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Stereoselective Isoxazolidine Synthesis Via Copper-Catalyzed Alkene Aminooxygenation

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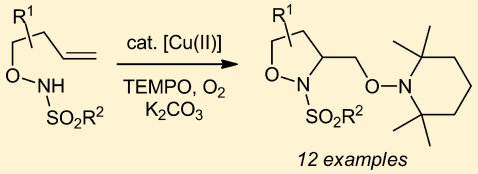
Supporting Information

ABSTRACT: Isoxazolidines are useful in organic synthesis, drug discovery, and chemical biology endeavors. A new stereoselective synthesis of methyleneoxy-substituted isoxazolidines is disclosed. The method involves copper-catalyzed aminooxygenation/cyclization of *N*-sulfonyl-*O*-butenyl hydroxylamines in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO) and O_2 and provides substituted isoxazolidines in excellent yields and diastereoselectivities. We also demonstrate selective mono N−O reduction followed by oxidation of the remaining N−O bond to reveal a 2-amino-γ-lactone. Reduction of the γ-lactone reveals the corresponding aminodiol.



Isoxazolidines have demonstrated a range of biological activities including antibiotic,[1] gene expression regulation[2] and cancer cell cytotoxicity.[3] While [3 + 2] dipolar cycloaddition reactions are most frequently used to synthesize isoxazolidines,[4,5] the intramolecular addition of hydroxylamines onto alkenes and allenes has emerged as an important alternative strategy.[6,7] These two synthetic strategies are largely complementary: the former is usually an entirely intermolecular process while the latter is intramolecular in the first step of the addition to the alkene. Because of these different aspects, different stereocontrolling elements are involved in each. Herein we report a copper-catalyzed addition of a nitrogen and oxygen across the alkene, resulting in methyleneoxy-functionalized isoxazolidines.

Our lab has recently disclosed that copper(II) salts can be used to efficiently promote and catalyze intramolecular alkene aminooxygenation.[8] This reaction has been used to synthesize methyleneoxy functionalized indolines, pyrrolidines and cyclic ureas. The present contribution broadens the scope of the copper-catalyzed alkene aminooxygenation reaction to the synthesis of isoxazolidines. The resulting methyleneoxy functionalized isoxazolidines might serve directly as pharmacological leads or alternatively N−O bond reduction/oxidation could lead to synthetically useful 2-amino-γ-lactones and 1,3-aminoalcohols (*vide infra*).

The *N*-sulfonyl-*O*-butenyl hydroxyl amine substrates **1** were synthesized via aldehyde allylation, subsequent Mitsunobu reaction with *N*-hydroxyphthalimide, *N*-deprotection and *N*-sulfonylation, as previously reported.[6,7] Substrates **1a−c** were then subjected to various copper(II)-catalyzed aminooxygenation conditions to determine the optimal protocol (Table 1). We found the reaction of *N*-tosyl-*O*-butenyl hydroxyl amine **1a** to be very efficient at 60 °C when $Cu(OTf)_2$ was used with the 2,2-isopropylidinebis(oxazoline) ligand **3** or when Cu(2-ethylhexanoate)$_2$ [$Cu(eh)_2$] was used as the catalyst (Table 1, entries 3 and 4). [We generally prefer Cu(2-ethylhexanoate)$_2$ in our copper-carboxylate promoted and catalyzed reactions due to its high solubility in nonpolar organic solvents.][8b,d] Substrate **1a** is significantly more reactive than the γ-pentenyl sulfonamide substrates we had previously examined in this aminooxygenation reaction[8] and **1a** actually suffered substantial decomposition at 110 and 120 °C, the temperatures previously examined substrates reacted best at.[8] The oxygen source in this aminooxygenation reaction is (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO) and the stoichiometric oxidant is O_2 (1 atm, balloon). We initially used 3 equiv of TEMPO based on our previously reported aminooxygenation reactions,[8] but we found midway during these studies that 1.2 equiv of TEMPO is sufficient for excellent conversion. We also found that a 10% O_2 in N_2 atmosphere (1 atm, balloon) is sufficient for good conversion (Table 1, entry 6), thereby enabling a safer process.

Substrates with α-substituents (**1b**, R^1 = Me and **1c**, R^1 = Ph) provided moderate 3,5-*cis* isoxazolidine diastereoselectivity with the $Cu(OTf)_2$•**3** catalyst and higher diastereoselectivity with $Cu(eh)_2$ as catalyst (Table 1, entries 8−12). The relative configuration of the major diastereomers were assigned by NOE.

A series of *N*-sulfonyl-*O*-butenylamines **1** were subjected to the optimal conditions (Table 1, entries 4 and 5) to establish the substrate scope (Scheme 1). A number of functional groups (aryl-Br, aryl-Cl, thiophene, Ns, SES, allyl) were stable to the reaction conditions. α-Substituted hydroxylamines provided the corresponding isoxazolidines **2d−j** and **2l** with good to excellent 3,5-*cis* diastereoselectivity while a β-phenyl substrate provided the 3,4-*trans* diastereomer **2k** selectively (stereochemistry assigned by NOE). Substrates with internal alkenes and ones that could potentially form 6-membered rings were not examined in this limited study.

The proposed reaction mechanism is outlined in Scheme 2.[8] *cis*-Aminocupration via the seven-membered chairlike transition

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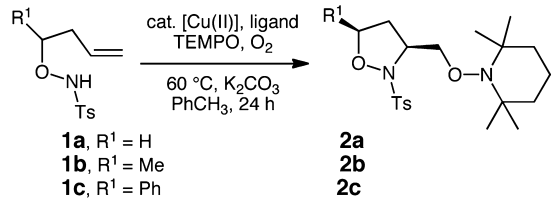
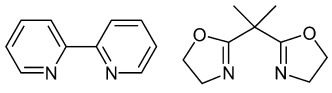
Table 1. Optimization of the Aminooxygenation[a]



entry	R^1	CuX_2	ligand	yield (%)	cis:trans
1[b]	H	$Cu(OTf)_2$		60[c]	
2[b]	H	$Cu(OTf)_2$	Bipy	55[c]	
3	H	$Cu(OTf)_2$	**3**	>95[c]	
4[b]	H	$Cu(eh)_2$		83	
5	H	$Cu(eh)_2$		81	
6[d]	H	$Cu(eh)_2$		70	
7[e]	H	$Cu(eh)_2$		65 (90[c])	
8[b]	Me	$Cu(OTf)_2$	**3**	95[c]	3:1
9[b]	Me	$Cu(eh)_2$		75	10:1
10[b]	Ph	$Cu(OTf)_2$	**3**	95[c]	8:1
11[b]	Ph	$Cu(eh)_2$		83	10:1
12	Ph	$Cu(eh)_2$		82	10:1

[a]Reaction conditions: **1** (0.165 mmol), K_2CO_3 (0.165 mmol) and TEMPO (0.198 mmol, 1.2 equiv) was added to a solution of CuX_2 (0.033 mmol, 20 mol %) [$Cu(OTf)_2$ and ligands (25 mol %) were complexed at 60 °C for 2 h prior to substrate addition] and the reaction mixture was heated at 60 °C under O_2 (1 atm, balloon) for 24 h. Yields are of product isolated after flash chromatography on SiO_2 unless otherwise noted. [b]3 equiv of TEMPO was used in this reaction. [c]% Conversion based on crude ^1H NMR analysis. [d]10% O_2 in N_2 (1 atm, balloon) was used. [e]15 mol % $Cu(eh)_2$ was used.



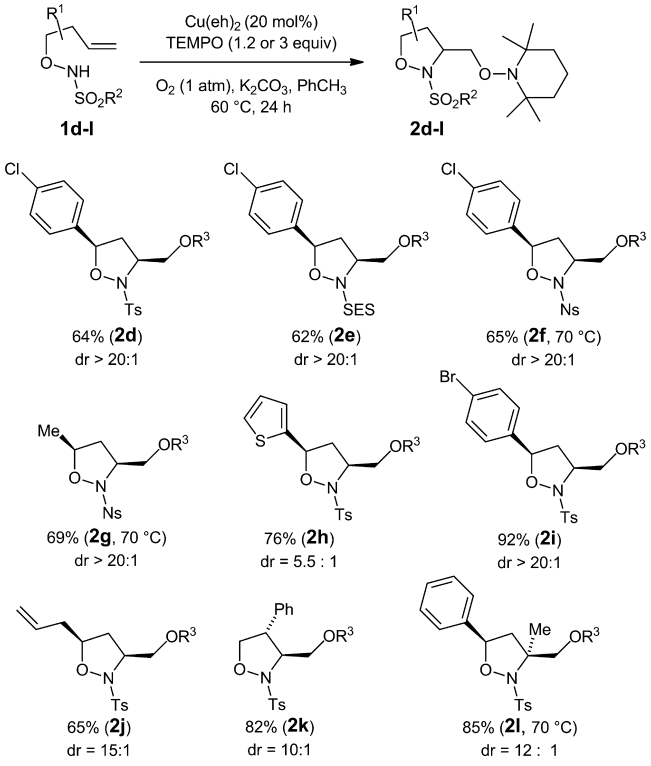
state **A** gives the unstable organocopper(II) intermediate. For the diastereoselective reactions, placement of the substituent in a less sterically demanding pseudoequatorial position leads to the major diasteromer. Homolysis of the carbon−copper bond gives Cu(I) and the carbon radical intermediate then undergoes rapid trapping with TEMPO radical to provide isoxazolidine **2**. Reoxidation of Cu(I) to Cu(II) by TEMPO/O_2 completes the catalytic cycle.

While isoxazolidines are useful in their own right, they can also be easily converted to 1,3-amino alcohols.[9] The ring N−O bond of isoxazolidine **2c** was selectively cleaved via hydrogenation, catalyzed by 20 mol % Pearlman's catalyst [20% (by weight) $Pd(OH)_2$ on carbon] to provide the acyclic 1,3-amino alcohol **4** in 70% yield along with 10% recovered **2c** (Scheme 3).[9c] We initially anticipated that oxidation of amino alcohol **4** with m-CPBA[8a,b] would provide the corresponding lactol. Instead, γ-lactone **5** was obtained exclusively. Lactone **5** could be reduced to the corresponding 1,4-diol **6** with $NaBH_4$. Such γ-lactones and 3-amino-1,4-diols are important intermediates in the synthesis of HPA-12, a CERT antagonist that can be used as a treatment for sphingolipid misregulation which in turn can cause autoimmune disorders.[10]

SUMMARY AND CONCLUSIONS

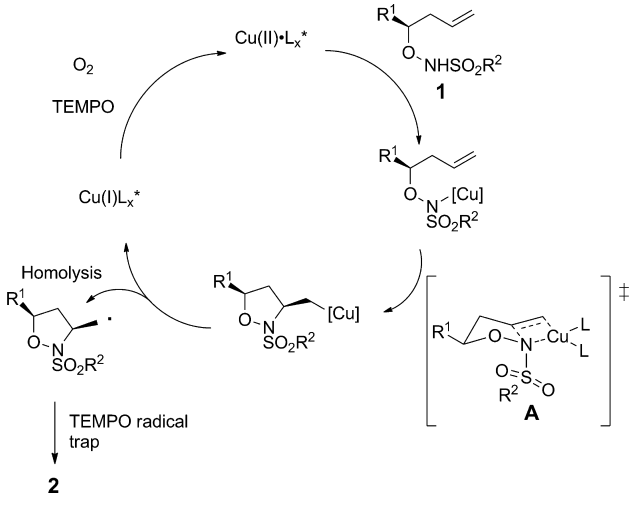
A very concise, efficient and diastereoselective method for the synthesis of variously functionalized isoxazolidines has been presented. Such compounds may prove useful in drug discovery and organic synthesis endeavors. This method could provide access to disubstituted chiral isoxazolidines if the synthetic route to the hydroxylamine substrate involved an enantioselective step,[6f,g] for example, an enantioselective aldehyde allylation reaction.[6j,11] Sequential N−O reduction and N−O oxidation reactions as shown in Scheme 3 can provide unnatural amino acid synthons such as γ-lactone **5** and structures related to CERT antagonists such as aminodiol **6**.

Scheme 1. Isoxazolidine Scope[a]



[a]R^3 = 2,2,6,6-tetramethylpiperidinyl.

Scheme 2. Proposed Reaction Mechanism



EXPERIMENTAL SECTION

General Experimental Information. Reagents were used as supplied unless otherwise noted. m-CPBA was 70−75% composition by weight. ^1H NMR spectra were recorded in $CDCl_3$, C_6D_6 or CD_3OD (referenced at 7.26 ppm, residual $CHCl_3$, 7.16 ppm, residual

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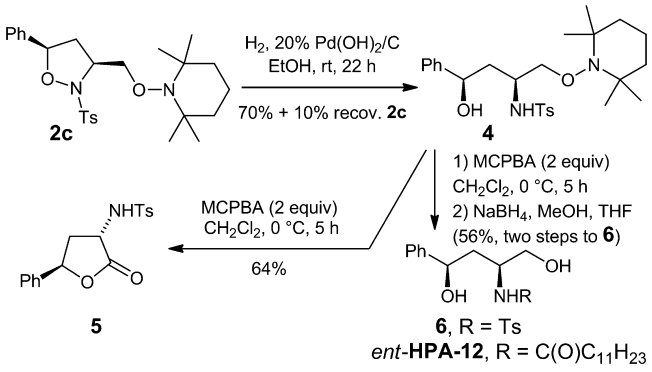
Scheme 3. N−O Bond Reduction and Oxidation



C_6H_6 and 3.34 ppm, residual CH_3OH) at 300, 400, or 500 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ (77.0 ppm as internal reference) at 75.5 MHz. Characteristic peaks in the IR spectra are reported in wave numbers, cm^{-1}. Melting points are reported as uncorrected. Reactions were run in oven-dried glassware under Argon unless otherwise noted. Solvents were dried under Argon using a commercial purification system involving filtration through alumina.

*N-(But-3-enyloxy)-4-methylbenzenesulfonamide (**1a**) (Representative Procedure).*[6,7] A 0 °C solution of 3-butene-1-ol (500.0 mg, 6.9 mmol), triphenylphosphine (2.2 g, 8.3 mmol) and *N*-hydroxyphthalimide (1.3 g, 8.3 mmol) in THF (56 mL) was treated with diethylazodicarboxylate (3.6 mL, 8.3 mmol, 40 wt % in toluene), added over 30 min. The reaction was warmed to rt and stirred for 4 h, then hydrazine monohydrate (0.77 mL, 15.8 mmol) was added dropwise. After 2 h, the mixture was filtered through Celite and concentrated in vacuo. The resulting hydroxylamine was dissolved in CH_2Cl_2 (69 mL), treated with pyridine (1.7 mL, 20.8 mmol) and p-TsCl (1.6 g, 8.3 mmol) and stirred for 16 h at rt. The mixture was quenched with water and extracted with CH_2Cl_2 (2 × 30 mL). The organics were washed with 1 M HCl (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on SiO_2 (10−30% EtOAc in hexanes) gave *N*-tosyl hydroxylamine **1a** (600 mg, 30% yield, yellow oil). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 5.78−5.74 (m, 1 H), 5.13−5.05 (m, 2 H), 4.05 (t, J = 12.0 Hz, 2 H), 2.46 (s, 3 H), 2.46−2.34 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.7, 134.1, 133.4, 129.5, 128.5, 116.9, 76.1, 32.4, 21.5; IR (thin film) 3222, 2946, 1642, 1598, 1335, 1164 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{11}H_{15}O_3N_1Na_1S_1$: 264.0666, found 264.0665.

*(±)-4-Methyl-N-(pent-4-en-2-yloxy)benzenesulfonamide (**1b**).* Pent-4-en-2-ol was converted to **1b** (326 mg, 22% yield, clear oil). ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.99 (s, 1H), 5.80−5.68 (m, 1H), 5.08−5.03 (m, 2H), 4.21−4.15 (m, 1H), 2.43 (s, 3H), 2.39−3.30 (m, 1H), 2.25−2.18 (m, 1H), 1.18 (d, J = 9.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.7, 133.9, 133.6, 129.5, 128.5, 117.4, 81.8, 39.1, 21.6, 18.2; IR (thin film) 3222, 1314, 1167, 1091 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{12}H_{17}O_3N_1S_1$: 255.09152, found 255.0924.

*(±)-4-Methyl-N-(1-phenylbut-3-enyloxy)benzenesulfonamide (**1c**).*[7] 1-Phenyl-but-3-en-1-ol[12] was converted to **1c** (481.2 mg, 42% yield, white solid). mp = 105 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2 H), 7.36−7.28 (m, 5H), 7.28−7.25 (m, 2H), 6.67 (s, 1H), 5.80−5.71 (m, 1H), 5.10−5.01 (m, 3H), 2.68−2.60 (m, 1H), 2.49 (s, 3H), 2.48−2.45 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 139.6, 133.8, 133.7, 129.6, 128.7, 128.4, 128.2, 127.1, 117.6, 88.0, 39.6, 21.6; IR (thin film) 3224, 1642, 1598, 1339, 1166 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{19}O_3N_1S_1$: 340.0978, found 340.0975.

*(±)-N-(1-(4-Chlorophenyl)but-3-enyloxy)-4-methylbenzenesulfonamide (**1d**).* 1-(4-Chlorophenyl)-but-3-en-1-ol[12] was converted to **1d** (1.5 g, 81% yield, white solid). mp = 107−110 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2 H), 7.33−7.28 (m, 4H), 7.19 (d, J = 8.5 Hz, 2H), 6.77 (s, 1H), 5.76−5.68 (m, 1H), 5.08−4.99 (m, 3H), 2.65−2.58 (m, 1H), 2.45 (s, 3H), 2.45−2.41 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.9, 138.1, 133.9, 133.5, 133.2, 129.6, 128.6, 128.6, 128.5, 117.9, 87.2, 39.5, 21.6; IR (thin film) 3189, 1643, 1592, 1333, 1158, 913 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{18}O_3N_1S_1Cl_1Na_1$: 374.0588, found 374.0586.

*(±)-N-(1-(4-Chlorophenyl)but-3-enyloxy)-2-(trimethylsilyl)-ethanesulfonamide (**1e**).* 1-(4-Chlorophenyl)-but-3-en-1-ol[12] was converted to **1e** (104 mg, 26% yield, white solid) as above except with 2-trimethylsilylethanesulfonyl chloride. mp = 92−94 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 7.30 (d, J= 8.8 Hz, 2 H), 6.72 (s, 1H), 5.83−5.76 (m, 1H), 5.12−5.06 (m, 2H), 5.00 (dd, J = 6.4 Hz, J = 7.6 Hz, 1 H), 3.15−3.08 (m, 2H), 2.68−2.64 (m, 1H), 2.49−2.46 (m, 1H), 1.05−0.89 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 134.1, 133.2, 128.6, 128.5, 117.9, 86.9, 45.5, 39.5, 9.7, 0.0, IR (thin film) 3223, 2923, 2852, 1597, 1338, 1167, 1091, 919, 813, 705; HRMS (ESI) calcd for $[M + Na]^+$ $C_{15}H_{24}Cl_1NO_3S_1Si_1Na_1$: 384.0827, found 384.0832.

*(±)-N-(1-(4-Chlorophenyl)but-3-enyloxy)-4-nitrobenzenesulfonamide (**1f**).* 1-(4-Chlorophenyl)-but-3-en-1-ol[12] was converted to **1f** (126 mg, 30% yield, yellow solid) as above except with 4-nitrobenzenesulfonyl chloride. mp = 127−129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 6.95 (s, 1H), 5.78−5.69 (m, 1H), 5.14−5.04 (m, 3H), 2.66−2.58 (m, 1H), 2.49−2.42 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 150.8, 142.2, 137.5, 134.5, 133.1, 130.0, 128.8, 128.5, 124.2, 118.3, 88.9, 39.4; IR (thin film) 3224, 1606, 1531, 1348, 1312, 1173, 1089, 1013, 854, 744 cm^{-1}; HRMS (EI) calcd for $[M - C_3H_5]^+$ $C_{13}H_{10}N_2O_5Cl_1S_1$: 340.9977, found 340.9993.

*(±)-4-Nitro-N-(pent-4-en-2-yloxy)benzenesulfonamide (**1g**).* Pent-4-en-2-ol was converted to sulfonamide **1g** (1.20 g, 64% yield, white solid) as above except with 4-nitrobenzenesulfonyl chloride. mp = 72−75 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 8.5 Hz, 2H), 8.12 (d, J = 9.0 Hz, 2H), 7.14 (s, 1H), 5.79−5.74 (m, 1H), 5.10−5.06 (m, 2H), 4.27−4.23 (m, 1H), 2.36−2.32 (m, 1H), 2.28−2.24 (m, 1H), 1.21 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.7, 142.3, 133.7, 129.9, 124.1, 117.8, 82.6, 39.1, 30.9, 18.2; IR (thin film) 3212, 1608, 1535, 1445, 1348, 1167 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{11}H_{14}O_5N_2S_1$: 286.0625, found 286.0618.

*(±)-4-methyl-N-(1-(thiophen-2-yl)but-3-enyloxy)-benzenesulfonamide (**1h**).*[7] 1-(Thiophen-2-yl)but-3-en-1-ol[12] was converted to **1h** (90 mg, 44% yield, yellow solid). mp = 80−82 °C; ^1H NMR (400 MHz, $CDCl_3$), δ 7.72 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 5.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.88 (dd, J = 3.4 Hz, 5.0 Hz, 1H), 6.75 (s, 1H), 5.76−5.66 (m, 1H), 5.18 (t, J = 7.0 Hz, 1H), 5.07−5.01 (m, 2H), 2.70−2.63 (m, 1H), 2.54−2.46 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 142.2, 133.6, 133.2, 129.6, 128.6, 127.1, 126.6, 125.8, 118.0, 83.2, 39.6, 29.6, 21.6; IR (thin film) 3223, 2923, 1339, 1167, 1091, 920, 813, 705 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{15}H_{17}O_3N_1Na_1S_2$: 346.0542, found 346.0526.

*(±)-N-(1-(4-Bromophenyl)but-3-enyloxy)-4-methylbenzenesulfonamide (**1i**).* 1-(4-Bromophenyl)-but-3-en-1-ol[12] was converted to **1i** (1.2 g, 70% yield, white solid). mp = 115−118 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.75 (s, 1H), 5.76−5.69 (m, 1H), 5.08−5.04 (m, 2H), 5.00 (t, J = 5.6 Hz, 1H), 2.62−2.58 (m, 1H), 2.45 (s, 3H), 2.45−2.39 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.9, 138.6, 133.5, 133.2, 131.6, 129.6, 128.9, 128.6, 122.2, 118.0, 87.3, 39.4, 21.7; IR (thin film) 3213, 1597, 1166, 1091, 732 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{18}O_3N_1S_1Br_1Na_1$: 420.0063, 418.0088, found 420.0051; 418.0109.

*(±)-N-(Hepta-1,6-dien-4-yloxy)-4-methylbenzenesulfonamide (**1j**).* Hepta-1,6-dien-4-ol[13] was converted to **1j** (162 mg, 26% yield, white solid). mp = 52−54 °C; ^1H NMR (400 MHz, $CDCl_3$), 7.81 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 5.84−5.73 (m, 1H), 5.10−5.05 (m, 4H), 4.20−4.16 (t, J = 6.0 Hz, 1H), 2.44 (s, 3H), 2.35−2.32 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 133.9, 133.6, 129.6, 128.4, 117.6, 85.0, 41.0, 36.6, 21.7; IR (thin film), 3220, 2929, 1642, 1334, 1168, 1091, 1019, 918, 814, 731 cm^{-1}; HRMS (ESI) calcd. for $[M + Na]^+$ $C_{14}H_{19}O_3N_1Na_1S_1$: 304.0987, found 304.0978.

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*(±)-4-Methyl-N-(2-phenylbut-3-enyloxy)benzenesulfonamide (**1k**).* 2-Phenyl-but-3-en-1-ol[14] was converted to **1k** (120 mg, 56% yield, clear oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.37−7.19 (m, 7H), 6.93 (s, 1 H), 6.02−5.90 (m, 1 H), 5.16−5.07 (m, 2H), 4.31 (d, J= 10.0 Hz, 2H), 3.76−3.68 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.7, 140.3, 137.8, 133.3, 129.5, 128.5, 128.4, 128.0, 126.8, 116.5, 79.7, 48.2, 21.6; IR (thin film) 3223, 2960, 1453, 1336, 1167, 1091, 918, 757 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{19}O_3N_1Na_1S_1$: 340.0969, found 340.0978.

*(±)-4-Methyl-N-(3-methyl-1-phenylbut-3-enyloxy)-benzenesulfonamide (**1l**).* 3-Methyl-1-phenylbut-3-en-1-ol[15] was converted to **1l** (105 mg, 51% yield, yellow solid). mp = 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.33−7.27 (m, 7H), 6.62 (s, 1H), 5.15 (dd, J = 5.6 Hz, 8.0 Hz, 1H), 4.83 (s, 1H), 4.73 (s, 1H), 2.59 (dd, J = 8.4 Hz, 14.4 Hz, 1H), 2.41 (s, 3 H), 2.35 (dd, J = 5.2 Hz, 14.4 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.7, 141.3, 140.0, 133.7, 129.6, 128.7, 127.1, 113.5, 88.2, 44.1, 23.4, 21.7; IR (thin film) 3223, 2923, 1597, 1454, 1339, 1167, 812, 727 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{18}H_{21}O_3N_1Na_1S_1$: 354.1134, found 354.1134.

*(±)-2,2,6,6-Tetramethyl-1-((2-tosylisoxazolidin-3-yl)methoxy)-piperidine (**2a**) (Representative Procedure).* *N*-Tosyl hydroxylamine **1a** (40 mg, 0.165 mmol), copper(II) 2-ethylhexanoate (11.5 mg, 0.033 mmol), TEMPO (30.9 mg, 0.198 mmol) and K_2CO_3 (22.8 mg, 0.165 mmol) were placed in a 100 mL flask (14/20 neck) and dissolved in toluene (1.65 mL). O_2 (1 atm) was introduced via balloon attached to a short vacuum hose, that in turn was attached to an adapter (14/20). The solution was heated to 60 °C and stirred for 24 h, then was diluted with EtOAc, filtered through Celite and concentrated. Flash chromatography on SiO_2 (10−30% EtOAc:hexanes) afforded 51.6 mg of isoxazolidine **2a** as a white solid in 79% yield. mp = 101−102 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 7.98 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 7.5 Hz, 2 H), 4.58−4.56 (m, 1H), 4.07−4.04 (m, 1H), 4.00 (dd, J = 7.5 Hz, 15.7 Hz, 1H), 3.85 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 3.55−3.51 (m, 1H), 1.97−1.94 (m, 1H), 1.79 (s, 3H), 1.69−1.66 (m, 1H), 1.42−1.40 (m, 4H), 1.28−1.15 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 133.1, 129.6, 129.1, 77.7, 69.8, 59.9, 57.6, 39.5, 33.0, 31.9, 30.8, 21.6, 20.0, 16.9 ; IR (thin film) 1361, 1329, 1162, 1088 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{33}O_4N_2S_1$: 397.2156, found 397.2159.

*(±)-2,2,6,6-Tetramethyl-1-(((3S,5S)-5-methyl-2-tosylisoxazolidin-3-yl)methoxy)piperidine (**2b**).* **1b** was converted to (48 mg, 75% yield, white solid, d.r. = 10:1) **2b** as above (except 3 equiv of TEMPO was used). The diastereomers were separated by HPLC (5% EtOAc in hexanes). Major diastereomer: mp = 111−113 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 8.01 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 4.65−4.61 (m, 1H), 4.51−4.46 (m, 1H), 4.20 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 3.96 (dd, J = 6.4 Hz, 9.0 Hz, 1H), 2.12 (ddd, J = 6.0 Hz, 8.0 Hz, 11.1 Hz, 1H), 1.81 (s, 3H), 1.48−1.18 (m, 5H), 1.14−1.13 (m, 12H), 0.91 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.7, 133.4, 129.6, 129.1, 78.3, 77.8, 59.9, 58.4, 39.5. 30.9, 21.6, 18.1, 17.0; IR (film) 1598, 1359, 1333, 1166, 813 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{35}O_4N_2S_1$: 411.2312, found 411.2310.

*(±)-2,2,6,6-Tetramethyl-1-(((3S,5R)-5-phenyl-2-tosylisoxazolidin-3-yl)methoxy)piperidine (**2c**).* **1c** was converted to **2c** (49.4 mg, 83% yield, 10:1 dr). The diastereomers were separated by HPLC (5% EtOAc in hexanes). Major diastereomer: white solid, mp = 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.28−7.21 (m, 7H), 5.16 (dd, J = 6.4 Hz, 10.0 Hz, 1H), 4.50−4.46 (m, 1H), 4.11−4.08 (dd, J = 6.0 Hz, 9.2 Hz, 1H), 3.88 (dd, J = 6.6 Hz, 9.4 Hz, 1H), 2.76 (ddd, J = 6.4 Hz, 8.2 Hz, 12.4 Hz, 1H), 2.38 (s, 3H), 2.13 (ddd, J = 7.2 Hz, 10.2 Hz, 12.8 Hz, 1H), 1.51−1.39 (m, 4H), 1.15−1.09 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 137.1, 133.3, 129.6, 129.3, 128.63, 128.57, 126.9, 83.1, 78.2, 60.1, 58.7, 40.5, 39.6, 33.9, 21.7, 20.1, 17.1 ; IR (thin film) 1598, 1360, 1333, 1164, 813 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{37}O_4N_2S_1$: 473.2469, found 473.2474.

*(±)-1-(((3S,5R)-5-(4-Chlorophenyl)-2-tosylisoxazolidin-3-yl)-methoxy)-2,2,6,6-tetramethylpiperidine (**2d**).* **1d** was converted to **2d** (50.8 mg, 64% yield, white solid, >20:1 d.r.) using the conditions for **2b**. mp = 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.32−7.21 (m, 6H), 5.21 (dd, J = 6.6 Hz, 9.8 Hz, 1H), 4.55−4.48 (m, 1 H), 4.04 (dd, J= 6.0 Hz, 9.2 Hz, 1H), 3.89 (dd, J= 6.6 Hz, 8.4 Hz, 1H), 2.79 (ddd, J= 6.6 Hz, 8.2 Hz, 12.6 Hz, 1H), 2.43 (s, 3H), 2.12 (ddd, J = 7.2 Hz, 10.0 Hz, 12.2 Hz, 1H), 1.55−1.41(m, 4H), 1.28−1.07 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.9, 135.7, 134.4, 133.1, 129.2, 128.7, 128.2, 82.3, 78.0, 60.1, 58.6, 40.4, 39.6, 33.0, 30.9, 21.7, 20.1, 17.0; IR (thin film) 1596, 1492, 1360, 1166, 817 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{36}O_4N_2S_1Cl_1$: 507.2085, found 507.2088.

*(±)-1-(((3S,5R)-5-(4-Chlorophenyl)-2-(2-(trimethylsilyl)-ethylsulfonyl)isoxazolidin-3-yl)methoxy)-2,2,6,6-tetramethylpiperidine (**2e**).* **1e** was converted to **2e** (35.2 mg, 62% yield, white solid) in >20:1 d.r. mp = 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 4H), 5.47 (dd, J = 7.2 Hz, 1H), 4.59−4.55 (m, 1H), 4.00 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 3.88 (dd, J = 6.4 Hz, 8.8 Hz, 1H), 3.29−3.13 (m, 2H), 2.85 (ddd, J = 7.2 Hz, 12.0 Hz, 17.8 Hz, 1H), 2.15 (ddd, J = 6.8 Hz, 9.8 Hz, 12.5 Hz, 1H), 1.54−1.44 (m, 4H), 1.19−1.09 (m, 12H), 0.03 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.8, 134.4, 128.8, 128.3, 82.9, 77.8, 60.1, 56.9, 47.1, 40.0, 39.6, 33.0, 20.1, 16.9, 9.5, 0.0; IR (thin film) 2930, 1599, 1493, 1469, 1333, 1251, 1172, 1148, 1091, 1056, 1015, 860, 830, 736, 701 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{24}H_{42}O_4N_2Cl_1S_1Si_1$: 517.2318, found 517.2335.

*(±)-1-((((3S,5R)-5-(4-Chlorophenyl)-2-(4-nitrophenylsulfonyl)-isoxazolidin-3-yl)methoxy)-2,2,6,6-tetramethylpiperidine (**2f**).* **1f** was converted (at 70 °C) to **2f** (36.6 mg, 65% yield, white solid, >20:1 d.r.). mp = 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 5.41 (dd, J = 6.8 Hz, 1H), 4.69−4.67 (m, 1 H), 4.04 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 3.94 (dd, J = 5.4 Hz, 9.4 Hz, 1H), 2.88 (ddd, J= 8.4 Hz, 12.6 Hz, 17.1 Hz, 1H), 2.16 (ddd, J= 7.2 Hz, 10.0 Hz, 12.6 Hz, 1H), 1.46−1.43 (m, 4H), 1.25−1.14 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.7, 142.5, 135.1, 134.7, 130.3, 128.9, 128.2, 124.1, 83.0, 77.6, 60.1, 58.3, 39.9, 39.6, 39.9, 32.9, 20.1, 17.0; IR (thin film), 2973, 2930, 1607, 1533, 1493, 1469, 1348, 1310, 1261, 1167, 1132, 1091, 1048, 1014, 955, 910, 854, 739, 622, 620 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{25}H_{33}O_6N_3Cl_1S_1$: 538.1773, found 538.1759.

*(±)-2,2,6,6-Tetramethyl-1-(((3S,5S)-5-methyl-2-(4-nitrophenylsulfonyl)isoxazolidin-3-yl)methoxy)piperidine (**2g**).* **1g** was converted to **2g** (49 mg, 69% yield, white solid, >20:1 d.r.) using the above conditions except at 70 °C with 3 equiv TEMPO. mp = 146−147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 8.5 Hz, 2H), 4.52−4.45 (m, 2H), 3.95 (dd, J= 6.7 Hz, 9.2 Hz, 1H), 3.83 (dd, J = 5.7 Hz, 9.2 Hz, 1H), 2.60 (ddd, J = 6.5 Hz, 8.0 Hz, 12.2 Hz, 1H), 1.72 (ddd, J = 7.0 Hz, 10.0 Hz, 12.2 Hz, 1H), 1.52−1.43 (m, 4H), 1.25 (s, 3H), 1.22−1.10 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.6, 142.8, 130.2, 124.0, 78.4, 77.8, 60.0, 58.2, 39.5, 39.0, 33.0, 32.8, 30.9, 18.0, 16.9; IR (thin film) 1607, 1534, 1349, 1263, 1172 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{20}H_{31}O_6N_3S_1$: 441.1928, found 441.1932.

*(±)-2,2,6,6-Tetramethyl-1-(((3S,5R)-5-(thiophen-2-yl)-2-tosylisoxazolidin-3-yl)methoxy)piperidine (**2h**).* **1h** was converted to **2h** (43.6 mg, 76% yield, white solid, 5.5:1 d.r.). Major diastereomer: mp = 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 7.5 Hz, 1 H), 7.06 (d, J = 3.0 Hz, 1H), 6.95 (t, J = 5.4 Hz, 1H), 5.57 (dd, J = 6.3 Hz, 7.8 Hz, 1H), 4.60−4.56 (m, 1H), 4.08 (dd, J = 6.3 Hz, 8.7 Hz, 1H), 3.93 (dd, J = 6.8 Hz, 9.0 Hz, 1H), 2.92−2.82 (m, 1H), 2.43 (s, 1H), 2.28 (ddd, J = 7.0 Hz, 10.0 Hz, 12.4 Hz, 1H), 1.52−1.38 (m, 4H), 1.25−1.11 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 139.4, 133.2, 129.6, 129.2, 127.2, 126.7, 126.5, 78.8, 77.9, 60.0, 58.5, 40.3, 39.6, 33.1, 32.9, 21.6, 20.1, 17.0 ; IR (thin film) 2927, 1451, 1359, 1332, 1162, 1092, 1048, 812, 705, 671; HRMS (ESI) calcd for $[M + H]^+$ $C_{24}H_{35}O_4N_2S_2$: 479.2026, found 479.2033.

*(±)-1-(((3S,5R)-5-(4-Bromophenyl)-2-tosylisoxazolidin-3-yl)-methoxy)-2,2,6,6-tetramethylpiperidine (**2i**).* **1i** was converted to **2i** (51.1 mg, 92% yield, white solid, >20:1 d.r.) using the method for **2b**. mp = 137−138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.21 (dd, J = 6.4 Hz, 9.4 Hz, 1H), 4.55−4.52 (m, 1H),

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4.06 (dd, J = 6.0 Hz, 8.8 Hz, 1H), 3.91 (dd, J = 6.6 Hz, 9.0 Hz, 1H), 2.81 (ddd, J = 6.8 Hz, 8.0 Hz, 12.5 Hz, 1H), 2.43 (s, 3H) 2.13 (ddd, J = 7.2 Hz, 9.8 Hz, 11.7 Hz, 1H), 1.45−1.43 (m, 4H), 1.18−1.09 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.9, 136.3, 133.1, 131.7, 129.6, 129.2, 128.5, 122.5, 82.4, 77.9, 60.1, 58.6, 40.4, 39.6, 33.1, 30.1, 21.7, 20.1, 17.1; IR (thin film) 1596, 1360, 1334, 1163, 671 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{36}O_4N_2S_1Br_1$: 551.1574, found 551.1583.

*(±)1-(((3R,5R)-5-Allyl-2-tosylisoxazolidin-3-yl)methoxy)-2,2,6,6-tetramethylpiperidine (**2j**).* **1j** was converted to **2j** (42.5 mg, 65% yield, colorless oil, 15:1 d.r.). The diastereomers were separated by HPLC (10% EtOAc in hexanes). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1, Hz, 2H), 5.77−5.63 (m, 1H), 5.08−5.05 (m, 2H), 4.42−4.25 (m, 2H), 3.97 (dd, J = 8.0 Hz, 12.2 Hz, 1H), 3.80 (dd, J = 8.0 Hz, 12.2 Hz, 1H), 2.48 (ddd, J = 6.4 Hz, 8.4 Hz, 12.2 Hz, 1H), 2.45 (s, 3H), 2.39−2.33 (m, 1H), 2.28−2.20 (m, 1H), 1.80 (ddd, J = 6.4 Hz, 9.4 Hz, 12.3 Hz, 1H), 1.45−1.43 (m, 4H), 1.16−1.09 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.7, 133.4, 133.0, 129.6, 129.1, 117.8, 80.8, 78.2, 60.0, 58.1, 39.6, 37.2, 33.1, 32.8, 21.7, 20.1, 17.0; IR (thin film) 2928, 1451, 1334, 1359, 1164, 1056, 918, 813, 671 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{23}H_{37}O_4N_2S_1$: 437.2455, found 437.2469.

*(±)-2,2,6,6-Tetramethyl-1-(((3S,4R)-4-phenyl-2-tosylisoxazolidin-3-yl)methoxy)piperidine (**2k**).* **1k** was converted to **2k** (48.8 mg, 82% yield), clear oil, 10:1 d.r. The diastereomers were separated by HPLC (5% EtOAc in hexanes). Major diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ 8.05 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.2 Hz, 2H), 7.08 (t, J = 7.2 Hz, 2H), 6.99 (t, J = 5.2 Hz, 1H), 6.74 (d, J = 7.6 Hz, 2H), 4.78−4.73 (m, 1H), 4.39−4.36 (m, 1H), 4.32 (dd, J = 6.0 Hz, 10.0 Hz, 1H), 4.24 (dd, J = 6.4 Hz, 10.2 Hz, 1H), 3.84 (t, J = 8.0 Hz, 1H), 3.57−3.50 (m, 1H), 1.81 (s, 3H), 1.44−1.42 (m, 4H), 1.26−1.03 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.9, 136.4, 133.2, 129.7, 129.3, 128.8, 128.0, 127.6, 65.1, 59.9, 52.3, 39.6, 32.9, 21.7, 20.0, 17.0; IR (thin film) 2919, 1458, 1360, 1338, 1164, 1092, 1052, 908, 732 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{37}O_4N_2S_1$: 473.2484, found 473.2469.

*(±)-2,2,6,6-Tetramethyl-1-(((3S,5S)-3-methyl-5-phenyl-2-tosylisoxazolidin-3-yl)methoxy)piperidine (**2l**).* **1l** was converted to **2l** (49.5 mg, 85% yield, white solid, 12:1 d.r.) using the conditions for **2f**. Major diastereomer: mp = 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.37−7.23 (m, 7H), 5.54 (t, J = 8.4 Hz, 1H), 3.88 (ABq, $\Delta\nu_{AB}$ = 88.6 Hz, J_{AB} = 8.6 Hz, 2H), (dd, J = 8.0 Hz, 12.2 Hz, 1H), 2.42 (dd, J = 8.0 Hz, 12.2 Hz, 1H), 2.37 (s, 3H), 1.93 (s, 3H), 1.48−1.42 (m, 4H), 1.20−1.16 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.1, 137.7, 135.9, 129.2, 128.7, 128.4, 128.3, 126.6, 81.5, 70.5, 60.2, 48.5, 39.7, 21.5, 21.3, 20.2, 16.9; IR (thin film) 2926, 1597, 1452, 1331, 1160, 1091, 812, 756; HRMS (ESI) calcd for $[M + H]^+$ $C_{27}H_{39}O_4N_2S_1$: 487.2623, found 487.2623.

*(±)-N-((2S,4R)-4-Hydroxy-4-phenyl-1-(2,2,6,6-tetramethylpiperidin-1-yloxy)butan-2-yl)-4-methylbenzenesulfonamide (**4**).* A solution of isoxazolidine **2c** (40 mgs, 0.08 mmol) and Pearlman's catalyst [$Pd(OH)_2$ on carbon, wet. Degussa type, 20% (wt.)] (6 mg, 0.017 mmol, 10 mol %) in EtOH (8 mL) was shaken under 3 atm H_2 pressure (hydrogenator) for 18 h.[9c] Additional catalyst (6 mg, 10 mol %) was added and the mixture was shaken for 4 h. The mixture was diluted with EtOAc, filtered through Celite and concentrated under reduced pressure. Flash chromatography (10−60% EtOAc in hexanes) afforded 28 mg (70%) of amino-alcohol **4** (colorless oil). **2c** (4 mg, 10%) was recovered. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 8.0 Hz, 2H), 7.32−7.23 (m, 7H), 5.08 (d, J = 8.0 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 3.71 (dd, J = 4.4 Hz, 8.8 Hz, 1H), 3.61 (dd, J = 5.6 Hz, 9.2 Hz, 1H), 3.50−3.46 (m, 1H), 2.39 (s, 3H), 1.98 (t, J = 8.0 Hz, 2H), 1.42−1.35 (m, 4H), 1.03−0.95 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 144.1, 143.4, 137.4, 129.6, 128.5, 127.7, 127.2, 125.8, 77.5, 72.1, 59.9, 51.8, 41.7, 39.6, 32.9, 21.4, 20.1, 16.9; IR (thin film) 3484 (br), 3279, 2928, 1598, 1494, 1453, 1374, 1330, 1159, 1093, 1047, 972, 910, 814, 732, 700, 665 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$ $C_{26}H_{39}N_2O_4S_1$: 475.2625; found 475.2636.

*(±)-4-Methyl-N-((3S,5R)-2-oxo-5-phenyl-tetrahydrofuran-3-yl)-benzenesulfonamide (**5**).* Sulfonamide **4** (15 mg, 0.032 mmol) in CH_2Cl_2 (0.3 mL) was treated with m-CPBA (14.3 mg, 0.083 mmol of 77% pure material, 2 equiv), added over 5 min. After being stirred for 5 h, the mixture was quenched with Na_2SO_3 (aq) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on SiO_2 (20−80% EtOAc in hexanes) afforded lactone **5** (6.8 mg, 64% yield) as a waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.41−7.21 (m, 7H), 5.69 (d, J = 8.0 Hz, 1H), 5.14 (d, J = 3.2 Hz, 1H), 4.02−3.96 (m, 1H), 2.83 (dd, J = 2.0 Hz, 8.6 Hz, 1H), 2.80 (dd, J = 2.0 Hz, 8.0 Hz, 1H) 2.42 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 173.9, 144.3, 138.1, 135.8, 129.9, 129.0, 128.6, 127.2, 124.7, 78.6, 50.7, 37.6, 21.6; IR (thin film) 3264, 2924, 1786, 1597, 1496, 1452, 1333, 1254, 1161, 1092, 1009, 916 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{17}O_4N_1Na_1S_1$: 354.0757, found 354.0771.

*N-((2S,4R)-1,4-Dihydroxy-4-phenylbutan-2-yl)-4-methylbenzenesulfonamide (**6**).* Crude **5** [obtained from **4** (58.5 mg, 0.12 mmol) as above] in EtOH (5 mL) and $NaBH_4$ (22.7 mg, 0.6 mmol) were stirred at rt. After 6 h, the mixture was quenched with 5% K_2CO_3 (aq) (8 mL) and EtOH was removed *in vacuo*. The mixture was extracted with Et_2O (4 × 20 mL) and the organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography on SiO_2 (30−90% EtOAc in hexanes) provided amino-diol **6** (22.8 mg) in 56% yield (white solid). mp = 125−127 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.31−7.23 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H) 4.60 (t, J = 6.8 Hz, 1H), 3.52 (dd, J = 4.0 Hz, 11.2 Hz, 1H), 3.41 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.24−3.22 (m, 1H), 2.48 (s, 1H), 1.98−1.95 (m, 1H), 1.81−1.75 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 145.7, 144.6, 139.9, 130.7, 129.2, 128.3, 128.1, 127.3, 72.0, 64.9, 54.2, 41.8, 21.5; IR (thin film) 3461, 3288, 2924, 2853, 1454, 1323, 1156, 1093, 1051, 815 cm^{-1}; HRMS ESI calcd for $[M + Na]^+$ $C_{17}H_{21}O_4N_1Na_1S_1$: 358.1091, found 358.1084.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds, NMR spectra supporting stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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