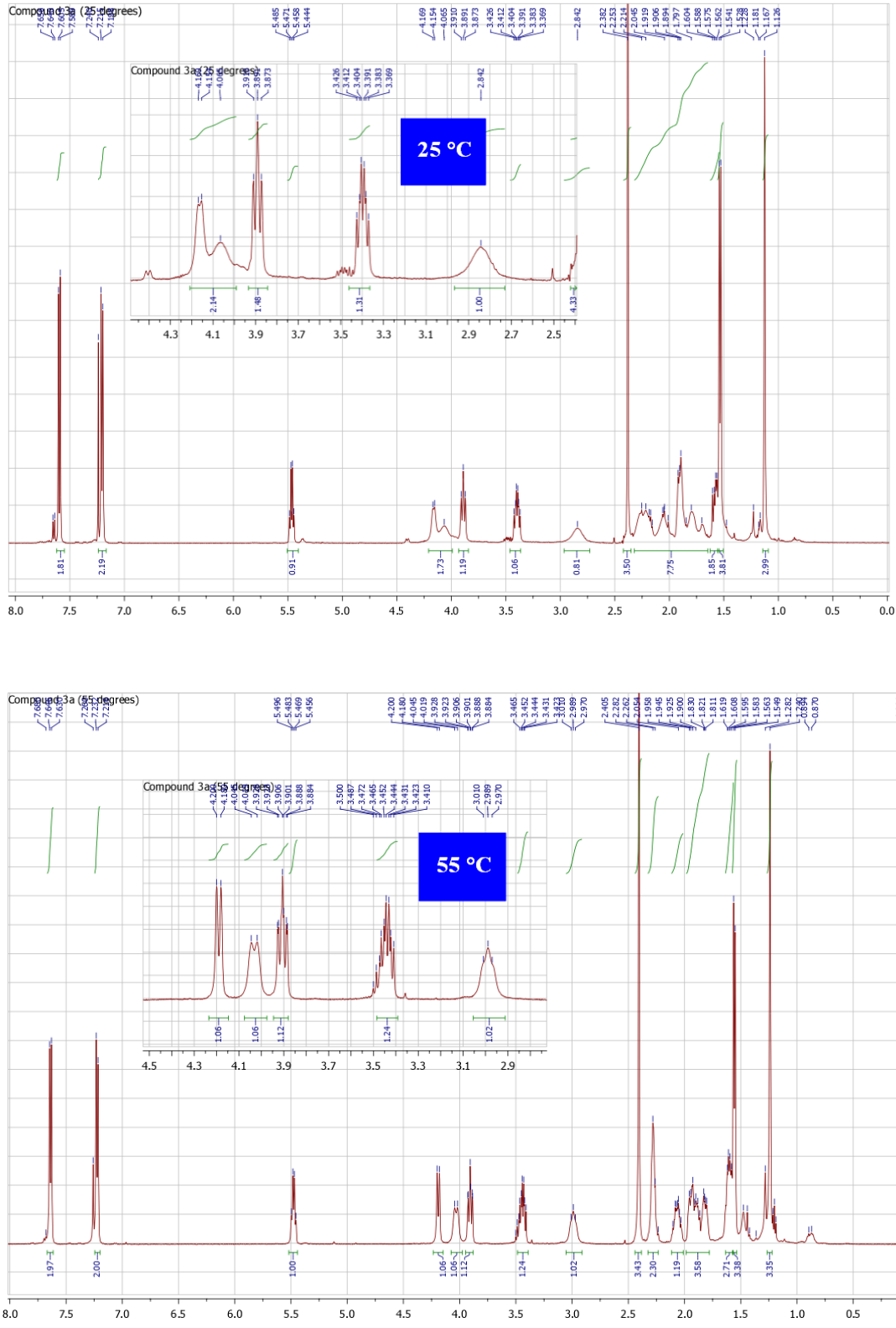
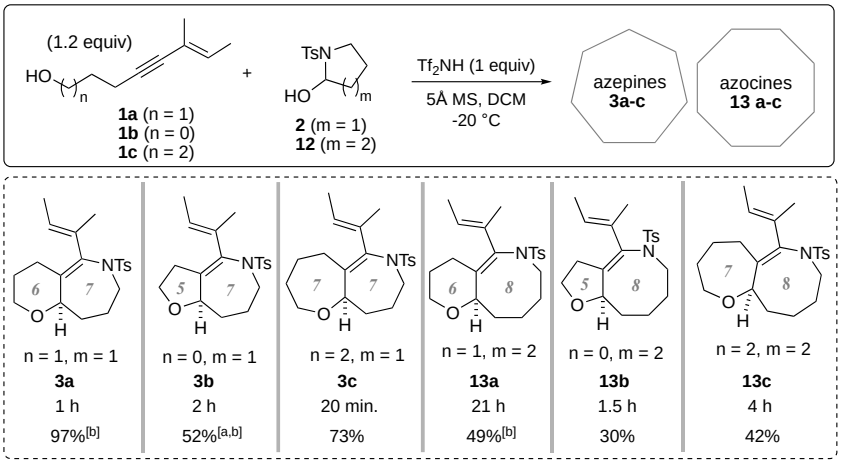


Figure S1: ^{1}H NMR spectra azepine **3a** at 25°C (top) and 55°C.

Cyclization Reaction to Azepines 3a-c and Azocines 13a-c:



[a] $CHCl_3$ used as reaction solvent. [b] 0.25 equiv of promoter used.

Scheme S5. Synthesis of various Azepine-(**3**) and Azocine-fused (**13**) ring systems.

3a: (*vide supra*, page S9)

3b: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 52% yield (50 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 5.56 (q, *J* = 6.0 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H), 4.17 (d, *J* = 14.4 Hz, 1H), 3.85 (dd, *J* = 8.6, 5.0 Hz, 2H), 2.77 (dt, *J* = 17.6, 9.8 Hz, 2H), 2.40 (s, *J* = 8.2 Hz, 3H), 2.04 – 1.93 (m, 1H), 1.88 (dd, *J* = 12.5, 3.0 Hz, 1H), 1.75 (d, *J* = 13.0 Hz, 1H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.44 – 1.34 (m, 2H), 1.31 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.0, 142.3, 138.9, 133.8, 132.7, 129.2, 127.4, 127.0, 81.0, 67.2, 51.2, 32.3, 31.1, 27.7, 21.6, 14.1, 13.6. **HRMS** Calculated for $C_{19}H_{25}NO_3S$ ($[M+H]^+$): m/z 348.1633, found: 348.1625

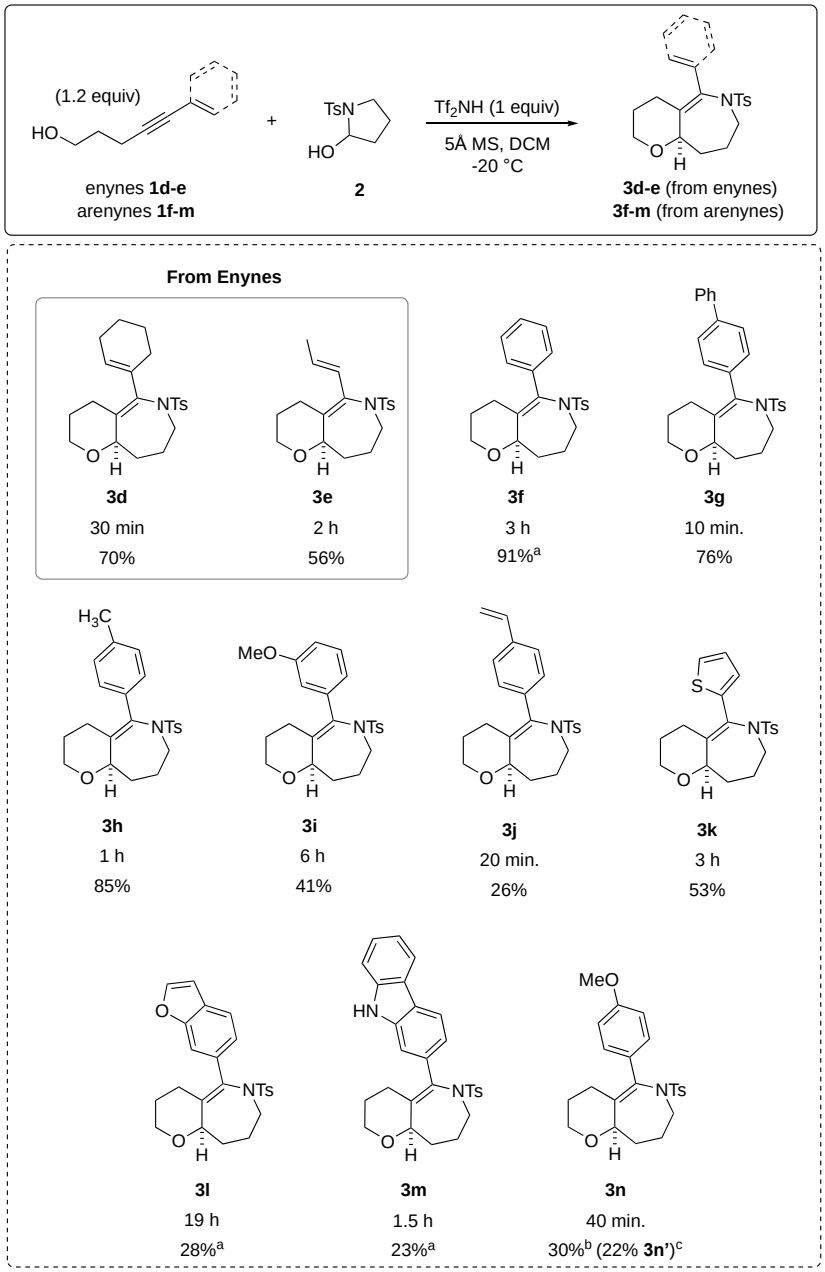
3c: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale yellow oil was obtained in 73% yield (54 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 6H), 7.23 (d, *J* = 8.1 Hz, 6H), 5.62 – 5.54 (m, 3H), 4.35 (dd, *J* = 10.8, 2.1 Hz, 3H), 4.01 (ddd, *J* = 11.2, 7.7, 4.1 Hz, 7H), 3.31 – 3.24 (m, 3H), 2.81 – 2.73 (m, 3H), 2.41 (d, *J* = 11.2 Hz, 11H), 2.29 (ddd, *J* = 12.4, 5.3, 2.9 Hz, 4H), 2.16 – 2.05 (m, 8H), 1.97 – 1.79 (m, 8H), 1.73 – 1.62 (m, 12H), 1.58 (d, *J* = 6.8 Hz, 10H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.3, 142.7, 139.2, 136.7, 132.1, 129.1, 127.6, 127.1, 81.4, 71.6, 49.9, 30.8, 30.3, 29.5, 28.2, 27.9, 21.5, 14.4, 13.4. **HRMS** Calculated for $C_{21}H_{29}NO_3S$ ($[M+H]^+$): m/z 376.1946, found: 376.1940

13a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 49% yield (36 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.48 (q, *J* = 6.7 Hz, 1H), 4.19 (d, *J* = 9.1 Hz, 1H), 4.03 (d (broad), *J* = 14.8 Hz, 1H), 3.99 – 3.86 (m, 2H), 3.58 – 3.40 (m, 2H), 2.99 (s, 1H), 2.41 (s, 3H), 2.34 – 2.22 (m, 2H), 2.12 – 2.00 (m, 1H), 1.98 – 1.75 (m, 5H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8, 139.6, 137.0, 131.4, 129.1, 128.0, 127.3, 125.0, 79.1, 64.7, 51.9, 29.4, 28.6, 27.2, 25.7, 24.0, 21.5, 14.7, 13.5. **HRMS** Calculated for $C_{21}H_{29}NO_3S$ ($[M+H]^+$): m/z 376.1946, found: 376.1940

13b: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 30% yield (21 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 9.5 Hz, 2H), 5.51 (q, *J* = 7.0 Hz, 1H), 4.74 (t, *J* = 8.5 Hz, 1H), 4.32 – 4.10 (m, 2H), 4.00 – 3.92 (m, 1H), 3.67 (dt, *J* = 17.2, 8.7 Hz, 1H), 3.50 (dd, *J* = 12.8, 8.9 Hz, 1H), 2.92 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.68 – 2.62 (m, 2H), 2.41 (s, 3H), 2.29 – 1.67 (m, 3H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.2, 137.8, 132.1, 129.8, 129.4, 128.6, 127.9, 127.3, 82.0, 66.6, 48.0, 33.7, 32.2, 29.9, 25.2, 21.7, 15.3, 13.8. **HRMS** Calculated for $C_{20}H_{27}NO_3S$ ($[M+H]^+$): m/z 362.1790, found: 362.1783

13c: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 42% yield (33 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 9.5 Hz, 2H), 5.65 (q, *J* = 5.5 Hz, 1H), 5.06 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.88 (d (broad), *J* = 12.3 Hz, 1H), 3.71 (t, *J* = 11.7 Hz, 1H), 3.59 (ddd, *J* = 22.0, 7.5, 2.5 Hz, 1H), 2.91 (ddd, *J* = 15.0, 7.5, 2.5 Hz, 1H), 2.43 (s, 3H), 2.35 – 2.27 (m, 1H), 2.03 (td, *J* = 12.3, 2.6 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.80 – 1.66 (m, 5H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.54 – 1.46 (m, 2H), 1.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.0, 143.0, 137.8, 137.4, 131.5, 129.2, 128.0, 127.4, 79.2, 68.3, 48.5, 33.9, 30.7, 28.9, 27.2, 26.1, 22.1, 21.6, 16.2, 13.3. **HRMS** Calculated for $C_{22}H_{31}NO_3S$ ([M+H]$^+$): m/z 406.6050, found: 406.6051

Cyclization Reaction of Enyne and Arenyne Variants:



[a] 0.25 equiv of promoter used. . [b] 2.0 equiv Tf_2NH used. [c] Dihydropyran side product observed; see Scheme S8.

Scheme S6. Enyne/Arenyne (**1**) Substrate Scope.

3a: (*vide supra*, page S9)

3d: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 70% yield (54 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.64 (s (broad), 1H), 4.20 (d, *J* = 9.8 Hz, 1H), 4.05 (s (broad), 1H), 3.91 (t (broad), *J* = 10.0 Hz, 1H), 3.42 (dd, *J* = 17.6, 10.5 Hz, 1H), 2.90 (s (broad), 1H), 2.41 (s, 3H), 2.37 – 2.17 (m, 2H), 2.07 (s (broad), 1H), 1.99 (s (broad), 2H), 1.96 – 1.88 (m, 2H), 1.83 – 1.74 (m, 1H), 1.70 – 1.48 (m, 5H), 1.46 – 1.34 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8, 139.2, 135.6, 132.9, 129.2, 127.4, 79.1, 64.3, 51.6, 29.8, 29.3, 27.5, 27.4, 25.3, 23.1, 22.7, 21.9, 21.6. **HRMS** Calculated for $C_{22}H_{29}NO_3S$ ($[M+H]^+$): m/z 388.1946, found: 388.1940

3e: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 56% yield (39 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.08 (d, *J* = 15.2 Hz, 1H), 5.47 (dd, *J* = 15.0, 7.0 Hz, 1H), 4.03 (d, *J* = 10.4 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.79 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.30 – 3.23 (m, 1H), 2.80 – 2.69 (m, 1H), 2.57 – 2.47 (m, 1H), 2.39 (s, 3H), 2.29 – 2.16 (m, 1H), 2.00 – 1.91 (m, 2H), 1.71 (d (broad), *J* = 12.6 Hz, 1H), 1.64 (d, *J* = 6.5 Hz, 3H), 1.62 – 1.55 (m, 2H), 1.45 – 1.32 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.2, 141.1, 139.5, 131.4, 129.5, 128.4, 127.5, 124.3, 78.1, 63.1, 48.6, 29.9, 26.9, 23.0, 21.6, 21.0, 18.1. **HRMS** Calculated for $C_{19}H_{25}NO_3S$ ($[M+H]^+$): m/z 348.1633, found: 348.1626

3f: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a clear oil in 91% yield (69 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.06 (m, 5H), 7.05 – 6.97 (m, 4H), 4.38 (s(broad), 1H), 4.18 – 4.04 (m, 1H), 3.97 (d, *J* = 9.7 Hz, 1H), 3.55 (td, *J* = 10.7, 6.6 Hz, 1H), 3.13 (s, 1H), 2.33 (s, 3H), 2.24 – 2.15 (m, 3H), 1.99 – 1.80 (m, 3H), 1.74 – 1.61 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.6, 138.4, 136.3, 129.3, 129.1, 128.4, 128.0, 127.7, 127.0, 125.4, 79.2, 64.3, 51.5, 34.3, 29.4, 27.2, 25.0, 21.5. **HRMS** Calculated for $C_{22}H_{25}NO_3S$ ($[M+H]^+$): m/z 384.1633, found: 384.1627

3g: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a white solid in 76% yield (69 mg) , m.p. 141-142°C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.36 (dd, *J* = 14.2, 7.5 Hz, 3H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 7.7 Hz, 2H), 4.42 (s (broad), 1H), 4.19 (s (broad), 1H), 4.00 (t, *J* = 9.5 Hz, 1H), 3.58 (dd, *J* = 17.2, 10.6 Hz, 1H), 3.19 (s (broad), 1H), 2.47 – 2.33 (m, 1H), 2.30 (s, 3H), 2.09 – 1.82 (m, 4H), 1.79 – 1.56 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.5, 141.1, 140.8, 139.2, 135.7, 133.4, 129.9, 129.1, 129.0, 127.6, 127.2, 127.2, 126.7, 79.3, 64.7, 51.9, 29.5, 27.2, 25.5, 24.2, 21.4. **HRMS** Calculated for $C_{28}H_{29}NO_3S$ ($[M+H]^+$): m/z 460.1946, found: 460.1936

3h: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 85% yield (68 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.5 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 2H), 6.97 – 6.87 (m, 4H), 4.35 (d, *J* = 9.6 Hz, 1H), 4.09 (s (broad), 1H), 3.95 (t, *J* = 9.0 Hz, 1H), 3.54 (dd, *J* = 16.8, 10.5 Hz, 1H), 3.23 (s (broad), 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.31 – 2.13 (m, 3H), 2.09 – 1.99 (m, 1H), 1.97 – 1.85 (m, 2H), 1.82 – 1.61 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.5, 139.1, 137.5, 133.9, 133.7, 129.5, 129.0, 128.7, 127.2, 79.2, 64.6, 51.7, 29.5, 27.1, 25.4, 24.0, 21.4, 21.2. **HRMS** Calculated for $C_{23}H_{27}NO_3S$ ($[M+H]^+$): m/398.1790, found: 398.1785

3i: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale, yellow oil in 41% yield (34 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.3 Hz, 2H), 7.08 (d, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 7.1 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 6.9 Hz, 1H), 6.47 (s, 1H), 4.40 (d (broad) , *J* = 8.6 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.96 (t, *J* = 9.3 Hz, 1H), 3.64 (s, 3H), 3.60 – 3.49 (m, 1H), 3.21 (s (broad), 1H), 2.33 (s, 3H), 2.28 – 2.16 (m, 2H), 2.08 – 1.99 (m, 1H), 1.96 – 1.85 (m, 2H), 1.78 – 1.62 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.1, 143.0, 140.0, 139.5, 138.2, 134.0, 129.5, 129.5, 127.6, 122.7, 115.4, 114.2, 79.7, 65.1, 55.6, 52.2, 31.3, 30.3 (s (minor)), 29.9, 27.6, 25.9, 24.6 (s (minor)), 21.8. **HRMS** Calculated for $C_{23}H_{27}NO_4S$ ($[M+H]^+$): m/z 414.1739, found: 414.1733

3j: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a brownish-orange oil in 26% yield (21 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.11 (m, 4H), 6.97 (dd, *J* = 13.9, 7.6 Hz, 4H), 6.68 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.71 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 4.36 (s (broad), 1H), 4.16 (s (broad), 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.62 – 3.46 (m, 1H), 3.22 – 3.07 (m, 1H), 2.33 (s, 3H), 2.28 – 1.80 (m, 5H), 0.94 – 0.73 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.6, 138.5, 136.3, 129.3, 129.1, 128.4, 127.7, 127.0, 125.9, 125.8, 125.5,

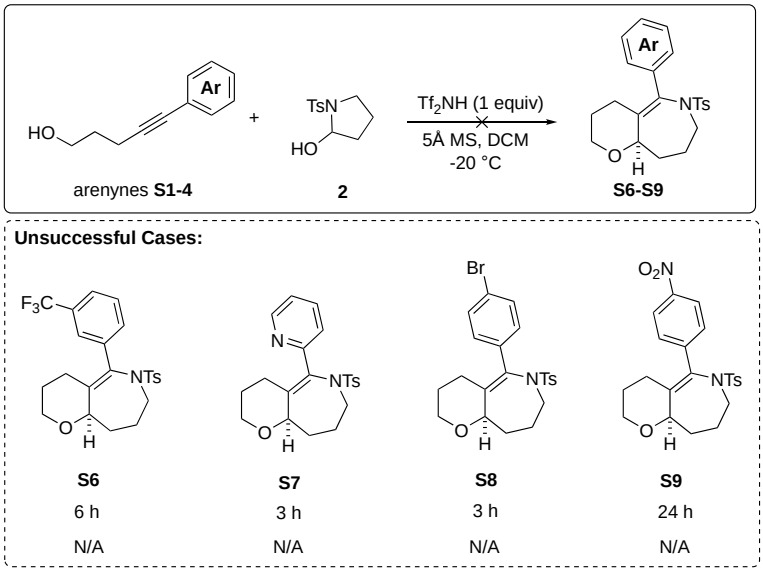
114.2, 79.2, 64.3, 51.5, 29.9, 29.4, 27.2, 25.0, 21.6. **HRMS** Calculated for $C_{24}H_{27}NO_3S$ ([M+H]$^+$): m/z 410.1790, found: 410.1784

3k: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a yellow oil in 53% yield (41 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.87 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.84 – 6.82 (m, 1H), 4.41 (s (broad), 1H), 4.08 – 3.98 (m, 1H), 3.94 (t, *J* = 10.0 Hz, 1H), 3.58 – 3.41 (m, 1H), 3.01 (s (broad), 1H), 2.54 – 2.40 (m, 1H), 2.34 (s, 3H), 2.31 – 2.10 (m, 2H), 2.05 – 1.92 (m, 2H), 1.91 – 1.77 (m, 1H), 1.75 – 1.67 (m, 1H), 1.66 – 1.50 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8, 138.6, 138.5, 129.4, 129.2, 128.6, 127.8, 126.9, 126.4, 125.9, 78.9, 63.7, 50.3, 33.1 (s (minor)), 29.3, 27.3, 24.7 (s (minor)), 24.3, 23.2, 22.5 (s (minor)), 21.6, 19.8 (s (minor)). **HRMS** Calculated for $C_{20}H_{23}NO_3S_2$ ([M+H]$^+$): 390.1198 m/z, found: 390.1191

3l: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a yellow orange in 28% yield (24 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.92 (d, *J* = 7.9 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 2H), 6.55 (s, 1H), 4.52 (s (broad), 1H), 4.14 – 4.06 (m, 1H), 3.99 (t, *J* = 9.7 Hz, 1H), 3.67 – 3.45 (m, 2H), 2.21 (s, 3H), 2.26 – 2.16 (m, 2H), 2.18 – 1.64 (m, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.5, 145.1, 142.7, 138.1, 130.5, 129.8, 129.1, 128.2, 128.1, 126.7, 126.3, 123.2, 121.7, 106.8, 80.0, 64.8, 51.6, 31.1 (s (minor)), 30.4, 30.0, 28.3, 25.3, 23.8, 21.9. **HRMS** Calculated for $C_{24}H_{25}NO_4S$ ([M+H]$^+$): m/z 424.1583, found: 424.1577

3m: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a clear oil in 23% yield (22 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 6.1 Hz, 2H), 7.37 – 7.18 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 2H), 4.95 (dd, *J* = 8.0, 3.9 Hz, 1H), 4.49 (s (broad), 1H), 4.20 (s (broad), 1H), 4.04 – 3.97 (m, 1H), 3.76 – 3.69 (m, 1H), 3.64 – 3.48 (m, 2H), 3.23 (s (broad), 1H), 2.35 (s, 3H), 2.11 – 2.02 (m, 1H), 2.00 – 1.86 (m, 2H), 1.72 (dt, *J* = 13.2, 7.3 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.6, 140.1, 139.2, 135.5, 129.6, 128.8, 127.6, 126.9, 126.2, 124.9, 121.6, 120.4, 119.7, 118.0, 113.8, 111.7, 110.8, 110.7, 79.3, 63.9, 49.6, 36.6, 29.4, 24.2, 21.5, 21.3. **HRMS** Calculated for $C_{28}H_{28}N_2O_3S$ ([M+H]$^+$): m/z 473.1899, found: 473.1896

Cyclization Reaction of Arenynes S1-4:



Scheme S7. Attempted cyclization of arenynes **S1-S4**.

In electron-deficient arenyne cases, *N,O*-acetal formation proceeds unimpeded, however this intermediate readily decomposes under the reaction conditions producing complex product mixtures. It is worth mentioning that *N,O*-acetal intermediate is isolable and possesses a characteristic signal at ~ δ5.2 ppm in the ^{1}H NMR spectrum corresponding

the methine of the cyclic *N,O*-acetal. A representative ^{1}H NMR spectrum of *N,O*-acetal **S10** is provided below, obtained from premature quenching of reaction of arenyne **S4** with hemiaminal **2**.

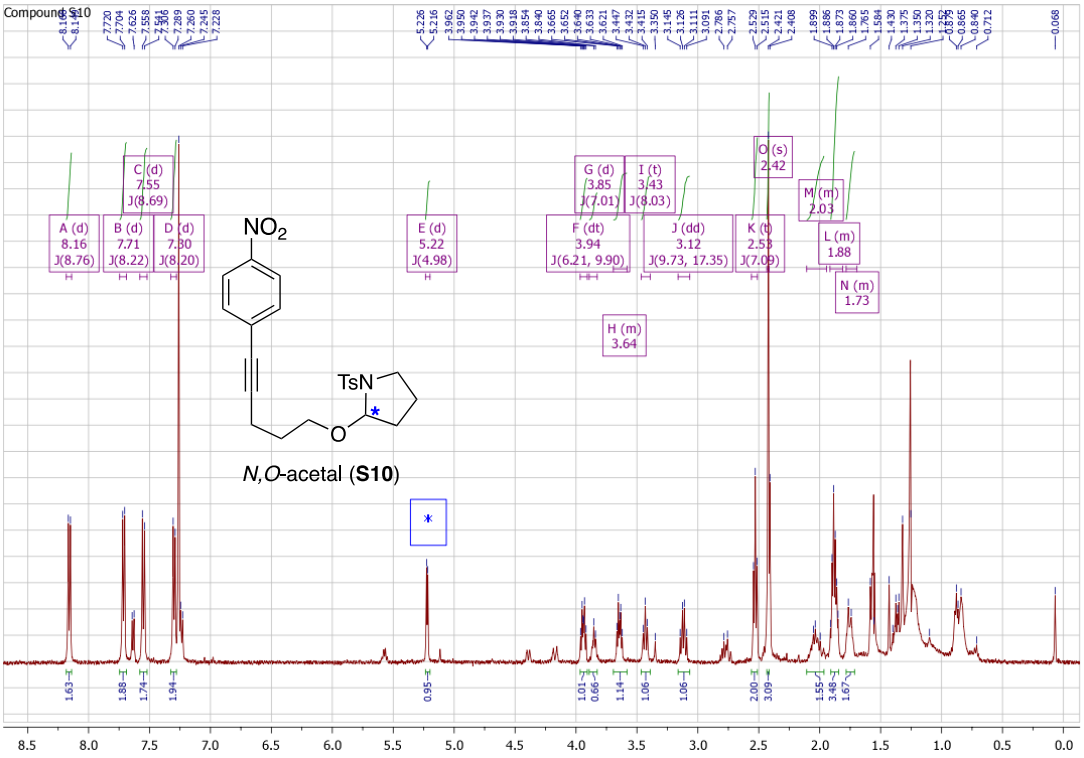
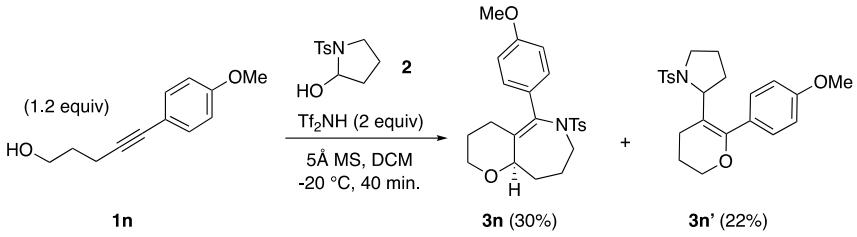


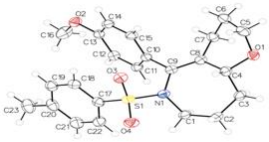
Figure S2: ^{1}H NMR spectra of *N,O*-acetal **S10** from attempted cyclization of arenyne **S4** (characteristic methine proton of *N,O*-acetal labeled with blue asterisk).

Cyclization Reaction of Arenyne 1n:



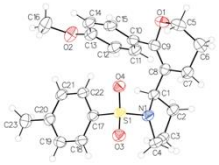
Scheme S8: Production of azepine **3n** and dihydropyran **3n'** under double annulation conditions with **1n**.

3n: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) resulted in the isolation of a white solid which upon recrystallization in 10:1 Pentanes/Et_2O with gentle heating with a heat gun afforded sparkling white crystals suitable for X-Ray crystallographic analysis in 30% yield (25 mg), m.p. 128-129 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 4.37 (d, *J* = 9.6 Hz, 1H), 4.08 (d (broad), *J* = 12.5 Hz, 1H), 4.01 – 3.90 (m, 1H), 3.79 (s, 3H), 3.55 (td, *J* = 10.7, 6.4 Hz, 1H), 3.22 (s (broad), 1H), 2.34 (s, 3H), 2.26 – 2.20 (m, 2H), 2.09 – 2.01 (m, 1H), 1.96 – 1.85 (m, 3H), 1.76 – 1.63 (m, 2H). **^{13}C NMR** (101 MHz, CHCl3) δ 159.2, 142.5, 138.7, 133.1, 130.5, 129.0,



128.8, 127.7, 127.0, 113.4, 79.2, 64.2, 55.4, 51.5, 29.9, 27.1, 24.8, 23.1, 21.3. **HRMS** Calculated for $C_{23}H_{27}NO_4S$ ($[M+H]^+$): m/z 414.1739, found: 414.1733

3n': Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) resulted in the isolation of a white solid which upon recrystallization in 10:1 Pentanes/Et_2O with gentle heating with a heat gun afforded off-white crystals suitable for X-Ray crystallographic analysis in 22% yield (18 mg), m.p. 133-134 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 4.01 – 3.91 (m, 2H), 3.84 (s, *J* = 5.2 Hz, 3H), 3.63 – 3.51 (m, 2H), 3.39 – 3.17 (m, 1H), 3.10 – 2.96 (m, 2H), 2.39 (s, 3H), 2.03 – 1.10 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3, 131.7, 131.3, 128.4, 127.8, 123.9, 118.8, 89.8, 64.5, 40.1, 29.2, 29.0, 27.0, 24.9, 17.4, 16.1, 14.1. **HRMS** Calculated for $C_{23}H_{27}NO_4S$ ($[M+H]^+$): m/z 414.1739, found: 414.1733



Conformational Isomerism of Azepine 3n:

As we worked to characterize the novel oxacyclo[3,2-*c*]-azepines and azocines, we discovered that the vast majority of these molecules display complex conformational profiles at room temperature, evidenced by indistinct, blobby multiplets within the aliphatic region of the ^{1}H NMR spectra.[22] X-Ray crystallography provided useful insight into this phenomenon, as structural data acquired for azepine **3n** reveals the cocrystallization of two (enantiomorphic) conformational isomers in a 78:22 ratio (bold and dashed, respectively; Figure S3, left). At room temperature, the crystal structure of azepine 3n undergoes boat-to-chair and chair-to-boat interconversion within the oxa- and azacyclic subunits, respectively. Taken together with extensive 2D-NMR spectroscopic studies, the protons of the ^{1}H NMR spectra displayed as indistinct multiplets are in excellent agreement with carbons of the southern hemisphere (denoted with grey spheres in Figure S3, right) which exhibit dynamic behavior in the crystal structure.

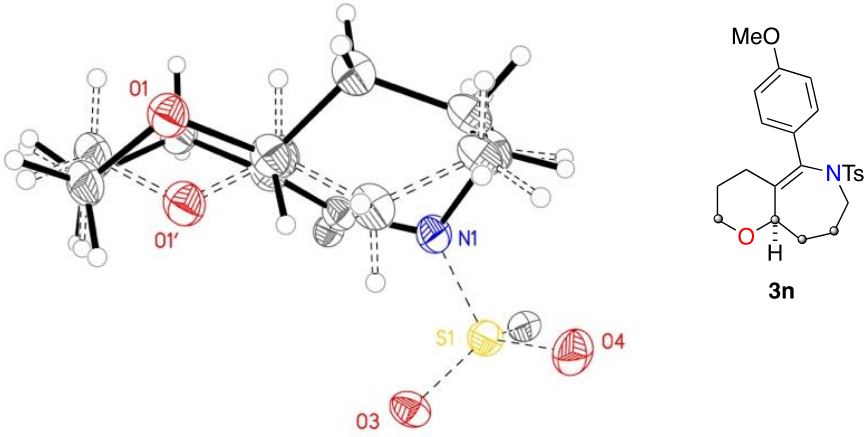
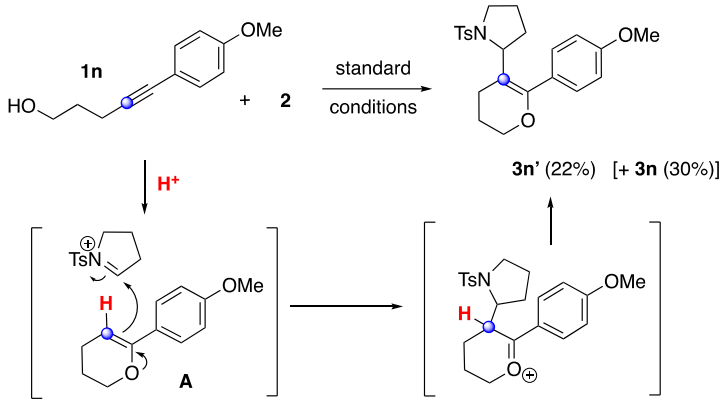


Figure S3: Conformational isomerism of **3n** by X-Ray crystallographic analysis (aryl groups removed for clarity)

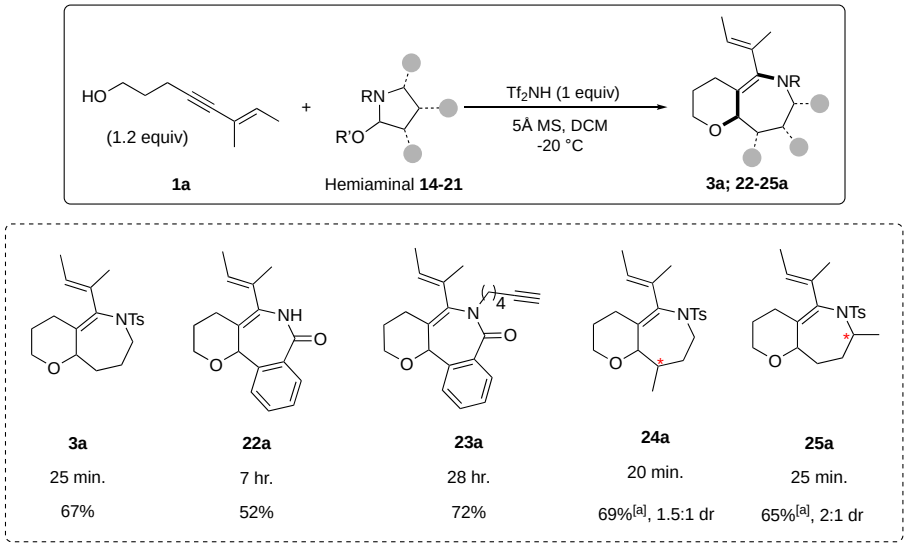
Mechanistic Proposal for the Formation of Dihydropyran 3n':



Scheme S8: Tentative mechanistic proposal for the reactivity of arenyne towards the production of **3n'**.

A tentative mechanism for the formation of dihydropyran **3n'** is outlined in the Scheme S8. Under the acidic reaction conditions, the electron-rich alkyne could first suffer protonation, followed by capture of vinyl cation by the pendent alcohol. This would generate the especially nucleophilic species **A**, which can engage in undesirable reaction pathways; in this case, attack on the iminium species. We conclude from this that in electron-rich alkynes, alkyne protonation (intramolecular) competes with dehydrative condensation (intermolecular), compromising reaction efficiency and lowering yields.

Cyclization Reaction of Hemiaminal Variants:



[a] 0.25 equiv of promoter used.

Scheme S9. Hemiaminal substrate scope.

3a: Isolated as a clear oil in 67%. (*vide supra*, page S9)

22a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale yellow oil in 52% yield (28 mg). **^{1}H NMR (**500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 1H), 7.60 – 7.47 (m, 3H), 7.06 (s, 1H), 5.97 (s, 1H), 5.79 – 5.73 (m, 1H), 3.57 (dd, *J* = 15.1, 6.1 Hz, 1H), 3.40 – 3.30 (m, 1H), 2.36 (t, *J* = 6.7 Hz, 2H), 1.74 (dd, *J* =

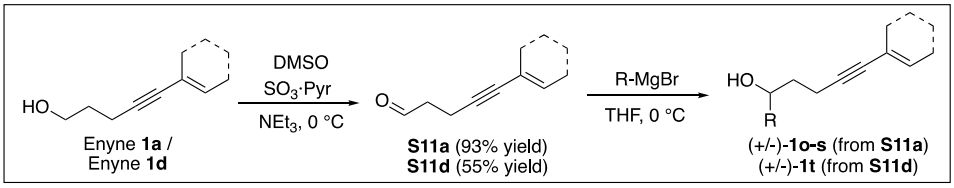
12.8, 6.4 Hz, 2H), 1.69 (s, 3H), 1.62 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.2, 143.3, 132.7, 132.1, 131.3, 131.0, 130.0, 127.3, 123.9, 123.7, 118.7, 84.1, 63.3, 28.9, 16.0, 14.4, 13.5. **HRMS** Calculated for $C_{17}H_{19}NO_2$ ($[M+H]^+$): m/z 270.1494, found: 270.1488

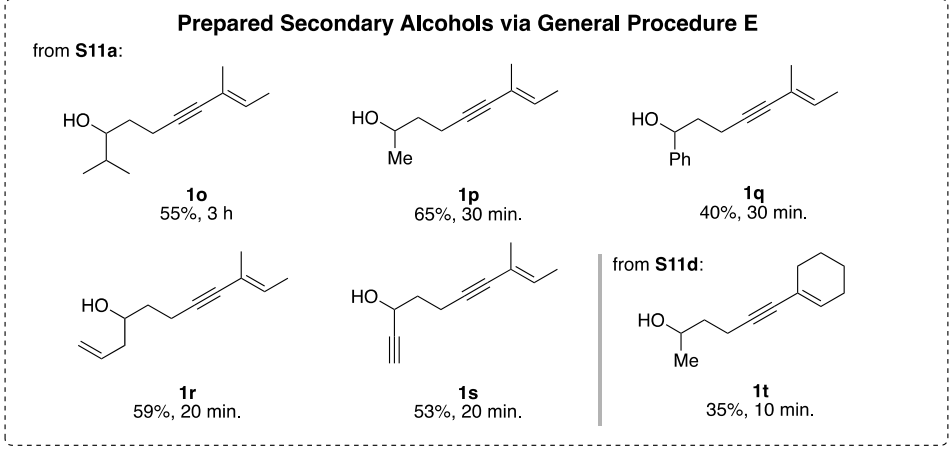
23a: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded a clear oil in 72% yield (50 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.3 Hz, 1H), 7.62 – 7.48 (m, 3H), 5.89 (s, 1H), 5.74 (q, *J* = 5.5 Hz, 1H), 3.83 (dt, *J* = 15.3, 7.7 Hz, 1H), 3.25 (ddt, *J* = 26.5, 8.9, 5.9 Hz, 2H), 3.07 – 2.98 (m, 1H), 2.40 – 2.33 (m, 2H), 2.30 – 2.21 (m, 2H), 1.96 – 1.92 (m, 1H), 1.85 – 1.75 (m, 2H), 1.69 (s, 3H), 1.64 (d, *J* = 6.9 Hz, 3H), 1.62 – 1.55 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 141.0, 133.1, 132.0, 131.3, 131.0, 130.0, 127.3, 123.6, 118.7, 86.0, 84.8, 68.8, 60.6, 39.0, 28.8, 27.3, 25.9, 18.2, 17.2, 16.0, 14.0. **HRMS** Calculated for $C_{22}H_{25}NO_2$ ($[M+H]^+$): m/z 350.2120, found: 350.2122

24a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale yellow oil in 69% yield as a 1.5:1 mixture of diastereomers (52 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 3H), 7.24 – 7.19 (m, 3H), 5.53 – 5.40 (m, 2H), 4.13 (s, 1H), 4.03 – 3.89 (m, 3H), 3.85 (t , *J* = 9.1 Hz, 1H), 3.41 (td, *J* = 11.0, 6.1 Hz, 1H), 3.32 (dd, *J* = 18.5, 9.5 Hz, 1H), 3.12 (dd, *J* = 18.9, 7.5 Hz, 1H), 2.96 – 2.81 (m, 1H), 2.40 (s, 6H), 2.32 – 2.10 (m, 5H), 2.01 – 1.61 (m, 5H), 1.57 (d, *J* = 6.7 Hz, 4H), 1.53 (d, *J* = 6.7 Hz, 5H), 1.18 (s, 2H), 1.14 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 2H), 0.96 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8 (s (minor)), 142.7, 139.1, 138.8 (s (minor)), 137.2, 131.1 (s(minor)), 130.9, 129.1, 129.0, 127.3, 127.2, 127.1 (s(minor)), 82.9, 82.5 (s (minor)), 65.7, 49.9, 34.1 (s (minor)), 32.8, 32.1, 30.5 (s (minor)), 29.8, 21.6, 18.2 (s (minor)), 14.6, 14.5 (s(minor)), 13.6 (s (minor)), 13.5. **HRMS** Calculated for $C_{21}H_{29}NO_3S$ ($[M+H]^+$): m/z 376.1946, found: 376.1940

25a: Purification by Prep TLC using 60% Hex/EtOAc (1% triethylamine) afforded a pale yellow oil in 65% yield as a 2:1 mixture of diastereomers (49 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 3H), 5.54 – 5.41 (m, 2H), 4.16 – 4.08 (m, 2H), 4.03 – 3.81 (m, 4H), 3.43 (ddd, *J* = 16.4, 11.6, 6.2 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.20 – 3.05 (m, 1H), 2.89 (s (broad) (minor), 1H), 2.40 (s, 5H), 2.30 – 2.14 (m, 4H), 1.57 (d (minor), *J* = 6.9 Hz, 3H), 1.54 (d, *J* = 6.3 Hz, 4H), 1.17 (s (minor), 2H), 1.14 (s, 3H), 1.01 (d (minor), *J* = 6.4 Hz, 2H), 0.96 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 142.4 (s(minor)), 139.6, 136.9, 132.0, 131.6 (s(minor)), 129.1, 129.0, 128.8 (s (minor)), 128.6 (s (minor)), 127.8, 127.2, 81.6 (s (minor)), 79.2, 69.1 (s (minor)), 64.5, 55.1 (s (minor)), 53.5, 34.2 (s (minor)), 32.2, 31.9 (s (minor)), 29.8 (m (minor)), 29.3, 25.6, 25.4 (s (minor)), 24.3, 21.6, 20.5, 20.1 (s (minor)), 15.5, 13.9. **HRMS** Calculated for $C_{21}H_{29}NO_3S$ ($[M+H]^+$): m/z 376.1946, found: 376.1943

General Procedure E for the Synthesis of Racemic Secondary Alcohols (+/-)1o-t:





Scheme S10. Secondary Racemic Alcohols **1o-t** synthesized via General Procedure E.

General Parikh-Doering Oxidation Method: To a round-bottom flask, enyne **1a** or **1d** was dissolved in DCM and following triethylamine was added and stirred at 0 °C. Following cooling to 0 °C, a solution of 1M solution of sulfur trioxide pyridine complex in DMSO was added slowly/dropwise at 0 °C. Following consumption of starting material (as monitored by TLC analysis), the reaction was quenched with 1M HCl (2x the volume of the reaction mixture) and then extracted until a pH =1 was obtained. The combined organics were washed with water 2x, followed by satd. brine solution, dried with $MgSO_4$, filtered and then concentrated to afford the aldehyde product **S11a** (from **1a**) and **S11d** (from **1d**) in 93% (1.28 g) and 55% yield (65 mg) respectively.

Grignard Addition Method: Crude aldehyde **S11a/S11d** (1 mmol) was dissolved in dry Et_2O and cooled to 0 °C. Following cooling to 0°C, 1.2 equiv Grignard (1M in THF) (1.2 mmol) was added dropwise over 30 min. The reaction was monitored by TLC analysis and upon the observed consumption of starting material, the reaction was quenched with NH_4Cl, washed with brine, dried with $MgSO_4$ filtered and concentrated to afford the secondary alcohol (**1o-t**) which was purified via column chromatography using 80% Hex/EtOAc as the lead eluent.

1o: Purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to afford the product as a clear oil in 55% yield (50 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.82 (q, *J* = 6.8 Hz, 1H), 3.53 – 3.47 (m, 1H), 2.43 (td, *J* = 7.0, 3.1 Hz, 2H), 1.75 (s, 3H), 1.73 – 1.67 (m, 2H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.62 – 1.54 (m, 1H), 0.92 (dd, *J* = 6.8, 1.2 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.3, 118.7, 85.9, 84.4, 76.2, 33.8, 33.2, 18.8, 17.5, 17.3, 16.4, 14.1. **HRMS** Calculated for $C_{12}H_{20}O$ ($[M+H]^+$): m/z 181.1592, found: 181.1589

1p: Purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to afford the product as a pale yellow oil in 65% yield (49 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.84 – 5.76 (m, 1H), 3.93 (q, *J* = 6.1 Hz, 1H), 2.43 – 2.35 (m, 2H), 1.99 (s(broad), 1H), 1.72 (s, 3H), 1.66 – 1.61 (m, 5H), 1.19 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.9, 118.7, 85.5, 84.4, 67.4, 37.9, 23.4, 17.2, 16.0, 14.0 **HRMS** Calculated for $C_{10}H_{16}O$ ($[M+H]^+$): m/z 153.1279, found: 153.1276

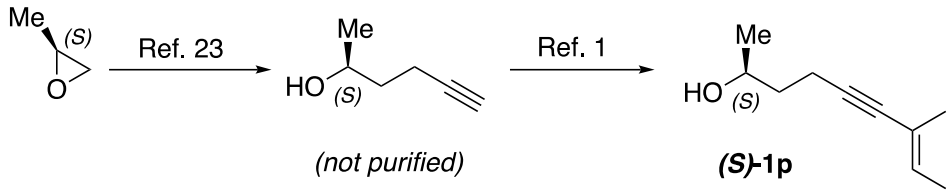
1q: Purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to afford the product as a viscous clear oil in 40% yield (43 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 5.85 (q, *J* = 8.0 Hz, 1H), 4.90 – 4.81 (m, 1H), 2.51 – 2.26 (m, 2H), 2.06 – 1.87 (m, 2H), 1.77 (s, 3H), 1.67 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.3, 131.4, 128.6, 127.8, 126.0, 118.7, 85.4, 84.7, 73.7, 38.1, 17.3, 16.2, 14.1. **HRMS** Calculated for $C_{15}H_{18}O$ ($[M+H]^+$): m/z 215.1436, found: 215.1431

1r: Purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to afford the product as a yellow-orange oil in 59% yield (53 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 – 5.76 (m, 2H), 5.14 (d, *J* = 5.9 Hz, 1H), 5.11 (s, 1H), 3.82 – 3.74 (m, 1H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.34 – 2.14 (m, 2H), 1.96 – 1.84 (m, 1H), 1.73 (s, 3H), 1.77 – 1.59 (m, 2H), 1.64 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.7, 131.3, 118.7, 118.2, 85.5, 84.4, 70.1, 41.9, 35.7, 17.2, 16.0, 14.0. **HRMS** Calculated for $C_{12}H_{18}O$ ($[M+H]^+$): m/z 179.1436, found: 179.1434

1s: Purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to afford the product as a light brown oil in 53% yield (43 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.82 (q, *J* = 7.3 Hz, 1H), 4.54 (t, *J* = 6.5 Hz, 1H), 2.58 – 2.39 (m, 3H), 1.99 – 1.89 (m, 3H), 1.73 (s, 3H), 1.64 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.6, 118.6, 84.7, 84.6, 73.5, 61.4, 36.6, 17.2, 15.4, 14.0. **HRMS** Calculated for $C_{11}H_{14}O$ ($[M+H]^+$): m/z 163.1123, found: 163.1130

1t: Purified by column chromatography (using a step gradient of 100% hexanes/DCM to 100% DCM/hexanes) to afford the product as a light yellow oil in 35% yield (31 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.04 – 5.99 (m, 1H), 4.00 – 3.90 (m, 1H), 2.45 – 2.38 (m, 2H), 2.12 – 2.00 (m, 4H), 1.82 (s(broad), 1H), 1.69 – 1.51 (m, 6H), 1.21 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.8, 120.9, 86.6, 83.2, 67.5, 37.9, 29.6, 25.7, 23.5, 22.5, 21.7, 16.1. **HRMS** Calculated for $C_{12}H_{18}O$ ($[M+H]^+$): m/z 179.1436, found: 179.1434

Synthesis of Enantiopure Secondary Alcohol *(S)*-1p[1,23]



Scheme S11. Synthesis of ***(S)*-1p.**

A round-bottom flask was charged with a stir-bar and purged with argon multiple times. Triethylamine (10 ml) was added and the solvent was degassed by sparging with argon through a long needle. $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol, 5 mol%), copper iodide (76 mg, 0.4 mmol, 10 mol%) and vinyl bromide (2.16 g, 16 mmol, 4.0 equiv.) were added successively, while still degassing. After 10 min of continued degassing, crude-hex-5-yn-2-ol (392 mg, 4 mmol, 1.0 equiv.) was added dropwise. Degassing was ceased and the reaction was carried out at 50 °C for 16 h until consumption of starting material was observed by TLC, upon which Et_2O (equal to the initial volume of triethylamine) was added. The reaction was filtered over Celite 545. The filtrate was transferred to a separating funnel and washed repeatedly (typically twice) with 1 M aq. HCl until the obtained aqueous layer was roughly pH = 1 and all triethylamine was removed from the organic layer. The remaining organic layer was then washed with a saturated aqueous solution of $NaHCO_3$ and water (both equal to the initial amount of Et_2O) and the organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by column chromatography (eluting gradients of Et_2O in PhMe) to obtain pure ***(S)*-1p** (334 mg, 55% yield over two steps) as a yellow oil. The analytical data obtained matches the analytical data of racemic compound **1p**.

Chiral shift NMR: ***(S)*-1p** (5 mg) and $Eu(hfc)_3$ (15 mg) were dissolved in $CDCl_3$ (0.4 ml) and a ^1H NMR spectrum was collected. The obtained spectrum was compared to the ^1H NMR spectrum obtained from racemic **1p** (5 mg) and $Eu(hfc)_3$ (15 mg) in $CDCl_3$ (0.4 ml) (Figure S4).

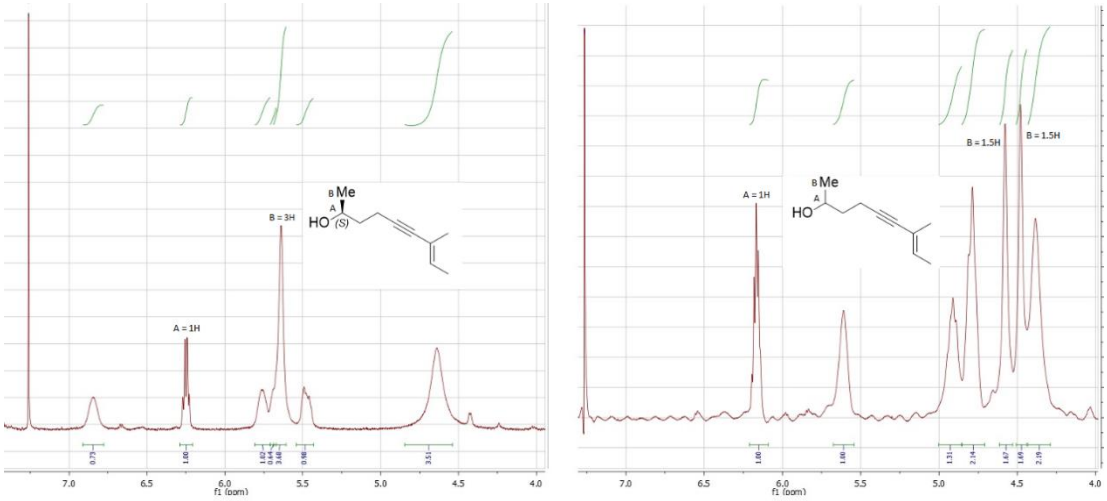
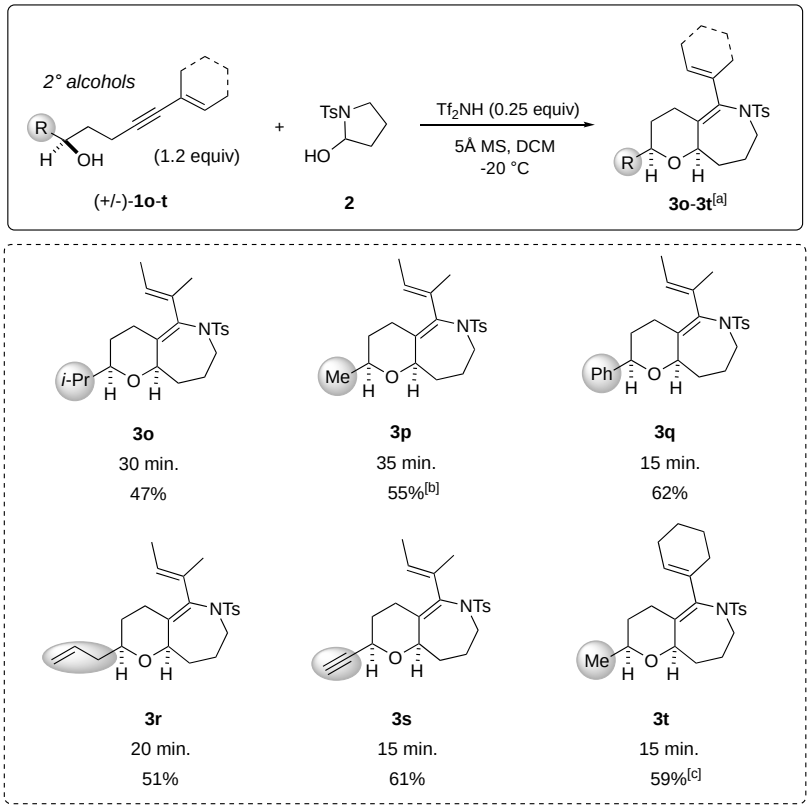


Figure S4. Chiral shift NMR data of enantiopure ***(S)*-1p** (left) and racemic **1p** (right).

Cyclization Reaction of Secondary Alcohol Variants:



[a] Diastereoselectivity was >19:1 for all annulations: a single diastereoisomer was observed by ^{1}H NMR. [b] With reactant ***(S)*-1o** (>99:1 er), **3o** is isolated in 54% yield, >19:1 dr; > 99:1 er (HPLC analysis). [c] Reaction performed at -40 °C.

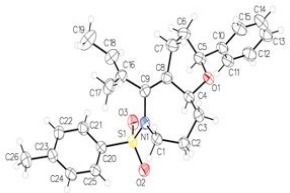
Scheme S12. Diastereoselective synthesis of azepines **3o-t.**

3o: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded the product as clear viscous oil in 47% yield (38 mg) as one isomer (>19:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 5.50 (q, *J* = 7.0 Hz, 1H), 4.19 – 4.01 (m, 2H), 2.88 (dd, *J* = 15.3, 7.6 Hz, 1H), 2.79 (s (broad), 1H), 2.40 (s, 3H), 2.37 – 2.26 (m, 1H), 2.10 (s (broad), 2H), 1.95 – 1.68 (m, 3H), 1.67 – 1.60 (m, 3H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.18 (s, 3H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.84 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 139.5, 136.27, 131.6, 129.1, 127.6, 126.8, 79.9, 79.4, 51.7, 33.9, 29.8, 29.4, 27.6, 23.7, 21.5, 18.8, 18.0, 14.6, 13.4. **HRMS** Calculated for $C_{23}H_{33}NO_3S$ ($[M+H]^+$): m/z 404.2259, found: 404.2258

(+/-) 3p: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded the product as a clear viscous oil in 55% yield (41 mg) as one isomer (>19:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 5.48 (q, *J* = 7.0 Hz, 1H), 4.22 (d, *J* = 9.6 Hz, 1H), 4.03 (s (broad), 1H), 3.54 – 3.44 (m, 1H), 2.99 (s (broad), 1H), 2.40 (s, 3H), 2.30 – 2.21 (m, 2H), 2.12 – 1.77 (m, 3H), 1.77 – 1.57 (m, 3H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.23 (s, *J* = 7.4 Hz, 3H), 1.19 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 139.8, 137.3, 136.9, 131.7, 129.1, 127.6, 127.1, 79.1, 71.3, 52.0, 34.0, 29.5, 27.1, 24.5, 22.3, 21.4, 14.7, 13.4. **HRMS** Calculated for $C_{21}H_{29}NO_3S$ ($[M+H]^+$): m/z 376.1946, found: 376.1945

***(S)*-3p:** Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded the product as a clear viscous oil in 54% yield (41 mg) as a single isomer (>19:1 dr; >99:1 er). Characterization data matches that of **(+/-)-3p**. See S23-S24 for chromatogram of chiral HPLC.

3q: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded a yellow oil which upon subjection to a 10:1 Pentanes/Et_2O mixture with gentle heating with a heat gun afforded produced pale-yellow crystals suitable for X-Ray crystallographic anaylsis in 62% yield (47 mg) as a single isomer (>19:1 dr); m.p. 167 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.0 Hz, 2H), 7.37 – 7.30 (m, 4H), 7.25 (d, *J* = 7.3 Hz, 3H), 5.55 (q, *J* = 6.0 Hz, 1H), 4.45 (dd, *J* = 9.9, 5.4 Hz, 1H), 4.39 (d, *J* = 8.9 Hz, 1H), 4.12 (s (broad), 1H), 3.14 (s (broad), 1H), 2.42 (s, 3H), 2.19 – 1.70 (m, 8H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.27 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.9, 142.8, 139.8, 137.5, 135.9, 131.7, 129.1, 128.4, 127.6, 127.3, 127.3, 125.9, 79.6, 77.4, 52.3, 34.6, 29.3, 26.7, 25.4, 21.4, 14.7, 13.4. **HRMS** Calculated for $C_{26}H_{31}NO_3S$ ($[M+H]^+$): m/z 438.2103, found: 438.2102;



<u>X-Ray Crystallographic analysis reveals a *syn* relationship within the dihydropyranyl ring at the 2-and 6-positions.</u>

3r: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded the product Isolated as pale yellow oil in 51% yield (50 mg) as one isomer (>19:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 5.88 – 5.74 (m, 1H), 5.53 – 5.42 (m, 1H), 5.13 – 4.98 (m, 2H), 4.17 (d, *J* = 9.5 Hz, 1H), 4.04 (s(broad), 1H), 3.44 – 3.32 (m, 1H), 2.95 (s (broad), 1H), 2.39 (s, 3H), 2.35 – 1.63 (m, 10H), 1.55 (d, *J* = 6.0 Hz, 3H), 1.23 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 139.5, 136.7, 135.1, 131.6, 129.1, 127.5, 127.0, 116.6, 79.3, 74.5, 51.8, 41.1, 31.6, 29.4, 27.3, 23.9, 21.5, 14.6, 13.4. **HRMS** Calculated for $C_{23}H_{31}NO_3S$ ($[M+H]^+$): m/z 402.2103, found: 402.2101

3s: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded the product as a pale yellow oil in 61% yield (39 mg) as one isomer (>19:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 5.53 – 5.43 (m, 1H), 4.26 (d, *J* = 9.1 Hz, 1H), 4.13 (t, *J* = 6.0 Hz, 1H), 4.05 (s (broad) , 1H), 2.99 (s (broad), 1H), 2.41 (s, 3H), 2.37 – 2.23 (m, 2H), 2.13 – 1.79 (m, 6H), 1.69 – 1.58 (m, 1H), 1.56 (d, *J* = 6.1 Hz, 3H), 1.23 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.9, 139.4, 137.9, 131.4, 129.2, 127.6, 127.6, 83.9, 79.6, 73.1, 64.9, 51.9, 33.0, 29.4, 27.1, 24.0, 21.5, 14.6, 13.5. **HRMS** Calculated for $C_{22}H_{27}NO_3S$ ($[M+H]^+$): m/z 386.1790, found: 386.1795

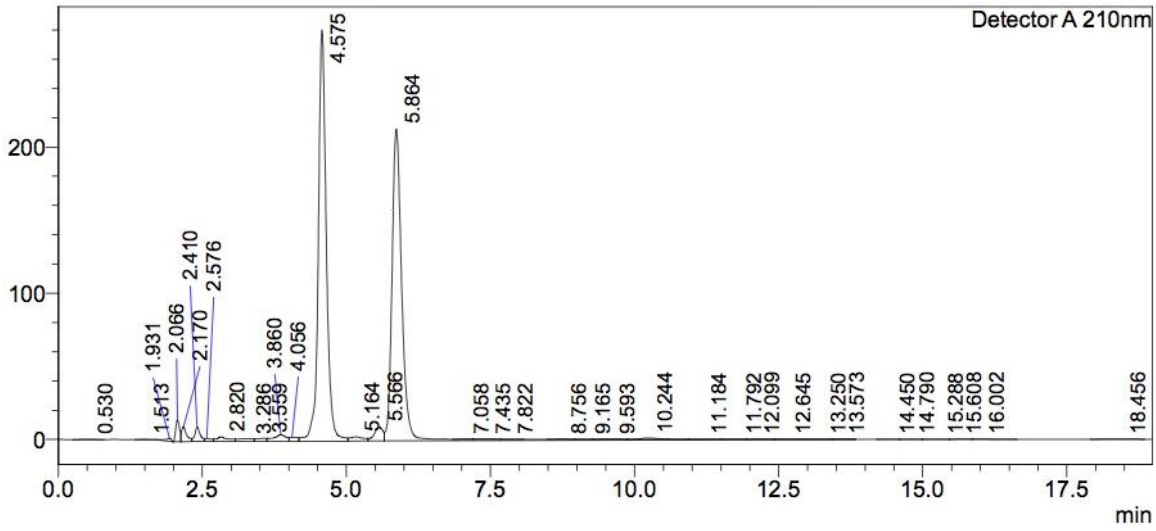
3t: Purification by Prep TLC using 80% Hex/EtOAc (1% triethylamine) afforded as a clear oil in 59% yield (49 mg) as one isomer (>19:1 dr). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.67 – 5.59 (m, 1H), 4.24 (d, *J* = 9.5 Hz, 1H), 4.09 – 3.91 (m, 1H), 3.49 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.03 – 2.86 (m, 1H), 2.43 – 2.38 (m, 3H), 2.36 – 2.20 (m, 2H), 2.15 – 1.89 (m, 6H), 1.87 – 1.34 (m, 8H), 1.19 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 139.8, 135.6, 133.5, 129.2, 129.1, 128.0, 127.6, 79.1, 71.1, 51.8, 33.8, 29.5, 27.3, 27.2, 25.3, 24.1, 22.3, 22.3, 22.0, 21.5. **HRMS** Calculated for $C_{23}H_{31}NO_3S$ ($[M+H]^+$): m/z 402.2103, found: 402.2100

Chromatogram of (+/-)-3p (Racemate):

<Chromatogram>

mV

(+/-)-3p (Racemate)



<Peak Table>

Detector A 210nm

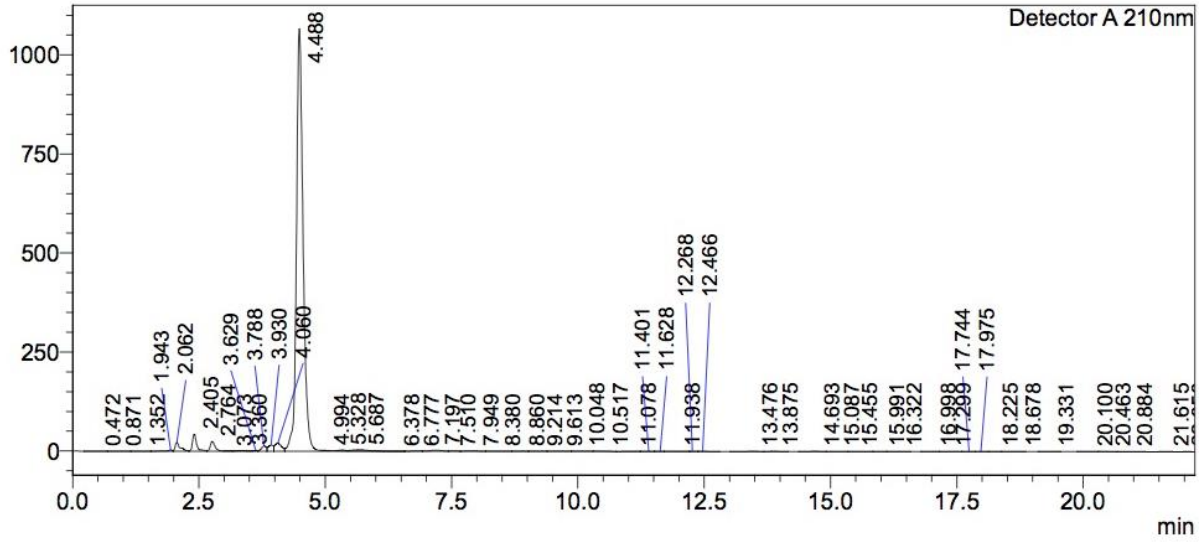
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	0.530	1858	111	0.000			
2	1.513	1247	142	0.000			
3	1.931	14256	1966	0.000			
4	2.066	69017	14948	0.000			
5	2.170	62647	9972	0.000		V	
6	2.410	65028	9807	0.000		V	
7	2.576	16888	2033	0.000		V	
8	2.820	48030	3182	0.000		V	
9	3.286	34871	1915	0.000		V	
10	3.559	24360	1946	0.000		V	
11	3.860	68397	4455	0.000		V	
12	4.056	26586	2617	0.000		V	
13	4.575	2699524	281303	0.000		V	
14	5.164	48278	2896	0.000		V	
15	5.566	99753	9589	0.000		V	
16	5.864	2655984	213275	0.000		SV	
17	7.058	1572	115	0.000		T	
18	7.435	3568	187	0.000		TV	
19	7.822	1379	96	0.000		TV	
20	8.756	3498	188	0.000		TV	
21	9.165	1900	126	0.000		TV	
22	9.593	7228	287	0.000		TV	

Chromatogram of-3p:

<Chromatogram>

mV

(S)-3p (Enantioenriched)



<Peak Table>

Detector A 210nm

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1	0.472	3772	208	0.000			
2	0.871	4672	265	0.000		V	
3	1.352	3420	256	0.000			
4	1.943	22210	3042	0.000		V	
5	2.062	152724	22919	0.000		V	
6	2.405	249275	43873	0.000		V	
7	2.764	193777	24866	0.000		SV	
8	3.073	1313	219	0.000		T	
9	3.360	9709	772	0.000		TV	
10	3.629	2356	497	0.000		T	
11	3.788	92304	13578	0.000		V	
12	3.930	109146	15922	0.000		V	
13	4.060	187119	20194	0.000		V	
14	4.488	9808048	1066202	0.000		SV	
15	4.994	1502	319	0.000		T	
16	5.328	13999	1648	0.000		TV	
17	5.687	62065	3303	0.000		TV	
18	6.378	1862	173	0.000		T	
19	6.777	8033	613	0.000			
20	7.197	42814	2690	0.000		V	
21	7.510	8039	691	0.000		V	
22	7.949	12542	610	0.000		V	

X-Ray Crystal Data for Compounds 3n, 3n' and 3q

Data collection

A crystal (0.141 x 0.091 x 0.037 mm^3) was placed onto a thin glass optical fiber or a nylon loop and mounted on a Rigaku XtaLab Synergy-S Dualflex diffractometer equipped with a HyPix-6000HE HPC area detector for data collection at 100.00(10) K. A preliminary set of cell constants and an orientation matrix were calculated from a small sampling of reflections.[24]A short pre-experiment was run, from which an optimal data collection strategy was determined. The full data collection was carried out using a PhotonJet (Cu) X-ray Source with frame times of 0.37 and 1.49 seconds and a detector distance of 31.2 mm. Series of frames were collected in 0.50º steps in ω at different 2θ, κ, and ϕ settings. After the intensity data were corrected for absorption, the final cell constants were calculated from the xyz centroids of 10552 strong reflections from the actual data collection after integration. [24] See Table S2, S3, and S4 for additional crystal and refinement information.

Structure solution and refinement

The structure was solved using ShelXT[25] and refined using ShelXL[26] The space group $P2_1/n$ was determined based on systematic absences. Most or all non-hydrogen atoms were assigned from the solution. Full-matrix least squares / difference Fourier cycles were performed which located any remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0415$ (F^2, $I > 2\sigma(I)$) and $wR2 = 0.1147$ (F^2, all data).

Structure description

The structure is the one suggested. The asymmetric unit contains one molecule in a general position. One segment (-C2-C3-C4-O1-C5-) of the molecule is modeled as disordered over two positions (0.78:0.22).

Structure manipulation and figure generation were performed using Olex2. [27] Unless noted otherwise all structural diagrams containing thermal displacement ellipsoids are drawn at the 50 % probability level.

Data collection, structure solution, and structure refinement were conducted at the X-ray Crystallographic Facility, B04 Hutchison Hall, Department of Chemistry, University of Rochester. The instrument was purchased with funding from NSF MRI program grant CHE-1725028.

Some equations of interest:

$$R_{int} = \Sigma\, |F_o^2 - \langle F_o^2 \rangle| \,/\, \Sigma |F_o^2|$$

$$R1 = \Sigma ||F_o| - |F_c|| \,/\, \Sigma |F_o|$$

$$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] \,/\, \Sigma\, [w(F_o^2)^2]]^{1/2}$$

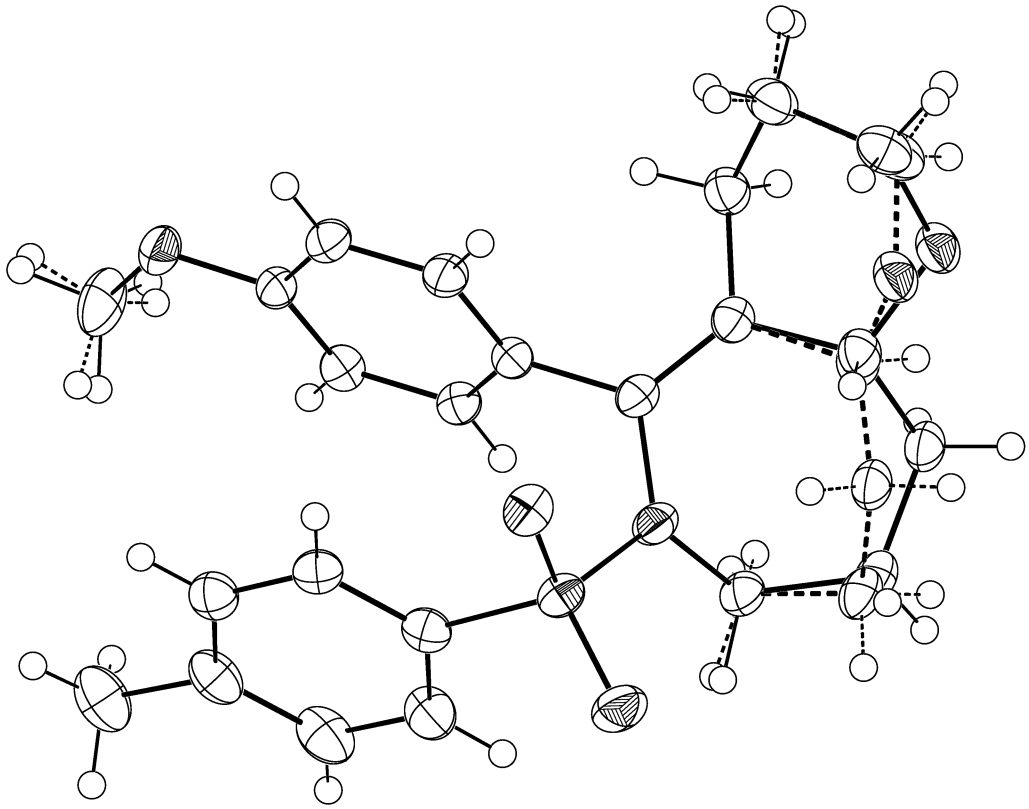
where $w = 1 \,/\, [\sigma^2 (F_o^2) + (aP)^2 + bP]$ and

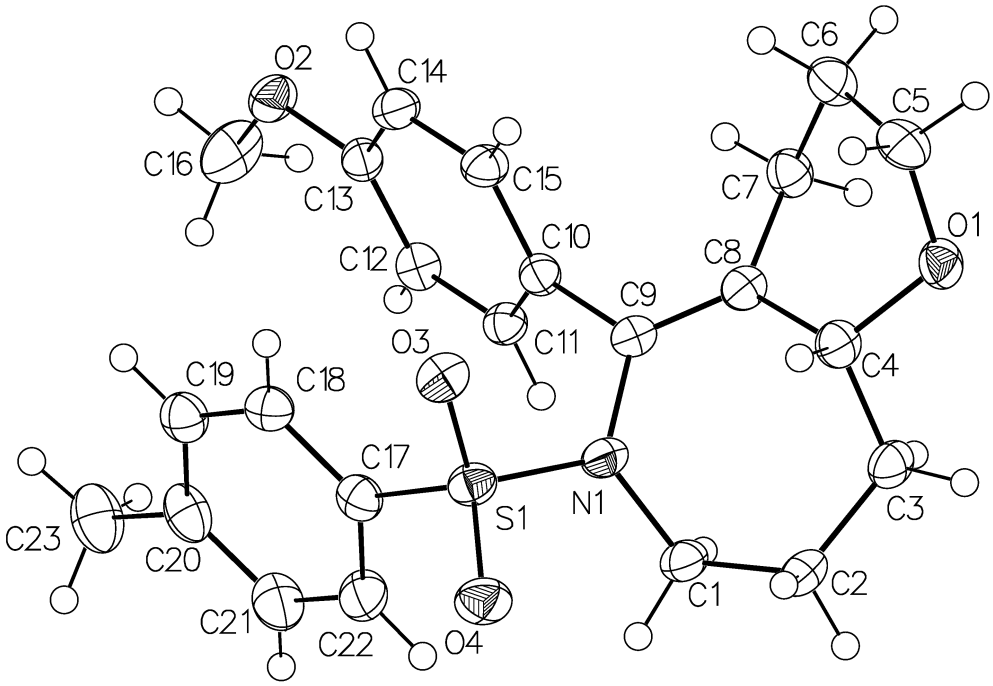
$$P = 1/3 \max (0, F_o^2) + 2/3\, F_c^2$$

$$\text{GOF} = S = [\Sigma[w(F_o^2 - F_c^2)^2] \,/\, (m-n)]^{1/2}$$

where m = number of reflections and n = number of parameters

X-Ray Crystal Data for Compound 3n




O2
C14
C6
C5
C16
C13
C15
C7
O1
C12
C10
C8
C9
O3
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C3
C23
C20
C1
C2
C21
C22
O4

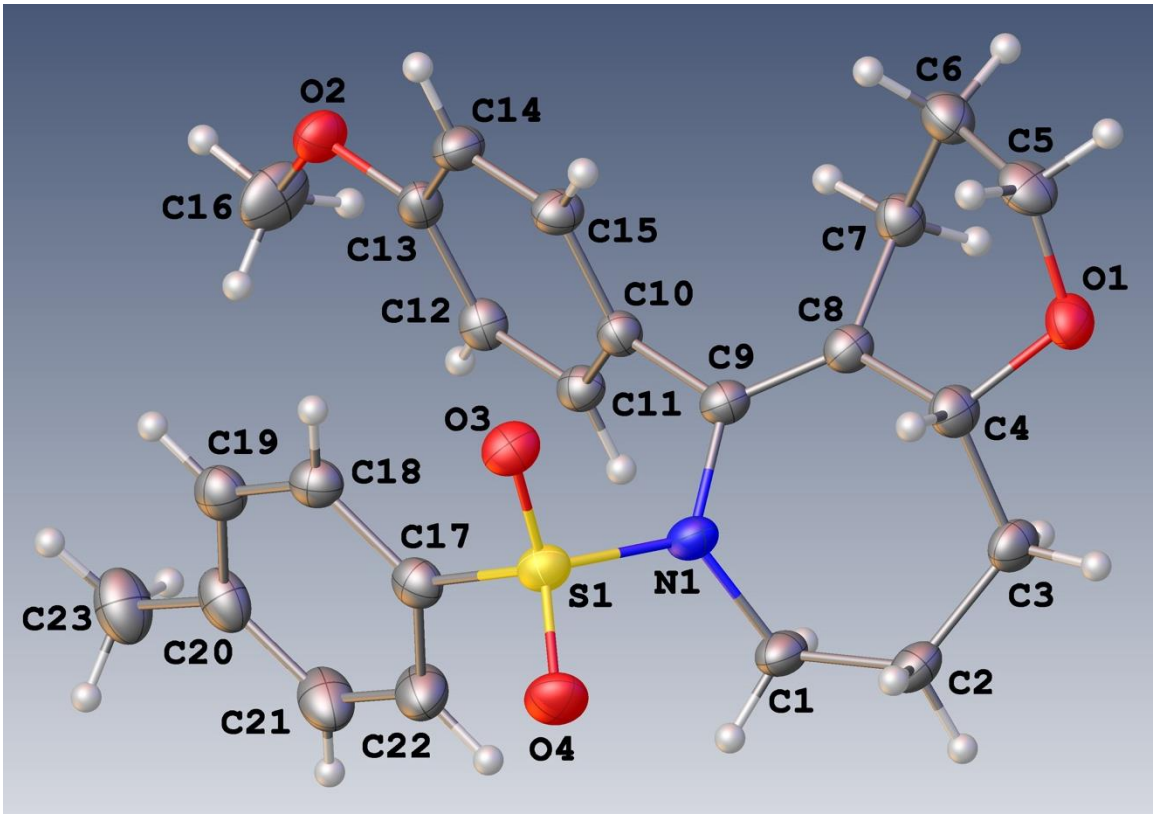
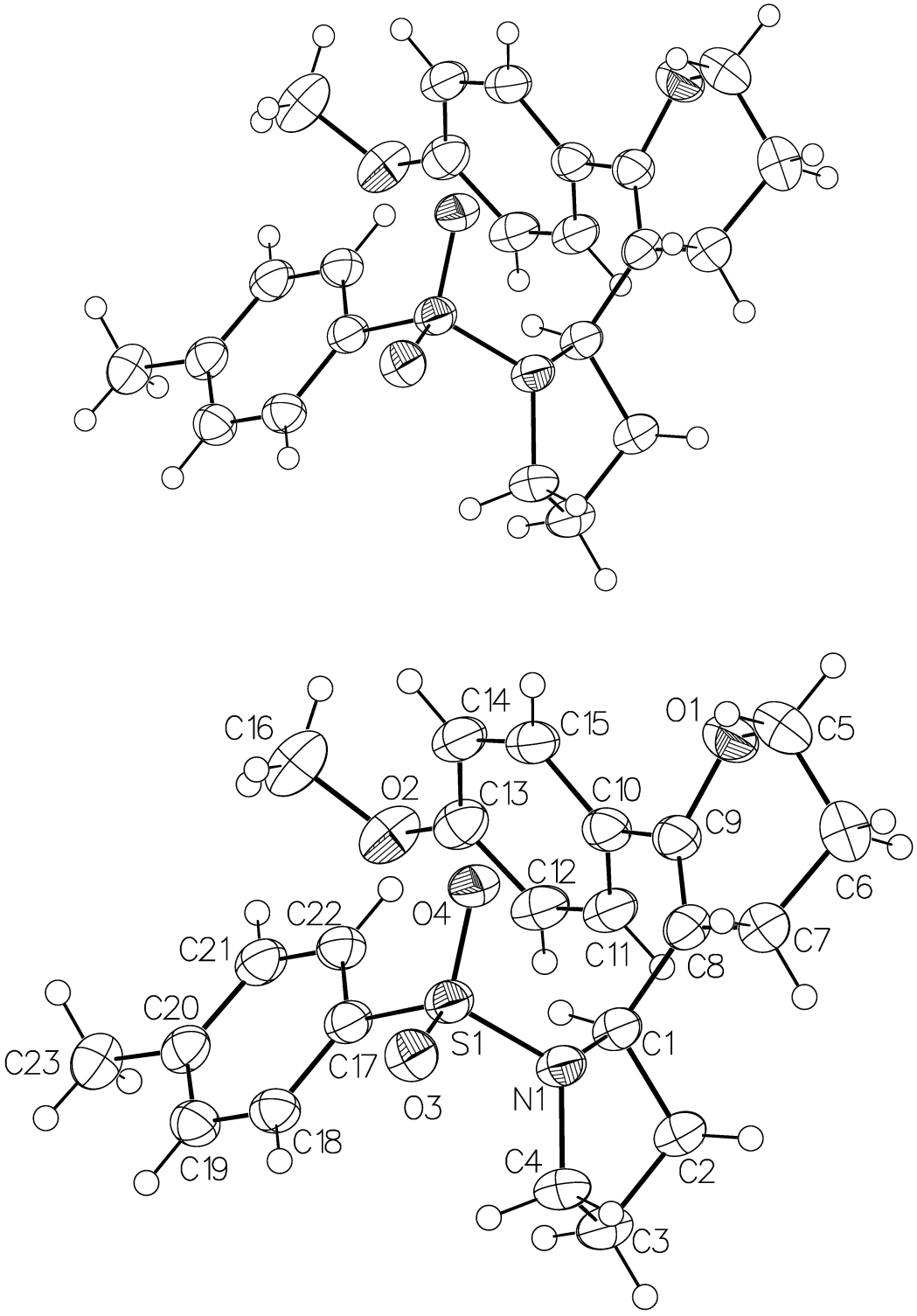
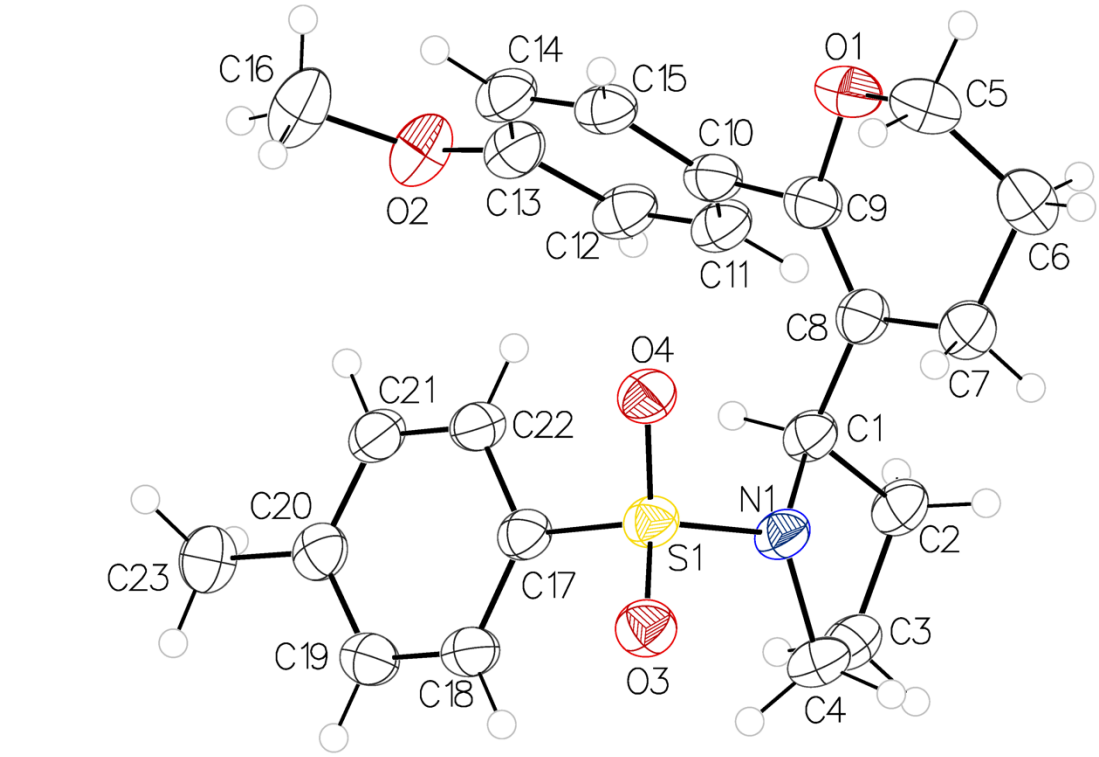

O2
C14
C6
C5
C16
C13
C15
C7
O1
C12
C10
C8
C9
C11
O3
C4
C19
C18
C17
S1
N1
C3
C23
C20
C1
C2
C21
C22
O4

Table S2. Crystal data and structure refinement for compound **3n**.

Identification code	Compound **3n**	
Empirical formula	C23 H27 N O4 S	
Formula weight	413.51	
Temperature	100.00(10) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.2817(2) Å	α = 90°
	b = 12.4470(2) Å	β = 92.4940(10)°
	c = 15.9520(2) Å	γ = 90°
Volume	2039.54(6) $Å^3$	
Z	4	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	1.656 mm^{-1}	
F(000)	880	
Crystal color, morphology	colourless, block	
Crystal size	0.141 x 0.091 x 0.037 mm^3	
Theta range for data collection	4.507 to 77.634°	
Index ranges	$-12 \le h \le 12$, $-12 \le k \le 15$, $-19 \le l \le 20$	
Reflections collected	17298	
Independent reflections	4274 [R(int) = 0.0406]	
Observed reflections	3879	
Completeness to theta = 74.504°	99.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.77822	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4274 / 10 / 279	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	$R1$ = 0.0415, $wR2$ = 0.1120	
R indices (all data)	$R1$ = 0.0448, $wR2$ = 0.1147	
Largest diff. peak and hole	0.316 and -0.471 e.$Å^{-3}$	

X-Ray Crystal Data for Compound 3n'




C16
C14
C15
O1
C5
O2
C13
C10
C9
C12
C11
C6
C8
C7
O4
C21
C22
C1
C20
N1
C2
S1
C23
C17
C3
C19
O3
C18
C4

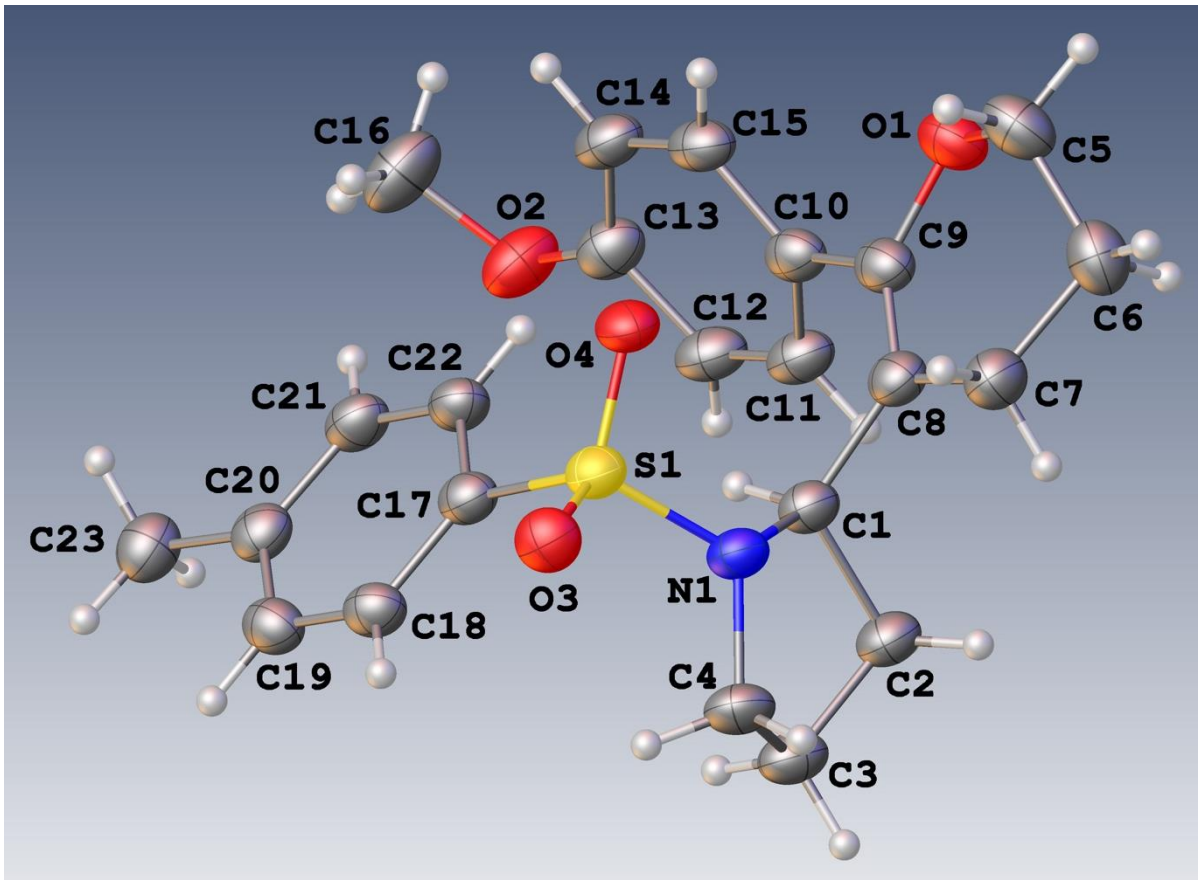
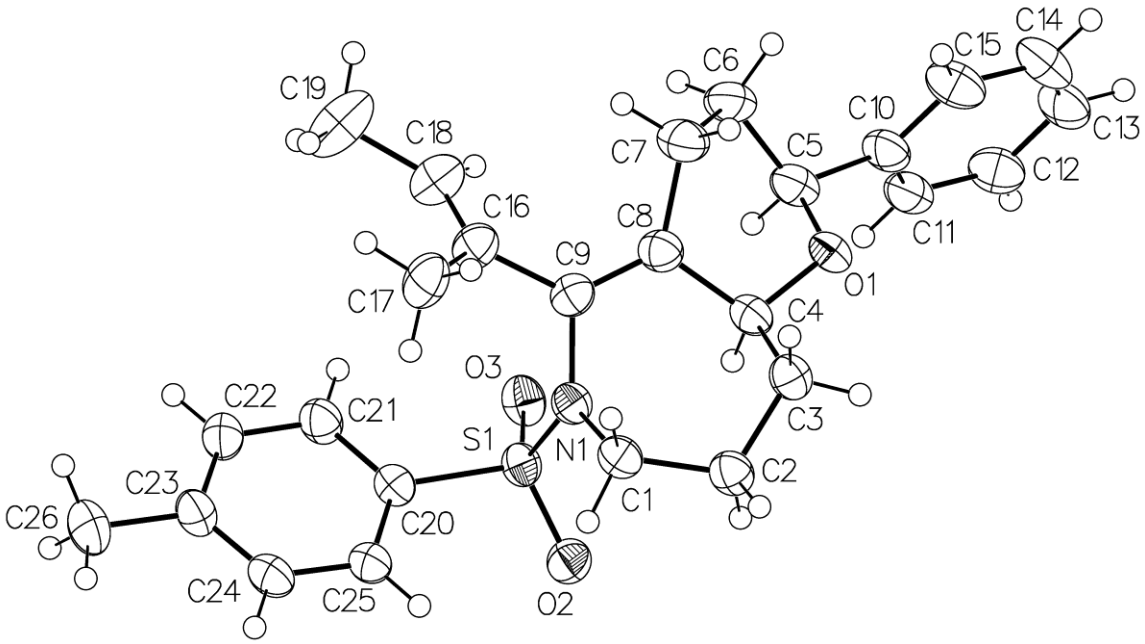

C14
C16
C15
O1
C5
O2
C13
C10
C9
C6
C12
C22
O4
C21
C11
C8
C7
S1
C20
C17
C1
C23
O3
N1
C18
C19
C4
C2
C3

Table S3. Crystal data and structure refinement for compound **3n'**.

Identification code	Compound **3n'**	
Empirical formula	C23 H27 N O4 S	
Formula weight	413.51	
Temperature	99.98(11) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.7024(2) Å	α = 90°
	b = 9.7412(2) Å	β = 90.413(2)°
	c = 22.0160(5) Å	γ = 90°
Volume	2080.74(8) $Å^3$	
Z	4	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	1.623 mm^{-1}	
F(000)	880	
Crystal color, morphology	colourless, block	
Crystal size	0.347 x 0.169 x 0.097 mm^3	
Theta range for data collection	4.016 to 77.681°	
Index ranges	$-12 \le h \le 12$, $-12 \le k \le 5$, $-27 \le l \le 25$	
Reflections collected	18174	
Independent reflections	4369 [R(int) = 0.0471]	
Observed reflections	3894	
Completeness to theta = 74.504°	99.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.76389	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4369 / 0 / 264	
Goodness-of-fit on F^2	1.087	
Final R indices [I>2sigma(I)]	$R1$ = 0.0442, $wR2$ = 0.1176	
R indices (all data)	$R1$ = 0.0482, $wR2$ = 0.1208	
Largest diff. peak and hole	0.291 and -0.391 e.$Å^{-3}$	

X-Ray Crystal Data for Compound 3q



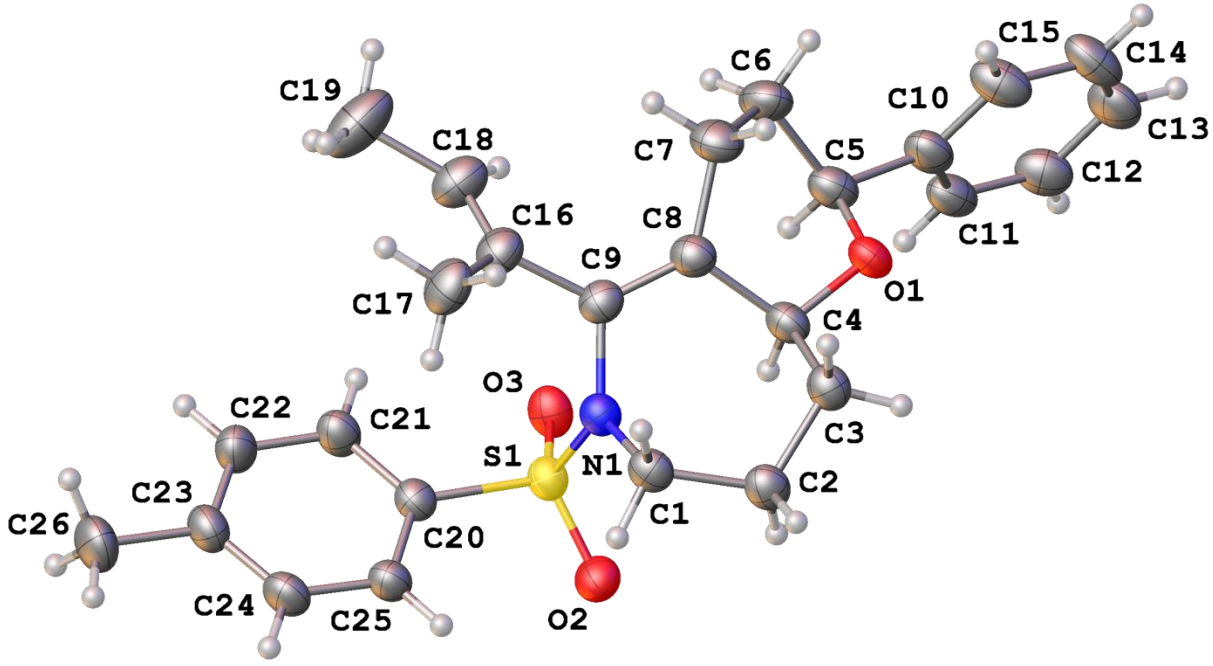


Table S4. Crystal data and structure refinement for compound **3q**.

Identification code	compound **3q**	
Empirical formula	C26 H31 N O3 S	
Formula weight	437.58	
Temperature	100.00(10) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 11.8073(2) Å	α = 90°
	b = 9.5486(2) Å	β = 102.611(2)°
	c = 21.3505(4) Å	γ = 90°
Volume	2349.05(8) Å^3	
Z	4	
Density (calculated)	1.237 Mg/m^3	
Absorption coefficient	1.433 mm^{-1}	
F(000)	936	
Crystal color, morphology	colourless, block	
Crystal size	0.169 x 0.083 x 0.04 mm^3	
Theta range for data collection	3.958 to 77.999°	
Index ranges	$-14 \le h \le 14$, $-11 \le k \le 9$, $-26 \le l \le 27$	
Reflections collected	21493	
Independent reflections	4923 [R(int) = 0.0452]	
Observed reflections	4308	
Completeness to theta = 74.504°	99.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.83105	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4923 / 0 / 283	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1311	
R indices (all data)	R1 = 0.0532, wR2 = 0.1350	
Largest diff. peak and hole	0.551 and -0.384 e.Å^{-3}	

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