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Alkene Oxyamination Using Malonoyl Peroxides: Preparation of Pyrrolidines and Isoxazolidines

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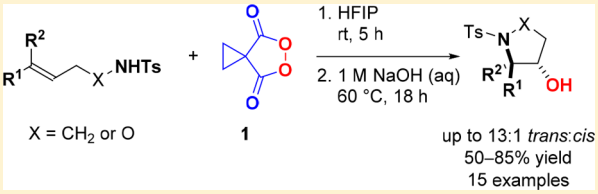
Supporting Information

ABSTRACT: Treatment of homoallylic *N*-tosyl amines or allylic *N*-tosyl hydroxylamines with 1.5 equiv of a malonoyl peroxide provides a stereoselective method to access functionalized pyrrolidines and isoxazolidines. This metal free alkene oxyamination proceeds in 50−85% yield and up to 13:1 *trans*-selectivity. In addition, the relative stereochemistry of the oxygen and nitrogen substituents can be inverted through an oxidation/reduction sequence or inverting the stereochemistry of the starting alkene. Mechanistic investigations show a higher reactivity for hydroxyl nucleophiles over sulfonamide nucleophiles revealing a preference for dioxygenation over oxyamination.

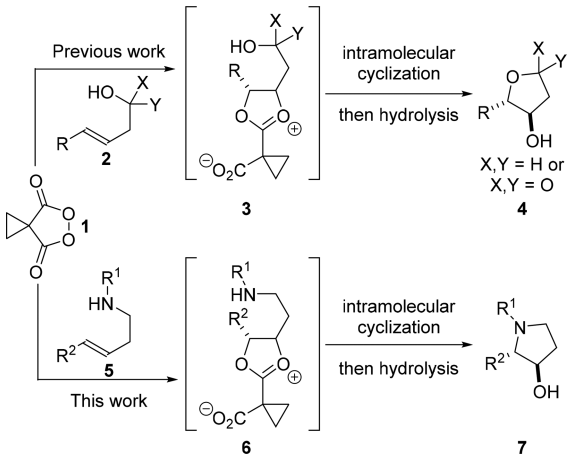


The vicinal functionalization of alkenes is one of the most studied transformations in organic synthesis. This is particularly the case for the introduction of new carbon—heteroatom bonds generating up to two new stereogenic centers. For example, exquisite success has been achieved in dihydroxylation processes whereby the majority of alkene building blocks can be transformed stereo- and enantioselectively into the corresponding *syn*- or *anti*-diol using commercial reagents under mild and efficient conditions.[1−3]

While significant efforts have been devoted to the dioxygenation of alkenes, methods for oxyamination are substantially less developed, despite the accordant potential for the products in pharmaceutical and agrochemical research.[4] The majority of methods developed for oxyamination involve the use of transition metal catalysts, including osmium,[5,6] rhodium,[7] palladium,[8] copper,[9] and iron.[10] Metal free methods have also been described and include both iodine(0)[11] and iodine(III)[12] species as the reagent. Despite the extensive inroads made in the development of effective methods for the oxyamination of alkenes using these processes, significant opportunities still exist in the area with regard to regio- and stereoselectivity along with substrate scope and the use of more environmentally benign catalysts, reagents, and reaction conditions.

We have recently shown that malonoyl peroxide **1** and its derivatives are versatile reagents for both the *syn*-[13] and *anti*-dioxygenation[14,15] of alkenes. In the preparation of oxygen heterocycles, transformations proceed through the reaction of the substrate alkene **2** with the malonoyl peroxide to give a dioxonium intermediate **3**,[16] which can react stereoselectively in an intramolecular fashion with either an alcohol or a carboxylic acid to give the corresponding tetrahydrofuran or γ-lactone, respectively (Scheme 1). Encouraged by the success of this work, we sought to discover if the overall strategy could be applied to the preparation of nitrogen containing heterocycles through the reaction of alkenes tethered directly to a nitrogen nucleophile (e.g., **5**). Within this paper, we describe the development of a simple and effective intramolecular oxyamination procedure to deliver 2-hydroxypyrrolidine derivatives **7** in a stereoselective manner.

Scheme 1. Intramolecular Oxidative Cyclizations



Our investigation began with the reaction of a homoallylic amine **8a** (R = Ts) with malonoyl peroxide **1** (Table 1).

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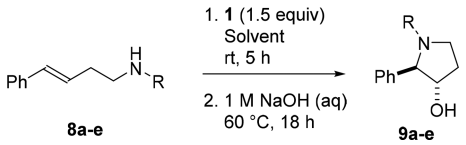
Table 1. Influence of a Nitrogen Substituent



entry	reactant	R	solvent	conversion[b] (%)	yield (%)[c]	*cis*/*trans*[b]
1	**8a**	Ts	$CHCl_3$	16		
2	**8a**	Ts	CH_2Cl_2	8		
3	**8a**	Ts	HFIP	100	69	1:9
4[d]	**8a**	Ts	HFIP	100	71	1:13
5	**8b**	Ac	HFIP	100		
6	**8c**	Boc	HFIP	100		
7	**8d**	Cbz	HFIP	100		
8	**8e**	DNs	HFIP	27		1:1

[a]All reactions performed in duplicate at 0.5 M concentration for 5 h. [b]Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Isolated yield of the major isomer. [d]Solvent dried over 3 Å molecular sieves for 24 h prior to use. DNs = 2,4-dinitrophenylsufonyl.

Chlorinated solvents, which had proved effective in both the *syn*- and *anti*-dioxygenation of alkenes,[13,14] led to a slow consumption of starting materials with no clear indication of the desired pyrrolidine product **9a** (R = Ts) (entries 1 and 2). However, reaction of **8a** with 1.5 equiv of malonoyl peroxide **1** at room temperature for 5 h in hexafluoroisopropanol (HFIP) followed by hydrolysis of the product led to the desired *trans*-3-hydroxypyrrolidine **9a** in an excellent 69% isolated yield and a 1:9 *cis*/*trans* selectivity (entry 3). Drying the HFIP solvent over 3 Å molecular sieves for 24 h prior to use provided the product in a similar yield and improved selectivity (entry 4; 71%; 1:13 *cis*/*trans*). Interestingly, despite extensive efforts to induce a similar reactivity with alternative amide **8b** (entry 5), carbamate **8c** and **8d** (entries 6 and 7), and sulfonamide **8e** (entry 8) substituents on the nitrogen nucleophile, similar reactivity patterns could not be observed upon complete consumption of starting material. In each of these transformations, numerous products were present in the ^{1}H NMR of the crude reaction mixture with no clear evidence for the formation of the target pyrrolidines. This suggests that both the electronics and sterics of the nitrogen nucleophile are crucial to observing the desired reactivity and that *N*-tosylsulfonamides provide the environment required to promote reactivity.

Confirmation of the structure of the cyclized pyrrolidine **10**, prior to hydrolysis, came from single crystal X-ray crystallography (Figure 1). This structure clearly shows the *trans*-relationship between the phenyl group from the alkene substrate and the ester group from the malonoyl peroxide reagent. Overall, this provides a convenient, mild, and effective method for the *anti*-oxyamination of alkenes.

Having established an efficient method for the oxyamination of **8a** (R = Ts), we went on to examine some of the scope of the process (Table 2). Substitution on all positions of the aromatic ring was tolerated with *p*- (entry 2; 66%; 1:7 *cis*/*trans*), *m*- (entry 3; 71%; 1:6 *cis*/*trans*), and *o*-tolyl (entry 4; 72%) substrates effectively undergoing the intramolecular oxyamination process. Chloride substitution was also well tolerated (entries 6 and 7), providing the products in up to 67% isolated yield, which could readily be diversified. Alternative substitution on the aromatic ring that was also investigated included a *p*-phenyl substituent (entry 5; 72%; 1:9 *cis*/*trans*) and an acetal group (entry 8; 55%; 1:9 *cis*/*trans*).

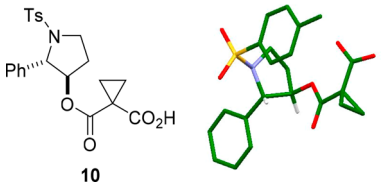
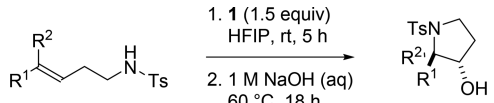
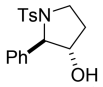
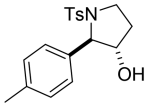
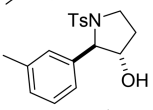
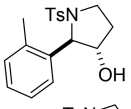
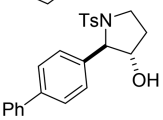
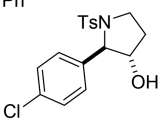
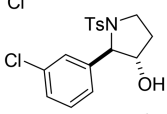
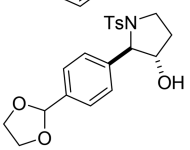
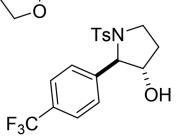
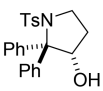
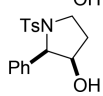


Figure 1. Single crystal X-ray structure of pyrrolidine **10**.

Table 2. Substrate Scope for the Oxyamination Procedure



entry	product	compd	yield[a]	*cis*:*trans*[b]
1		**9a**	71	1:13
2		**13**	66	1:7
3		**14**	71	1:6
4		**15**	72	-
5		**16**	72	1:9
6		**17**	67	1:9
7		**18**	52	1:6
8		**19**	55	1:9
9[c]		**20**	19	-
10		**21**	82	-
11[d]		**22**	50	5:1

[a]Yields quoted are isolated yields of the major isomer. [b]Diastereoselectivity determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Reaction conducted at 50 °C for 20 h. [d](*Z*)-Alkene substrate used.

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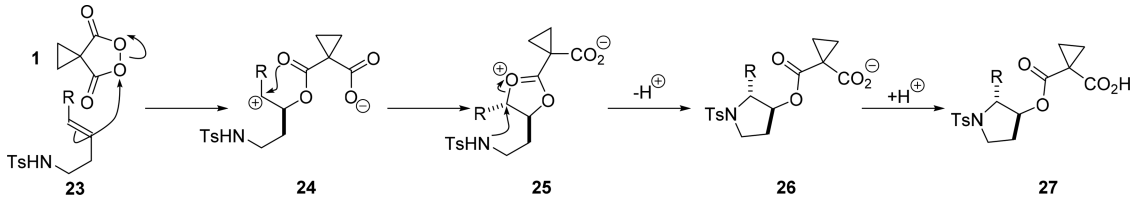


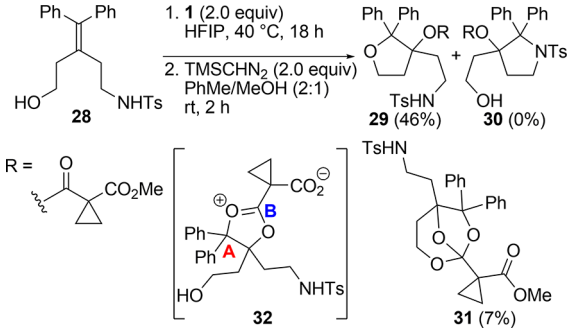
Figure 2. Proposed mechanistic pathway for the intramolecular oxyamination procedure.

A limitation was encountered with the introduction of the strongly electron withdrawing trifluoromethyl substituent, which was significantly slower than the other substrates examined. Conducting the reaction at a higher temperature of 50 °C for 20 h gave the product **20** in just 19% isolated yield (entry 9). While ^{1}H NMR spectroscopy supported the structure of **20**, it was not possible to determine the stereoselectivity due to overlapping signals. Introduction of an additional substituent on the alkene substrate was also possible with the diphenyl-substituted pyrrolidine **21** being isolated in an excellent 82% yield (entry 10), providing the most efficient pyrrolidine synthesis examined within this study. Use of a (*Z*)-alkene substrate gave the *cis*-pyrrolidine product **22** as a 5:1 mixture of *cis*- and *trans*-isomers (entry 11).

Mechanistically we believe that the reaction is proceeding as outlined in Figure 2. Nucleophilic attack of the substituted alkene **23** on the peroxide **1** leads to **24**, which cyclizes intramolecularly to give the dioxonium species **25** as defined previously for alkene dihydroxylation.[16] Subsequent cyclization of the nitrogen nucleophile forms the pyrrolidine ring **27** with a *trans*-relationship of the newly formed C−O and C−N bonds. This mechanistic pathway is consistent with previous investigations into the reactivity of malonoyl peroxide **1** and accounts for the stereoselectivities observed within the process.

In order to understand the mechanism of this transformation further, we prepared the probe molecule **28**, to ascertain if differences in nucleophilicity between heteroatoms could influence the outcome of the cyclization (Scheme 2).

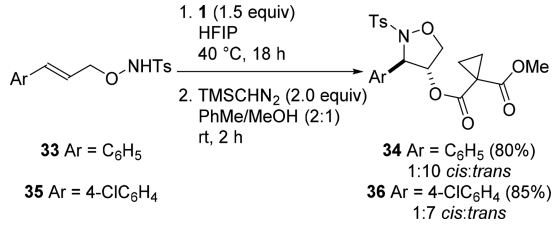
Scheme 2. Probe To Understand the Reaction Mechanism



Compound **28** is a tetrasubstituted alkene, which contains both an alcohol and a sulfonamide nucleophile. Reaction of **28** under standard cyclization conditions followed by esterification of the crude product gave tetrahydrofuran **29** (46%). Pyrrolidine **30** was not detected by ^{1}H NMR spectroscopy on the crude reaction mixture. This shows that on formation of a dioxonium ion intermediate **32** the more nucleophilic pendant heteroatom reacts selectively through carbon atom **A**. In addition, we also isolated a small amount of the bicyclic compound **31** (7%), which results from direct cyclization of the oxygen heteroatom on carbon atom **B** of the dioxonium intermediate **32**. We believe this product is formed due to the increased steric encumbrance of carbon atom **A**, reducing the reactivity of this center.

To expand the scope of the transformation to alternative nitrogen containing heterocycles, we prepared the hydroxylamine derivatives **33** and **35** and reacted each with 1.5 equiv of **1** (HFIP, 40 °C, 18 h) (Scheme 3). The elevated temperature

Scheme 3. Preparation of Isoxazolidines



and extended reaction times necessary to bring about reaction suggest a reduced nucleophilicity of the nitrogen heteroatom within these substrates. After treatment of the crude reaction mixture with $TMSCHN_2$, the isoxazolidines **34** (80%; 1:10 *cis*/*trans*) and **36** (85%; 1:7 *cis*/*trans*) were isolated after purification by column chromatography. This provides an efficient and highly stereoselective method for the preparation of the 4-hydroxyisoxazolidine framework from readily accessible alkene substrates.

The structure of the isoxazolidine product **37**, prior to esterification, was confirmed by single crystal X-ray crystallographic analysis (Figure 3). In contrast to the structure of the

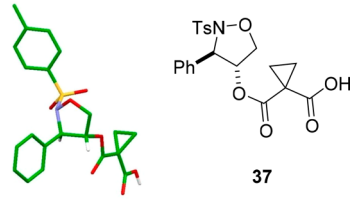


Figure 3. Single crystal X-ray structure of isoxazolidine **37**.

pyrrolidine analogue **10**, the nitrogen atom adopts a tetrahedral geometry in this structure, with the isoxazolidine ring having a more puckered conformation. The apparent reduced nucleophilicity of the hydroxylamine derivatives **33** and **35** was surprising. While we are unable to unequivocally explain this observation, the X-ray structures of compounds **10** and **37** suggest that the conformation of the substrates may affect reactivity.

Reaction of 3-hydroxypyrrolidine **9a** with IBX (3 equiv) in acetonitrile gave the pyrrolidinone **38** in 85% isolated yield (Scheme 4). Reduction of this ketone with DIBAL-H in THF at rt for 3 h gave the *cis*-substituted product **22** (6:1 *cis*/*trans*; 78%). This sequence provides an alternative access to the

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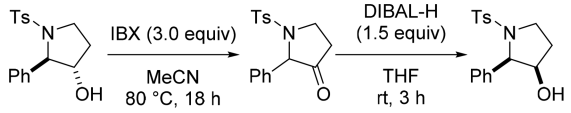
Scheme 4. Inverting Relative Stereochemistry of the Pyrrolidine Ring



9a 1:13 *cis*:*trans* — **38** (85%) — **22** (78%) 6:1 *cis*:*trans*

diastereomeric pyrrolidine product **22** without independent preparation of the (*Z*)-alkene substrate enhancing the overall use of the process described and the diversity of structures accessed using this methodology.

In summary, we have described a simple and effective method for the intramolecular oxyamination of alkenes. Through optimization of the nitrogen substituent, we have shown that the oxyamination procedure can be induced at room temperature by treatment of an alkene substrate with 1.5 equiv of malonoyl peroxide **1** in HFIP. The product can be isolated in a good yield and up to a 13:1 *trans*/*cis* ratio. The related isoxazolidines can also be prepared from the appropriate hydroxylamine substrate. In addition, the relative stereochemistry of the two newly formed carbon—heteroatom bonds can be changed by preparation of the (*Z*)-alkene substrate or through a simple oxidation−reduction sequence, further expanding the scope of this useful transformation. A mechanistic probe showed there is a preference for reaction of the dioxonium intermediate with an alcohol over a sulfonamide nucleophile, revealing a preference for dioxygenation over oxyamination. Current efforts are focused on developing an intermolecular variant of this procedure, and we will report on our findings in the near future.

EXPERIMENTAL SECTION

Synthesis of Malonoyl Peroxide (1).[15] Methane sulfonic acid (30 mL) was placed in a round-bottom flask equipped with a large magnetic stirrer bar and immersed in a bath of water at 22 °C. Urea hydrogen peroxide (9.8 g, 104.0 mmol) was added in a single portion, and the mixture was stirred for 30 s. Cyclopropane-1,1-dicarboxylic acid (5.0 g, 38.5 mmol) was added in a single portion, and the reaction was stirred vigorously for 18 h. The reaction mixture was poured into a mixture of ice (80 g) and ethyl acetate (100 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organics were washed with $NaHCO_3$ (2 × 50 mL) and brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the desired peroxide **1** (3.5 g, 27.3 mmol, 71%): mp 90 °C; IR (ATR)/cm^{-1} 1827, 1798, 1358; ^1H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 23.7, 19.9.

Synthesis of 2-(But-3-en-1-yl)isoindoline-1,3-dione.[17] A dry three-neck flask was charged with potassium phthalimide (3.6 g, 19.2 mmol) in DMF (12 mL). 4-Bromobut-1-ene (1.5 mL, 14.8 mmol) was added, and the mixture was stirred at reflux for 5 h. The mixture was allowed to cool to room temperature, poured onto ice, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with 0.2 M KOH (50 mL) and H_2O (50 mL), dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation to afford the title compound (2.8 g, 13.8 mmol, 93%) as a brown solid, which was used without further purification: mp 49−51 °C (lit.[18] 52−53 °C); IR (ATR)/cm^{-1} 3075, 2974, 2939, 1772, 1705; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85−7.81 (m, 2H), 7.72−7.68 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 2.47−2.42 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 134.6, 134.0, 132.3, 123.3, 117.7, 37.5, 33.0; LRMS (ES + APCI) *m*/*z* 202.1 $[M + H]^+$.

General Procedure 1 (Heck Coupling).[19] A dry three-neck flask fitted with a condenser was charged with aryl iodide (1.1 equiv) and Et_3N (2.0 equiv) in MeCN (0.05 M). 2-(But-3-en-1-yl)isoindoline-1,3-dione (1.0 equiv) was added followed by P(*o*-tol)$_3$ (10 mol %) and $Pd(OAc)_2$ (5 mol %). The mixture was stirred at reflux until completion by TLC. The solution was allowed to cool to room temperature and was passed through a plug of Celite, and the solvent was removed in vacuo. The crude residue was dissolved in EtOAc (100 mL) and washed with 2 M HCl (× 2) and H_2O (× 2), dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography with hexane/EtOAc mixtures afforded the target compounds.

(E)-2-(4-Phenylbut-3-en-1-yl)isoindoline-1,3-dione.[20] Phenyl iodide (1.7 mL, 14.8 mmol) and Et_3N (3.7 mL, 26.8 mmol) were dissolved in MeCN (270 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (2.7 g, 13.4 mmol), P(*o*-tol)$_3$ (407 mg, 1.3 mmol), and $Pd(OAc)_2$ (150 mg, 0.7 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 16 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (2.2 g, 7.9 mmol, 60%) as a white solid: mp 138−139 °C (lit.[20] 133.5−135.5 °C); IR (ATR)/cm^{-1} 3054, 3025, 2935, 1695; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H), 7.70−7.69 (m, 2H), 7.30−7.27 (m, 4H), 7.20−7.18 (m, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.18 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.85 (t, *J* = 7.1 Hz, 2H), 2.63−2.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 137.3, 133.9, 132.6, 132.1, 128.5, 127.2, 126.2, 126.1, 123.2, 37.6, 32.2; LRMS (ES + APCI) *m*/*z* 278.0 $[M + H]^+$.

(E)-2-(4-p-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione.[21] 4-Iodotoluene (600 mg, 2.7 mmol) and Et_3N (700 μL, 5.0 mmol) were dissolved in MeCN (50 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (500 mg, 2.5 mmol), P(*o*-tol)$_3$ (75 mg, 0.3 mmol), and $Pd(OAc)_2$ (28 mg, 0.1 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 24 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (432 mg, 1.5 mmol, 60%) as a white solid: mp 121−122 °C; IR (ATR)/cm^{-1} 3023, 2922, 2854, 1708; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84−7.81 (m, 2H), 7.71−7.68 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 15.9, 7.2 Hz, 1H), 3.83 (t, *J* = 7.2 Hz, 2H), 2.62−2.57 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 137.1, 134.6, 134.0, 132.6, 132.3, 129.3, 126.2, 125.2, 123.4, 37.8, 32.4, 21.3; LRMS (ES + APCI) *m*/*z* 292.0 $[M + H]^+$.

(E)-2-(4-m-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione.[21] 3-Iodotoluene (350 μL, 2.7 mmol) and Et_3N (700 μL, 5.0 mmol) were dissolved in MeCN (50 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (500 mg, 2.5 mmol), P(*o*-tol)$_3$ (75 mg, 0.3 mmol), and $Pd(OAc)_2$ (28 mg, 0.1 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 20 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (528 mg, 1.8 mmol, 73%) as a colorless oil: IR (ATR)/cm^{-1} 3055, 2940, 2857, 1712; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H), 7.70−7.68 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 (s, 1H), 7.11−7.09 (m, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.16 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.84 (t, *J* = 7.1 Hz, 2H), 2.63−2.58 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 138.1, 137.3, 134.0, 132.8, 132.3, 128.5, 128.2, 127.0, 126.0, 123.43, 123.37, 37.8, 32.4, 21.5; LRMS (ES + APCI) *m*/*z* 292.0 $[M + H]^+$.

(E)-2-(4-o-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione.[21] 2-Iodotoluene (350 μL, 2.7 mmol) and Et_3N (700 μL, 5.0 mmol) were dissolved in MeCN (50 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (500 mg, 2.5 mmol), P(*o*-tol)$_3$ (75 mg, 0.3 mmol), and $Pd(OAc)_2$ (28 mg, 0.1 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 16 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (300 mg, 1.0 mmol, 42%) as a white solid: mp 132−134 °C; IR (ATR)/cm^{-1} 3056, 3017, 2939, 2855, 1706; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84−7.83 (m, 2H), 7.71−7.69 (m, 2H), 7.35 (d, *J* = 6.9 Hz, 1H), 7.14−7.06 (m, 3H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.12 (dt, *J* = 15.6, 7.5 Hz, 1H), 3.86 (t, *J* = 7.0 Hz, 2H),

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2.66−2.61 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 136.6, 135.2, 134.1, 132.3, 130.8, 130.2, 127.7, 127.3, 126.2, 126.0, 123.4, 37.8, 32.6, 19.8; LRMS (ES + APCI) m/z 292.0 $[M + H]^+$.

(E)-2-(4-(4-Chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione.[22] 1-Chloro-4-iodobenzene (1.3 g, 5.5 mmol) and Et_3N (1.4 mL, 10.0 mmol) were dissolved in MeCN (100 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (1.0 g, 4.97 mmol), P(*o*-tol)$_3$ (151 mg, 0.5 mmol), and $Pd(OAc)_2$ (56 mg, 0.3 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 42 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (1.1 g, 3.4 mmol, 68%) as a white solid: mp 130−131 °C (lit.[22] 130.5−132.0 °C); IR (ATR)/cm^{-1} 3058, 3025, 3002, 2939, 1699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H), 7.71−7.69 (m, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.37 (d, J = 15.8 Hz, 1H), 6.15 (dt, J = 15.8, 7.1 Hz, 1H), 3.84 (t, J = 7.1 Hz, 2H), 2.62−2.58 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 135.9, 134.1, 133.0, 132.2, 131.5, 128.8, 127.5, 127.1, 123.4, 37.6, 32.4; LRMS (ES + APCI) m/z 328.9 $[M + NH_4]^+$.

(E)-2-(4-(3-Chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione.[23] 1-Chloro-3-iodobenzene (2.0 g, 8.4 mmol) and Et_3N (2.1 mL, 15.2 mmol) were dissolved in MeCN (150 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (1.53 g, 7.6 mmol), P(*o*-tol)$_3$ (232 mg, 0.8 mmol), and $Pd(OAc)_2$ (86 mg, 0.4 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 48 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (1.8 g, 5.8 mmol, 76%) as a brown solid: mp 106−108 °C; IR (ATR)/cm^{-1} 3056, 3025, 2935, 2854, 1708; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.81 (m, 2H), 7.72−7.68 (m, 2H), 7.26 (s, 1H), 7.21−7.14 (m, 3H), 6.36 (d, J = 15.8 Hz, 1H), 6.19 (dt, J = 15.8, 7.1 Hz, 1H), 3.84 (t, J = 7.1 Hz, 2H), 2.63−2.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 139.2, 134.6, 134.1, 132.2, 131.5, 129.8, 128.0, 127.3, 126.3, 124.5, 123.4, 37.6, 32.2; LRMS (ES + APCI) m/z 329.0 $[M + NH_4]^+$.

(E)-2-(4-([1,1′-Biphenyl]-4-yl)but-3-en-1-yl)isoindoline-1,3-dione. 4-Iodo-1,1′-biphenyl (1.7 g, 6.1 mmol) and Et_3N (1.5 mL, 11.0 mmol) were dissolved in MeCN (110 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (1.1 g, 5.5 mmol), P(*o*-tol)$_3$ (168 mg, 0.6 mmol), and $Pd(OAc)_2$ (62 mg, 0.3 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 72 h. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (0.8 g, 2.3 mmol, 41%) as a white solid: mp 198 °C (decomp); IR (ATR)/cm^{-1} 2987, 2935, 2879, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.82 (m, 2H), 7.72−7.67 (m, 2H), 7.59−7.56 (m, 2H), 7.53−7.50 (m, 2H), 7.44−7.40 (m, 2H), 7.38−7.36 (m, 2H), 7.35−7.30 (m, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.22 (d, J = 15.8, 7.1 Hz, 1H), 3.87 (t, J = 7.1 Hz, 2H), 2.67−2.61 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 140.9, 140.2, 136.5, 134.1, 132.31, 132.26, 128.9, 127.3, 127.1, 126.7, 126.5, 123.4, 37.7, 32.5 (1 carbon missing); LRMS (ES + APCI) m/z 371.1 $[M + NH_4]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{20}NO_2$ 354.1494, found 354.1491.

(E)-2-(4-(4-(1,3-Dioxalan-2-yl)phenyl)but-3-en-1-yl)isoindoline-1,3-dione. 2-(4-Iodophenyl)-1-dioxalane (3.0 g, 10.9 mmol) and Et_3N (2.8 mL, 19.7 mmol) were dissolved in MeCN (200 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (2.0 g, 9.9 mmol), P(*o*-tol)$_3$ (301 mg, 1.0 mmol), and $Pd(OAc)_2$ (111 mg, 0.5 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 72 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (1.6 g, 4.6 mmol, 46%) as a white solid: mp 120−121 °C; IR (ATR)/cm^{-1} 3026, 2945, 2883, 1706; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.80 (m, 2H), 7.71−7.67 (m, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 6.42 (d, J = 15.8 Hz, 1H), 6.19 (dd, J = 15.8, 7.1 Hz, 1H), 5.78 (s, 1H), 4.12−4.10 (m, 2H), 4.04−4.00 (m, 2H), 3.85 (d, J = 7.1 Hz, 2H), 2.63−2.59 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 138.4, 136.9, 134.1, 132.4, 132.2, 127.0, 126.8, 126.3, 123.4, 103.7, 65.4, 37.7, 32.4; LRMS (ES + APCI) m/z 350.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{20}NO_4$ 350.1392, found 350.1387.

(E)-2-(4-(4-Trifluoromethylphenyl)but-3-en-1-yl)isoindoline-1,3-dione.[24] 1-Iodo-4-(trifluoromethyl)benzene (803 μL, 5.5 mmol) and Et_3N (1.4 mL, 9.9 mmol) were dissolved in MeCN (100 mL) followed by the addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione (1.0 g, 5.0 mmol), P(*o*-tol)$_3$ (151 mg, 0.5 mmol), and $Pd(OAc)_2$ (56 mg, 0.3 mmol) according to General Procedure 1, and the resulting mixture was heated at reflux for 18 h. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (1.2 g, 3.5 mmol, 70%) as a white solid: mp 150 °C decomp; IR (ATR)/cm^{-1} 2997, 2866, 1699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.83 (m, 2H), 7.71−7.69 (m, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 6.45 (d, J = 15.8 Hz, 1H), 6.31−6.25 (m, 1H), 3.87 (t, J = 7.0 Hz, 2H), 2.66−2.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 140.8, 134.2, 134.1, 132.2, 131.5, 129.3, 127.7 (J_{C-F} = 348.5 Hz), 126.4, 125.6 (J_{C-F} = 3.75 Hz), 123.4, 37.5, 32.4; LRMS (ES + APCI) m/z 346.0 $[M + H]^+$.

Synthesis of 2-(4,4-Diphenylbut-3-en-1-yl)isoindoline-1,3-dione..[17,25−27] To a three-neck round-bottom flask dried and flushed with argon was added (3 hydroxypropyl)triphenylphosphonium bromide (2.6 g, 6.6 mmol) in anhydrous THF (12 mL). The resulting suspension was cooled to −10 °C using a NaCl/ice bath. A 1 M solution of LiHMDS (15 mL) was added dropwise, and the mixture was stirred at −10 °C for 1 h. Benzophenone (1.0 g, 5.5 mmol) was then added dropwise and stirred at −10 °C for 2 h. The mixture was allowed to warm to rt and stirred for a further 18 h. A saturated aqueous solution of NH_4Cl (50 mL) was then added. The organic layer was extracted with Et_2O (2 × 100 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40−60 °C)/EtOAc 6:4) afforded 4,4 diphenylbut 3-en-1-ol (1.0 g, 4.5 mmol, 81%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.36 (m, 2H), 7.34−7.26 (m, 2H), 7.25−7.19 (m, 6H), 6.15 (t, J = 7.5 Hz, 1H), 3.75 (t, J = 6.5 Hz, 2H), 2.46−2.41 (m, 2H), 1.39 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 142.4, 139.8, 129.9, 128.2, 128.1, 127.2, 127.1, 125.2, 62.6, 33.3.

To a solution of 4,4-diphenylbut-3-en-1-ol (300 mg, 1.3 mmol) in a 48% solution of HBr (1.6 mL) was added tetrabutylammonium bromide (17 mg, 0.1 mmol). The mixture was stirred at reflux for 18 h. The mixture was then allowed to cool to rt and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was extracted with CH_2Cl_2 (2 × 20 mL), washed with $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to afford (4-bromobut-1-ene-1,1-diyl)dibenzene (350 mg, 1.2 mmol, 91%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.27 (m, 5H), 7.25−7.22 (m, 3H), 7.19−7.17 (m, 2H), 6.09 (t, J = 7.3 Hz, 1H), 3.43 (t, J = 7.0 Hz, 2H), 2.71−2.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 142.1, 139.6, 129.7, 128.3, 128.1, 127.29, 127.26, 125.7, 32.9, 32.6.

A dry three-neck flask was charged with potassium phthalimide (360 mg, 1.9 mmol) in anhydrous DMF (10 mL). (4-Bromobut-1-ene-1,1-diyl)dibenzene (558 mg, 1.9 mmol) was added, and the mixture was stirred at reflux for 18 h. The mixture was allowed to cool to rt, poured into ice, and extracted with CH_2Cl_2 (3 × 50 mL). The organics were washed with 0.2 M KOH (50 mL) and H_2O (50 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40−60 °C)/EtOAc 9:1) afforded the title compound (600 mg, 1.7 mmol, 88%) as a white solid: mp 120−121 °C (lit.[28] 119−120 °C); IR (ATR)/cm^{-1} 2967, 2921, 2908, 2872, 1718, 1701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.78 (m, 2H), 7.71−7.66 (m, 2H), 7.27−7.18 (m, 8H), 7.02−6.99 (m, 2H), 6.07 (t, J = 7.6 Hz, 1H), 3.81−3.78 (m, 2H), 2.57−2.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 144.5, 142.5, 139.6, 134.0, 132.3, 129.8, 128.3, 128.2, 127.5, 127.2, 125.2, 123.3, 37.8, 29.0 (1 carbon missing); LRMS (ES + APCI) m/z 354.0 $[M + H]^+$.

General Procedure 2 (Removal of Phthalimide and Tosylation).[29] To a solution of (*E*)-2-(4-arylbut-3-en-1-yl)-isoindoline-1,3-dione (1.0 equiv) in EtOH (0.3 M) was added hydrazine monohydrate (2.0 equiv). The mixture was stirred at room temperature for 10 min and at reflux for a further 30 min. After the

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mixture cooled to room temperature, a 2 M solution of NaOH was added (50 mL). The solvent was evaporated before extracting the organics with EtOAc (3 × 50 mL) and drying over $MgSO_4$. The solvent was removed by rotary evaporation to give the free amine compound, which was used without further purification. The crude reaction mixture was dissolved in anhydrous CH_2Cl_2 (0.3 M) under an argon atmosphere, and Et_3N (1.5 equiv) was added. The mixture was cooled to 0 °C, and *p*-toluenesulfonyl chloride (1.0 equiv) and DMAP (0.3 equiv) were added in one portion. The mixture was stirred at room temperature for 24 h. The solution was diluted with CH_2Cl_2 and washed with 2 M HCl (100 mL) and brine (100 mL). The organics were dried over $MgSO_4$, and the solvent was removed by rotary evaporation to give a crude material, which was purified by silica gel chromatography eluting with hexane/EtOAc mixtures to afford the tosylated compound.

*(E)-4-Methyl-N-(4-phenylbut-3-en-1-yl)benzenesulfonamide (**8a**).*[29] To a solution of (*E*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione (2.2 g, 7.4 mmol) in EtOH (32 mL) was added hydrazine monohydrate (771 μL, 15.8 mmol) according to General Procedure 2 to give (*E*)-4-phenylbut-3-en-1-amine.

To a solution of (*E*)-4-phenylbut-3-en-1-amine (1.2 g, 7.9 mmol) in CH_2Cl_2 (65 mL) was added Et_3N (2.3 mL, 16.2 mmol) followed by *p*-TsCl (1.8 g, 9.8 mmol) and DMAP (0.6 g, 4.9 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded title compound **8a** (1.8 g, 6.0 mmol, 74%) as a white solid: mp 52−54 °C; IR (ATR)/cm^{-1} 3272, 3058, 3023, 2922; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.31−7.27 (m, 6H), 7.24−7.21 (m, 1H), 6.36 (d, J = 15.9 Hz, 1H), 5.98 (dt, J = 15.9, 7.1 Hz, 1H), 4.43 (bs, 1H), 3.13−3.09 (m, 2H), 2.43 (s, 3H), 2.39−2.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.2, 136.9, 133.5, 129.9, 128.7, 127.7, 127.3, 126.3, 125.6, 42.7, 33.2, 21.7; LRMS (ES + APCI) m/z 319.1 $[M + NH_4]^+$.

(E)-4-Methyl-N-(4-(p-tolyl)but-3-en-1-yl)benzenesulfonamide.[30] To a solution of (*E*)-2-(4-(*p*-tolyl)but-3-en-1-yl)isoindoline-1,3-dione (430 mg, 1.5 mmol) in EtOH (6.0 mL) was added hydrazine monohydrate (143 μL, 3.0 mmol) according to General Procedure 2 to give (*E*)-4-(*p*-tolylbut)-3-en-1-amine.

To a solution of (*E*)-4-(*p*-tolylbut)-3-en-1-amine (165 mg, 1.0 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (210 μL, 1.5 mmol) followed by *p*-TsCl (190 mg, 1.2 mmol) and DMAP (37 mg, 0.3 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (192 mg, 0.6 mmol, 61%) as a white solid: mp 82−84 °C; IR (ATR)/cm^{-1} 3276, 3047, 3017, 2939; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.32 (d, J = 15.8 Hz, 1H), 5.97 (dt, J = 15.8, 7.1 Hz, 1H), 4.37 (t, J = 5.4 Hz, 1H), 3.12−3.08 (m, 2H), 2.43 (s, 3H), 2.37−2.34 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.5, 137.2, 134.1, 133.4, 129.9, 129.4, 127.3, 126.2, 124.5, 42.7, 33.1, 21.7, 21.3; LRMS (ES + APCI) m/z 316.0 $[M + H]^+$.

(E)-4-Methyl-N-(4-(m-tolyl)but-3-en-1-yl)benzenesulfonamide.[21] To a solution of (*E*)-2-(4-(*m*-tolyl)but-3-en-1-yl)isoindoline-1,3-dione (340 mg, 1.2 mmol) in EtOH (4.5 mL) was added hydrazine monohydrate (113 μL, 2.3 mmol) according to General Procedure 2 to give (*E*)-4-(*m*-tolylbut)-3-en-1-amine.

To a solution of (*E*)-4-(*m*-tolylbut)-3-en-1-amine (189 mg, 1.2 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (245 μL, 1.8 mmol) followed by *p*-TsCl (223 mg, 1.2 mmol) and DMAP (43 mg, 0.4 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (145 mg, 0.5 mmol, 39%) as a colorless oil: IR (ATR)/cm^{-1} 3277, 3023, 2919, 2861; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 (s, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.33 (d, J = 15.8 Hz, 1H), 5.97 (dt, J = 15.8, 7.0 Hz, 1H), 4.66 (t, J = 5.8 Hz, 1H), 3.11−3.07 (m, 2H), 2.42 (s, 3H), 2.38−2.33 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 138.2, 137.1, 136.9, 133.4, 129.8, 128.6, 128.4, 127.3, 127.0, 125.5, 123.4, 42.7, 33.1, 21.6, 21.5; LRMS (ES + APCI) m/z 316.0 $[M + H]^+$.

(E)-4-Methyl-N-(4-(o-tolyl)but-3-en-1-yl)benzenesulfonamide.[21] To a solution of (*E*)-2-(4-(*o*-tolyl)but-3-en-1-yl)isoindoline-1,3-dione (275 mg, 0.9 mmol) in EtOH (3.6 mL) was added hydrazine monohydrate (92 μL, 1.9 mmol) according to General Procedure 2 to give (*E*)-4-(*o*-tolylbut)-3-en-1-amine.

To a solution of (*E*)-4-(*o*-tolylbut)-3-en-1-amine (151 mg, 0.9 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (200 μL, 1.4 mmol) followed by *p*-TsCl (179 mg, 0.9 mmol) and DMAP (35 mg, 0.3 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (64 mg, 0.2 mmol, 22%) as a colorless oil: IR (ATR)/cm^{-1} 3272, 3021, 2922, 2865; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 2H), 7.32−7.31 (m, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.15−7.11 (m, 3H), 6.58 (d, J = 15.7 Hz, 1H), 5.86 (dt, J = 15.7, 7.1 Hz, 1H), 4.65 (bs, 1H), 3.11 (t, J = 6.7 Hz, 2H), 2.42 (s, 3H), 2.42−2.37 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.2, 136.1, 135.2, 131.2, 130.4, 129.8, 127.5, 127.4, 127.0, 126.2, 125.6, 42.8, 33.4, 21.6, 19.9; LRMS (ES + APCI) m/z 316.0 $[M + H]^+$.

(E)-2-(4-([1,1′-Biphenyl]-4-yl)but-3-en-1-yl)-4-methylbenzenesulfonamide. To a solution of (*E*)-2-(4-([1,1′-biphenyl]-4-yl)but-3-en-1-yl)isoindoline-1,3-dione (300 mg, 0.9 mmol) in EtOH (3.5 mL) was added hydrazine monohydrate (82 μL, 1.7 mmol) according to General Procedure 2 to give (*E*)-4-([1,1′-biphenyl]-4-yl)but-3-en-1-amine.

To a solution of (*E*)-4-([1,1′-biphenyl]-4-yl)but-3-en-1-amine (189 mg, 0.9 mmol) in CH_2Cl_2 (3.0 mL) was added Et_3N (177 μL, 1.3 mmol) followed by *p*-TsCl (162 mg, 0.9 mmol) and DMAP (31 mg, 0.3 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded the title compound (75 mg, 0.2 mmol, 23%) as a white solid: mp 126−128 °C; IR (ATR)/cm^{-1} 3276, 3051, 3025, 2922, 2865; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.44 (at, J = 7.6 Hz, 2H), 7.36−7.34 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 6.40 (d, J = 15.9 Hz, 1H), 6.03 (dt, J = 15.9, 7.1 Hz, 1H), 4.59 (t, J = 6.0 Hz, 1H), 3.14−3.10 (m, 2H), 2.42 (s, 3H), 2.41−2.37 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 140.8, 140.4, 137.1, 136.0, 132.9, 129.9, 128.9, 127.5, 127.4, 127.3, 127.0, 126.7, 125.8, 42.7, 33.2, 21.7; LRMS (ES + APCI) m/z 378.0 $[M + NH_4]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO_2S$ 378.1528, found 378.1522.

(E)-N-(4-(4-Chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide.[31] To a solution of (*E*)-2-(4-(4-chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione (444 mg, 1.4 mmol) in EtOH (5.5 mL) was added hydrazine monohydrate (138 μL, 2.8 mmol) according to General Procedure 2 to give (*E*)-4-(4-chlorophenyl)but-3-en-1-amine.

To a solution of (*E*)-4-(4-chlorophenyl)but-3-en-1-amine (150 mg, 0.8 mmol) in CH_2Cl_2 (3.0 mL) was added Et_3N (172 μL, 1.2 mmol) followed by *p*-TsCl (157 mg, 0.8 mmol) and DMAP (30 mg, 0.3 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (57 mg, 0.2 mmol, 20%) as a white solid: mp 90−92 °C; IR (ATR)/cm^{-1} 3360, 3250, 2947, 2826; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 6.30 (d, J = 15.9 Hz, 1H), 5.96 (dt, J = 15.9, 7.0 Hz, 1H), 4.78 (t, J = 5.9 Hz, 1H), 3.10−3.07 (m, 2H), 2.41 (s, 3H), 2.37−2.33 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.1, 135.5, 133.1, 132.0, 129.9, 128.8, 127.5, 127.2, 126.6, 42.6, 33.1, 21.6; LRMS (ES + APCI) m/z 336.0 $[M + H]^+$.

(E)-N-(4-(3-Chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide. To a solution of (*E*)-2-(4-(3-chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione (1.8 g, 5.8 mmol) in EtOH (22 mL) was added hydrazine monohydrate (560 μL, 11.5 mmol) according to General Procedure 2 to give (*E*)-4-(3-chlorophenyl)but-3-en-1-amine.

To a solution of (*E*)-4-(3-chlorophenyl)but-3-en-1-amine (1.1 g, 5.8 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (1.2 μL, 8.7 mmol) followed by *p*-TsCl (1.1 g, 5.8 mmol) and DMAP (0.2 g, 1.7 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (0.4 g, 1.2 mmol, 21%) as a colorless oil: IR (ATR)/cm^{-1} 3272, 3060, 3025, 2921, 2870; ^1H NMR (500 MHz, $CDCl_3$) δ

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7.74 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.24 (m, 1H), 7.21−7.17 (m, 2H), 7.13 (d, J = 7.1 Hz, 1H), 6.29 (d, J = 15.9 Hz, 1H), 5.99 (dt, J = 15.9, 7.0 Hz, 1H), 4.68 (bs, 1H), 3.12−3.08 (m, 2H), 2.42 (s, 3H), 2.39−2.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 138.8, 137.1, 134.6, 131.9, 129.9, 127.5, 127.4, 127.3, 126.1, 124.6, 42.6, 33.1, 21.7 (1 carbon missing); LRMS (ES + APCI) m/z 352.9 $[M + NH_4]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{19}{}^{35}lNO_2S$ 336.0825, found 336.0823.

(E)-N-(4-(4-(1,3-Dioxalan-2-yl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide. To a solution of (*E*)-2-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)isoindoline-1,3-dione (400 mg, 1.1 mmol) in EtOH (4.5 mL) was added hydrazine monohydrate (111 μL, 2.3 mmol) according to General Procedure 2 to give (*E*)-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)-1-amine.

To a solution of (*E*)-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)-1-amine (250 mg, 1.1 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (240 μL, 1.7 mmol) followed by *p*-TsCl (217 mg, 1.1 mmol) and DMAP (42 mg, 0.3 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 6:4) afforded the title compound (260 mg, 0.7 mmol, 61%) as a colorless oil: IR (ATR)/cm^{-1} 3264, 3026, 2948, 2883; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.30−7.27 (m, 4H), 6.36 (d, J = 15.9 Hz, 1H), 5.99 (dt, J = 15.8, 7.1 Hz, 1H), 5.79 (s, 1H), 4.43 (t, J = 5.8 Hz, 1H), 4.15−4.11 (m, 2H), 4.05−4.01 (m, 2H), 3.13−3.08 (m, 2H), 2.42 (s, 3H), 2.39−2.34 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.8, 137.3, 137.1, 133.0, 130.0, 127.3, 126.9, 126.33, 126.26, 103.7, 65.4, 42.6, 33.2, 21.7; LRMS (ES + APCI) m/z 374.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{24}NO_4S$ 374.1426, found 374.1420.

(E)-4-Methyl-N-(4-(4-trifluoromethyl)phenyl)but-3-en-1-yl)-benzenesulfonamide. To a solution of (*E*)-2-(4-(4-trifluoromethylphenyl)but-3-en-1-yl)isoindoline-1,3-dione (1.0 g, 2.9 mmol) in EtOH (11 mL) was added hydrazine monohydrate (280 μL, 5.8 mmol) according to General Procedure 2 to give (*E*)-4-(4-(trifluoro)phenyl)but-3-en-1-amine.

To a solution of (*E*)-4-(4-(trifluoro)phenyl)but-3-en-1-amine (623 mg, 3.0 mmol) in CH_2Cl_2 (9.6 mL) was added Et_3N (604 μL, 4.3 mmol) followed by *p*-TsCl (551 mg, 2.9 mmol) and DMAP (106 mg, 0.9 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (409 mg, 1.1 mmol, 38%) as a white solid: mp 121−122 °C; IR (ATR)/cm^{-1} 3330, 3244, 2991, 2875; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.40 (d, J = 15.9 Hz, 1H), 6.14−6.08 (m, 1H), 4.39 (t, J = 5.9 Hz, 1H), 3.15−3.11 (m, 2H), 2.42 (s, 3H), 2.42−2.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 140.4, 137.1, 132.0, 129.9, 129.4 (d, J_{C-F} = 33.1 Hz), 128.7, 127.3, 126.4, 125.6 (q, J_{C-F} = 3.7 Hz), 124.3 (d, J_{C-F} = 272.0 Hz), 42.6, 33.3, 21.6; LRMS (ES + APCI) m/z 370.0 $[M + H]^+$.

N-(4,4-Diphenylbut-3-en-1-yl)-4-methylbenzenesulfonamide. To a solution of 2-(4,4-diphenylbut-3-en-1-yl)isoindoline-1,3-dione (280 mg, 0.8 mmol) in EtOH (3.0 mL) was added hydrazine monohydrate (77 μL, 1.6 mmol) according to General Procedure 2 to give 4,4-diphenylbut-3-en-1-amine.

To a solution of 4,4-diphenylbut-3-en-1-amine (176 mg, 0.8 mmol) in CH_2Cl_2 (2.6 mL) was added Et_3N (165 μL, 1.2 mmol) followed by *p*-TsCl (166 mg, 0.9 mmol) and DMAP (29 mg, 0.2 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (200 mg, 0.5 mmol, 67%) as a colorless oil: IR (ATR)/cm^{-1} 3281, 3053, 3023, 2922; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.38−7.29 (m, 3H), 7.27−7.22 (m, 5H), 7.20−7.15 (m, 2H), 7.12−7.10 (m, 2H), 5.97 (t, J = 7.4 Hz, 1H), 4.76 (bs, 1H), 3.07−3.02 (m, 2H), 2.41 (s, 3H), 2.30−2.24 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 143.4, 142.1, 139.6, 137.0, 129.8, 128.4, 128.2, 127.35, 127.31, 127.2, 124.7, 43.1, 29.9, 21.6; LRMS (ES + APCI) m/z 378.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO_2S$ 378.1528, found 378.1521.

*(E)-(4-Phenylbut-3-en-1-yl)acetamide (**8b**).*[32] To a cooled (0 °C) solution of (*E*)-4-phenylbut-3-en-1-amine (200 mg, 1.4 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (206 μL, 2.0 mmol) followed by the addition of acetyl chloride (97 μL, 1.4 mmol). The resultant mixture was then stirred at rt for 18 h, before washing with a 1 M HCl solution (20 mL) followed by a 1 M NaOH solution (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation affording title compound **8b** (190 mg, 1.0 mmol, 72%) as a yellow semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.35−7.28 (m, 4H), 7.22 (t, J = 7.1 Hz, 1H), 6.45 (d, J = 15.8 Hz, 1H), 6.14 (dt, J = 15.8, 7.1 Hz, 1H), 5.62 (bs, 1H), 3.42−3.37 (m, 2H), 2.45−2.39 (m, 2H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 137.3, 132.5, 128.7, 127.5, 127.0, 126.2, 39.1, 33.2, 23.5; LRMS (ES + APCI) m/z 190.1 $[M + H]^+$.

*tert-Butyl (E)-(4-Phenylbut-3-en-1-yl)carbamate (**8c**).*[33] To a solution of (*E*)-4-phenylbut-3-en-1-amine (316 mg, 2.1 mmol) in CH_2Cl_2 (4 mL) was added K_2CO_3 (591 mg, 4.3 mmol) followed by the addition of di-*tert*-butyl dicarbonate (468 mg, 2.1 mmol). The resultant mixture was then stirred at 40 °C for 18 h, before the addition of H_2O (20 mL), and the stirring was extended for an extra hour. Layers were separated, and the organic layer was washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane/EtOAc 9:1) afforded title compound **8c** (441 mg, 1.8 mmol, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.34 (m, 2H), 7.30 (at, J = 7.5 Hz, 2H), 7.21 (t, J = 7.1 Hz, 1H), 6.45 (d, J = 15.8 Hz, 1H), 6.15 (dt, J = 15.8, 7.1 Hz, 1H), 4.59 (bs, 1H), 3.30−3.25 (m, 2H), 2.43−2.38 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 137.4, 132.4, 128.7, 127.4, 127.2, 126.2, 40.2, 33.7, 28.6 (1 carbon missing); LRMS (ES + APCI) m/z 248.1 $[M + H]^+$.

*Benzyl (E)-(4-Phenylbut-3-en-1-yl)carbamate (**8d**).*[21] To a solution of (*E*)-4-phenylbut-3-en-1-amine (308 mg, 2.1 mmol) in H_2O (10 mL) and acetone (21 mL) was added $NaHCO_3$ (200 mg, 2.4 mmol) followed by the addition of benzyl chloroformate (335 μL, 2.4 mmol). The resultant mixture was then stirred at rt for 18 h, before evaporation of the solvent, and the precipitate was filtered affording title compound **8d** (498 mg, 1.8 mmol, 85%) as a white solid: mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 9H), 7.24−7.1 (m, 1H), 6.45 (d, J = 15.9 Hz, 1H), 6.14 (dt, J = 15.9, 7.3 Hz, 1H), 5.10 (s, 2H), 4.83 (bs, 1H), 3.38−3.34 (m, 2H), 2.46−2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 137.1, 136.6, 132.5, 128.6, 128.5, 128.5, 128.1, 127.3, 126.6, 126.1, 66.6, 40.5, 33.5; LRMS (ES + APCI) m/z 282.1 $[M + H]^+$.

*(E)-2,4-Dinitro-N-(4-phenylbut-3-en-1-yl)benzenesulfonamide (**8e**).* To a cooled (0 °C) solution of (*E*)-4-phenylbut-3-en-1-amine (200 mg, 1.4 mmol) in CH_2Cl_2 (14 mL) was added Et_3N (284 μL, 2.0 mmol) followed by the addition of 2,4-dinitrobenzenesulfonyl chloride (471 mg, 1.8 mmol). The resultant mixture was then stirred at rt for 18 h, before quenching with a saturated solution of NH_4Cl (20 mL). The organic layer was extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (100 mL), dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded title compound **8e** (502 mg, 1.3 mmol, 98%) as a yellow solid: mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.36−8.34 (m, 1H), 8.27−8.24 (m, 1H), 7.24−7.15 (m, 3H), 7.11−7.08 (m, 2H), 6.29 (d, J = 15.8 Hz, 1H), 5.83 (dt, J = 15.8, 7.3 Hz, 1H), 5.41 (bt, J = 5.6 Hz, 1H), 3.46−3.42 (m, 2H), 2.46−2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 147.7, 139.8, 136.2, 133.8, 131.9, 128.6, 128.1, 127.0, 125.9, 125.1, 120.7, 43.9, 33.5; LRMS (ES + APCI) m/z 378.1 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{16}N_3O_6S$ 378.0760, found 378.0746.

General Procedure 3 (Oxyamination Procedure for the Synthesis of Pyrrolidines). Malonoyl peroxide **1** (1.5 equiv) was added to a solution of alkene 11 (1.0 equiv) in HFIP (0.5 M). The mixture was stirred at rt for 5 h. The solvent was removed by rotary evaporation, and the resulting residue was directly treated with 1 M NaOH/THF (1:1 (0.1 M)). The solution was stirred at 60 °C for 18 h and allowed to cool to rt, and the aqueous phase was extracted with EtOAc (× 3). The combined organics were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure

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afforded the crude pyrrolidine product. Purification by silica gel flash column chromatography eluting with hexane/EtOAc mixtures afforded target compound **12**.

*(±)-2-Phenyl-1-tosylpyrrolidin-3-ol (**9a**).*[34] Reaction of (*E*)-4-methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide **8a** (25 mg, 0.08 mmol) and malonoyl peroxide **1** (16 mg, 0.12 mmol) in HFIP (0.2 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (0.8 mL, 1:1) gave the crude alcohol (1:13 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **9a** (18 mg, 0.06 mmol, 71%) as a white solid: mp 148−149 °C (lit.[34] 155−156 °C); IR (ATR)/cm^{-1} 3474, 3065, 3034, 2929, 2892; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.34−7.33 (m, 4H), 7.31 (d, J = 8.1 Hz, 2H), 7.28−7.26 (m, 1H), 4.66 (bs, 1H), 4.18 (bs, 1H), 3.73 (td, J = 9.4, 2.1 Hz, 1H), 3.53 (td, J = 9.9, 7.0 Hz, 1H), 2.43 (s, 3H), 2.07−2.00 (m, 1H), 1.77−1.73 (m, 1H), 1.37−1.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 139.9, 134.7, 129.7, 128.7, 128.9, 127.7, 126.3, 79.1, 72.0, 46.8, 31.5, 21.7; LRMS (ES + APCI) m/z 318.0 [M + H]$^+$.

*(±)-2-(p-Tolyl)-1-tosylpyrrolidin-3-ol (**13**).* Reaction of (*E*)-4-methyl-*N*-(4-(*p*-tolyl)but-3-en-1-yl)benzenesulfonamide (100 mg, 0.32 mmol) and malonoyl peroxide **1** (61 mg, 0.48 mmol) in HFIP (0.7 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (3.2 mL, 1:1) gave the crude alcohol (1:7 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **13** (69 mg, 0.21 mmol, 66%) as a white solid: mp 135−136 °C; IR (ATR)/cm^{-1} 3401, 3029, 2960, 2899; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.62 (bs, 1H), 4.13 (bs, 1H), 3.70 (ddd, J = 9.3, 8.6, 2.4 Hz, 1H), 3.50 (td, J = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 2.07−1.97 (m, 1H), 1.75−1.69 (m, 1H), 1.54 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.3, 137.1, 134.7, 129.7, 129.3, 127.9, 126.2, 79.0, 71.8, 46.8, 31.5, 21.7, 21.2; LRMS (ES + APCI) m/z 332.0 [M + H]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1316.

*(±)-2-(m-Tolyl)-1-tosylpyrrolidin-3-ol (**14**).* Reaction of (*E*)-4-methyl-*N*-(4-(*m*-tolyl)but-3-en-1-yl)benzenesulfonamide (50 mg, 0.16 mmol) and malonoyl peroxide **1** (30 mg, 0.24 mmol) in HFIP (0.3 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (1.9 mL, 1:1) gave the crude alcohol (1:6 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **14** (37 mg, 0.11 mmol, 71%) as a white solid: mp 102−104 °C; IR (ATR)/cm^{-1} 3525, 3489, 3478. 3462, 3447, 2950, 2921; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.21 (at, J = 7.5 Hz, 1H), 7.12−7.10 (m, 2H), 7.06 (d, J = 7.4 Hz, 1H), 4.63 (bs, 1H), 4.14 (bs, 1H), 3.71 (ddd, J = 9.4, 8.5, 2.4 Hz, 1H), 3.53 (td, J = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.07−1.98 (m, 1H), 1.76−1.70 (m, 1H), 1.55 (bd, J = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 139.9, 138.3, 134.8, 129.7, 128.6, 128.4, 127.8, 127.0, 123.4, 79.0, 72.0, 46.9, 31.5, 21.7, 21.6; LRMS (ES + APCI) m/z 332.0 [M + H]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1316.

*(±)-2-(o-Tolyl)-1-tosylpyrrolidin-3-ol (**15**).* Reaction of (*E*)-4-methyl-*N*-(4-(*o*-tolyl)but-3-en-1-yl)benzenesulfonamide (100 mg, 0.32 mmol) and malonoyl peroxide **1** (61 mg, 0.48 mmol) in HFIP (0.6 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (3.2 mL, 1:1) gave the crude alcohol (1:4.6 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **15** (76 mg, 0.23 mmol, 72%) as a white solid: mp 173−175 °C; IR (ATR)/cm^{-1} 3504, 3064, 2948, 2922, 2854; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.36−7.34 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.20−7.12 (m, 3H), 4.85 (bs, 1H), 4.06 (bs, 1H), 3.76 (td, J = 8.9, 1.6 Hz, 1H), 3.54 (ddd, J = 11.0, 9.3, 6.7 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.10−2.01 (m, 1H), 1.79−1.74 (m, 1H), 1.59 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 138.2, 134.8, 134.4, 130.5, 129.7, 127.8, 127.5, 126.4, 126.2, 77.6, 69.7, 46.9, 31.5, 21.7, 19.6; LRMS (ES + APCI) m/z 332.0 [M + H]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1317.

*(±)-2-([1,1′-Biphenyl]-4-yl)-1-tosylpyrrolidin-3-ol (**16**).* Reaction of (*E*)-2-(4-([1,1′-biphenyl]-4-yl)but-3-en-1-yl)-4-methylbenzenesulfonamide (40 mg, 0.11 mmol) and malonoyl peroxide **1** (20 mg, 0.16 mmol) in HFIP (0.2 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (1.0 mL, 1:1) gave the crude alcohol (1:9 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **16** (30 mg, 0.08 mmol, 72%) as a white solid: mp 190−192 °C (decomp); IR (ATR)/cm^{-1} 3450, 3010, 2947, 2920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 2H), 7.50−7.47 (m, 4H), 7.45−7.40 (m, 4H), 7.29−7.23 (m, 3H), 4.70 (bs, 1H), 4.22 (bs, 1H), 3.77−3.73 (m, 1H), 3.55 (dt, J = 16.8, 8.5 Hz, 1H), 2.43 (s, 3H), 2.11−2.05 (m, 1H), 1.79−1.75 (m, 1H), 1.50 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 140.9, 140.7, 139.0, 134.7, 129.7, 128.9, 127.9, 127.5, 127.3, 126.8, 79.1, 71.8, 46.9, 31.6, 21.7 (missing 1 carbon); LRMS (ES + APCI) m/z 394.0 [M + H]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{24}NO_3S$ 394.1477, found 394.1472.

*(±)-2-(4-Chlorophenyl)-1-tosylpyrrolidin-3-ol (**17**).* Reaction of (*E*)-*N*-(4-(4-chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and malonoyl peroxide **1** (57 mg, 0.45 mmol) in HFIP (0.6 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (2.6 mL, 1:1) gave the crude alcohol (1:9 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **17** (69 mg, 0.20 mmol, 67%) as a white solid: mp 169−171 °C; IR (ATR)/cm^{-1} 3558, 3499, 2937, 2889; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 7.7 Hz, 2H), 7.31−7.26 (m, 6H), 4.60 (bs, 1H), 4.11 (bs, 1H), 3.72−3.69 (m, 1H), 3.52−3.47 (m, 1H), 2.42 (s, 3H), 2.02−1.95 (m, 1H), 1.75−1.72 (m, 1H), 1.58 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 138.6, 134.4, 129.8, 128.8, 128.9, 127.9, 127.7, 78.9, 71.4, 46.9, 31.5, 21.7; LRMS (ES + APCI) m/z 351.9 [M]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{19}{}^{35}ClNO_3S$ 352.0774, found 352.0772.

*(±)-2-(3-Chlorophenyl)-1-tosylpyrrolidin-3-ol (**18**).* Reaction of (*E*)-*N*-(4-(3-chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (60 mg, 0.18 mmol) and malonoyl peroxide **1** (34 mg, 0.27 mmol) in HFIP (0.4 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (0.4 mL, 1:1) gave the crude alcohol (1:6 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **18** (33 mg, 0.09 mmol, 52%) as a white solid: mp 96−98 °C; IR (ATR)/cm^{-1} 3489, 3062, 2952, 2922, 2954; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.27 (s, 1H), 7.25−7.21 (m, 3H), 4.63 (bs, 1H), 4.12 (bs, 1H), 3.70 (td, J = 9.3, 2.3 Hz, 1H), 3.52 (td, J = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H), 2.06−1.96 (m, 1H), 1.77−1.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 142.2, 134.6, 134.5, 130.0, 129.9, 129.8, 127.8, 126.5, 124.6, 78.9, 71.4, 46.9, 31.6, 21.7; LRMS (ES + APCI) m/z 351.9 [M]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{19}{}^{35}ClNO_3S$ 352.0774, found 352.0770.

*(±)-2-(4-(1,3-Dioxalan-2-yl)phenyl)-1-tosylpyrrolidin-3-ol (**19**).* Reaction of (*E*)-*N*-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (200 mg, 0.54 mmol) and malonoyl peroxide **1** (103 mg, 0.80 mmol) in HFIP (1.1 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (5.3 mL, 1:1) gave the crude alcohol (1:9 *cis*/*trans*). Purification by silica gel flash column chromatography (hexane/EtOAc 1:1) gave title compound **19** (115 mg, 0.30 mmol, 55%) as a white solid: mp 146−148 °C; IR (ATR)/cm^{-1} 3517, 3054, 2922, 2887, 2852, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.79 (s, 1H), 4.66 (bs, 1H), 4.13−4.07 (m, 3H), 4.05−4.00 (m, 2H), 3.71−3.66 (m, 1H), 3.51 (dt, J = 9.9, 6.9 Hz, 1H), 2.41 (s, 3H), 2.01−1.92 (m, 1H), 1.73−1.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 141.1, 137.4, 134.7, 129.7, 127.9, 126.8, 126.4, 103.6, 78.9, 71.8, 65.4, 46.9, 31.4, 21.7; LRMS (ES + APCI) m/z 390.0 [M + H]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{24}NO_5S$ 390.1375, found 390.1370.

*(±)-1-Tosyl-2-(4-(trifluoromethyl)phenyl)pyrrolidine-3-ol (**20**).* Reaction of (*E*)-4-methyl-*N*-(4-(4-trifluoromethyl)phenyl)but-3-en-1-yl)-benzenesulfonamide (50 mg, 0.1 mmol) and malonoyl peroxide **1** (35

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mg, 0.3 mmol) in HFIP (0.6 mL) according to General Procedure 3, warming up to 50 °C, followed by hydrolysis in 1 M NaOH/THF (2.6 mL, 1:1) gave the crude alcohol. Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) gave title compound **20** (10 mg, 0.03 mmol, 19%) as a white solid: mp 119−120 °C; IR (ATR)/cm^{-1} 3541, 2996, 2888; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.69 (bs, 1H), 4.15 (bs, 1H), 3.74−3.70 (m, 1H), 3.55−3.50 (m, 1H), 2.42 (s, 3H), 2.01−1.95 (m, 1H), 1.78−1.74 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 144.0, 134.3, 130.0 (J_{C-F} = 13.8 Hz), 129.8, 127.9, 126.8, 125.7 (J_{C-F} = 3.6 Hz), 124.2 (J_{C-F} = 272.0 Hz), 78.9, 71.5, 47.0, 31.6, 21.7; LRMS (ES + APCI) m/z 386.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{19}F_3NO_3S$ 386.1038, found 386.1030.

*(±)-2,2-Diphenyl-1-tosylpyrrolidin-3-ol (**21**).* Reaction of *N*-(4,4-diphenylbut-3-en-1-yl)-4-methylbenzenesulfonamide (80 mg, 0.21 mmol) and malonoyl peroxide **1** (41 mg, 0.32 mmol) in HFIP (0.4 mL) according to General Procedure 3 followed by hydrolysis in 1 M NaOH/THF (2.1 mL, 1:1) gave the crude alcohol. Purification by silica gel flash column chromatography (hexane/EtOAc 6:4) gave title compound **21** (68 mg, 0.17 mmol, 82%) as a white solid: mp 153−154 °C; IR (ATR)/cm^{-1} 3502, 3054, 2980, 2954; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.43−7.34 (m, 3H), 7.30−7.25 (m, 3H), 7.20−7.17 (m, 2H), 6.96 (d, J = 8.1 Hz, 2H), 6.86−6.83 (m, 2H), 4.79 (dd, J = 7.9, 6.0 Hz, 1H), 4.04 (ddd, J = 9.4, 8.4, 3.9 Hz, 1H), 3.62 (ddd, J = 9.4, 8.4, 7.2 Hz, 1H), 2.33 (s, 3H), 2.17−2.10 (m, 1H), 1.77−1.67 (m, 1H), 1.43 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 139.0, 138.5, 138.2, 130.8, 130.0, 128.9, 127.93, 127.89, 127.7, 126.6, 79.2, 77.1, 46.4, 30.6, 21.5 (1 carbon missing); LRMS (ES + APCI) m/z 394.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO_3S$ 394.1477, found 394.1471.

*(±)-2-Phenyl-1-tosylpyrrolidin-3-ol (**22**).* Malonoyl peroxide **1** (45 mg, 0.35 mmol) was added to a solution of (*Z*)-4-methyl-*N*-(4-(*p*-tolyl)but-3-en-1-yl)benzenesulfonamide[21] (70 mg, 0.23 mmol) in HFIP (0.5 mL), and the mixture was stirred at rt for 5 h. The solvent was removed by rotary evaporation, and the resulting residue was directly treated with 1 M NaOH/THF (2 mL (1:1)). The solution was stirred at 60 °C for 18 h and allowed to cool to rt, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the crude pyrrolidine product (4:1 *cis*/*trans*). Purification by silica gel flash column chromatography (EtOAc/hexane 4:6) gave title compound **22** (37 mg, 0.11 mmol, 50%), as a white solid: mp 114−116 °C; IR (ATR)/cm^{-1} 3452, 2974, 2872, 1325, 1156; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.64 (m, 2H), 7.39−7.28 (m, 7H), 4.74 (d, J = 5.6 Hz, 1H), 4.25−4.15 (m, 1H), 3.80−3.70 (m, 1H), 3.64 (ddd, J = 10.7, 7.7, 4.9 Hz, 1H), 2.43 (s, 3H), 1.89 (ddt, J = 16.3, 6.5, 4.9 Hz, 1H), 1.80−1.69 (m, 1H), 1.09 (d, J = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 136.5, 135.0, 129.8, 128.8, 128.7, 128.3, 127.9, 127.7, 126.3, 73.7, 67.7, 47.2, 32.5, 21.7; LRMS (ES + APCI) m/z 318.0 $[M + H]^+$.

2-(3-Bromo-4,4-diphenylbut-3-en-1-yl)isoindoline-1,3-dione. Bromine (0.3 mL, 5.7 mmol) was added dropwise to a solution of 2-(4,4-diphenylbut-3-en-1-yl)isoindoline-1,3-dione (1.0 g, 2.8 mmol) in 1,2-DCE (5 mL) at room temperature. The resulting solution was stirred for 15 h before the solvent was removed under reduced pressure. The residue was dissolved with a solution of KOH (0.6 g, 11.3 mmol) in MeOH (10 mL) and stirred for 30 min. The solids were then separated by filtration, and the filtrate was concentrated under reduced pressure affording the title compound (1.2 g, 2.7 mmol, 98%) as a cream solid that was used without further purification: mp 192−193 °C; IR (ATR)/cm^{-1} 2942, 1699, 1123, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88−7.81 (m, 2H), 7.78−7.71 (m, 2H), 7.38−7.24 (m, 5H), 7.23−7.17 (m, 1H), 7.16−7.09 (m, 2H), 7.01−6.95 (m, 2H), 4.02 (t, J = 6.3 Hz, 2H), 3.08 (t, J = 6.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 144.4, 142.9, 139.8, 133.9, 132.3, 129.0, 128.5, 128.6, 128.1, 127.4, 127.4, 123.3, 122.9, 37.7, 37.0; LCMS (ES + APCI) m/z 331.9, 434.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{19}{}^{79}BrNO_2$ 432.0599, found 432.0589.

2-(3-(Diphenylmethylene)pent-4-en-1-yl)isoindoline-1,3-dione. To a solution of 2-(3-bromo-4,4-diphenylbut-3-en-1-yl)isoindoline-1,3-dione (1.0 g, 2.3 mmol) in degassed EtOH (10 mL) were added potassium vinyltrifluoroborate (0.4 g, 2.8 mmol) and $Pd(dppf)Cl_2$ (0.2 g, 0.2 mmol) under a N_2 atmosphere. The resulting mixture was stirred at rt before the addition of Et_3N (0.8 mL, 5.6 mmol). The mixture was then heated to 120 °C, and stirring was continued for 48 h. The reaction was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (20 mL), dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (petroleum ether (40−60 °C)/EtOAc 9:1) afforded the title compound (350 mg, 0.9 mmol, 40% (80% pure)) as a cream solid: mp 135−137 °C; IR (ATR)/cm^{-1} 3024, 1696, 1399, 1104, 988; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.37−7.14 (m, 8H), 7.09 (dd, J = 6.5, 3.1 Hz, 2H), 6.58 (dd, J = 17.5, 11.0 Hz, 1H), 5.61 (d, J = 17.5 Hz, 1H), 5.19 (d, J = 11.0 Hz, 1H), 3.89 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 144.4, 142.2, 141.9, 136.0, 133.7, 132.3, 130.2, 129.1, 128.9, 128.5, 128.2, 127.9, 126.9, 123.1, 114.5, 37.5, 28.1; LCMS (ES + APCI) m/z = 380.5 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{22}NO_2$ 380.1651, found 380.1638.

2-(3-(Diphenylmethylene)-5-hydroxypentyl)isoindoline-1,3-dione. To a solution of 2-(3-(diphenylmethylene)pent-4-en-1-yl)-isoindoline-1,3-dione (220 mg, 0.6 mmol) in anhydrous THF (2 mL) was added BH_3 (1.0 M in THF, 0.9 mL, 0.9 mmol) under a N_2 atmosphere. The resulting solution was stirred at rt for 4 h. After this time, a 2 M solution of NaOH (2 mL) was added followed by H_2O_2 (28% w/w, 2 mL), and the mixture was further stirred for 2 h. Upon completion, the reaction was quenched by the addition of a 2 M solution of HCl (10 mL), and the organic layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were washed with a saturated solution of $Na_2S_2O_5$ (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (petroleum ether (40−60 °C)/EtOAc 1:1) afforded the title compound (80 mg, 0.2 mmol, 33%) as a cream solid: mp 137−139 °C; IR (ATR)/cm^{-1} 3434, 2964, 1685, 1399, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 5.4, 3.2 Hz, 2H), 7.70 (dd, J = 5.4, 3.2 Hz, 2H), 7.31−7.24 (m, 2H), 7.21−7.07 (m, 4H), 7.06−7.00 (m, 2H), 6.87−6.83 (m, 2H), 3.81 (t, J = 6.5 Hz, 2H), 3.75 (t, J = 6.7 Hz, 2H), 2.68 (t, J = 6.5 Hz, 2H), 2.62 (t, J = 6.7 Hz, 2H), 1.77 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 143.7, 142.6, 142.1, 133.8, 132.4, 131.5, 129.0, 128.9, 128.2, 128.1, 126.5, 126.4, 123.1, 61.3, 36.4, 35.7, 30.6; LCMS (ES + APCI) m/z = 398.3 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{24}NO_3$ 398.1756, found 398.1755.

*N-(3-(Diphenylmethylene)-5-hydroxypentyl)-4-methylbenzenesulfonamide (**28**).* To a solution of 2-(3-(diphenylmethylene)-5-hydroxypentyl)isoindoline-1,3-dione (120 mg, 0.3 mmol) in EtOH (2 mL) was added hydrazine monohydrate (30 μL, 0.6 mmol) according to General Procedure 2 to give 5-amino-3-(diphenylmethylene)-pentan-1-ol.

To a solution of 5-amino-3-(diphenylmethylene)pentan-1-ol in CH_2Cl_2 (2.0 mL) was added Et_3N (60 μL, 0.3 mmol) followed by *p*-TsCl (58 mg, 0.3 mmol) and DMAP (11 mg, 0.09 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (cyclohexane/EtOAc 7:3) afforded the title compound **28** (67 mg, 0.2 mmol, 53%) as a colorless gum: IR (ATR)/cm^{-1} 2878, 1322, 1153, 700; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J = 8.1 Hz, 2H), 7.29−7.23 (m, 6H), 7.21−7.17 (m, 2H), 7.16−7.12 (m, 2H), 7.10−7.06 (m, 2H), 4.96 (t, J = 5.9 Hz, 1H), 3.64 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H), 2.43 (s, 3H), 2.42−2.38 (m, 4H), 1.75 (bs, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.6, 143.2, 142.4, 137.0, 131.4, 129.6, 129.5, 128.9, 128.8, 128.4, 128.2, 127.0, 126.6, 126.6, 61.0, 41.7, 35.2, 32.0, 21.6; LCMS (ES + APCI) m/z = 422.3 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{28}NO_3S$ 422.1790, found 422.1786.

*Oxidative Heterocyclization with a Probe Compound (**28**).* Reaction of *N*-(3-(diphenylmethylene)-5-hydroxypentyl)-4-methyl-

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benzenesulfonamide **28** (170 mg, 0.4 mmol) and malonoyl peroxide **1** (77 mg, 0.8 mmol) in HFIP (1.0 mL) according to General Procedure 5 to give a crude material. The crude was dissolved in PhMe (1.0 mL) and MeOH (0.5 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 1.0 mL, 2.02 mmol) according to General Procedure 5. Purification by silica gel flash column chromatography (cyclohexane/EtOAc 3:1) afforded the cyclized furan compound **29** (104 mg, 0.2 mmol, 46% over 2 steps) as a colorless gum and bicycle product (16 mg, 0.03 mmol, 7%) as a colorless gum.

*1-Methyl 1-(3-(2-((4-Methylphenyl)sulfonamido)ethyl)-2,2-diphenyltetrahydrofuran-3-yl)cyclopropane-1,1-dicarboxylate (**29**):* IR (ATR)/cm^{-1} 2954, 1722, 1438, 1323; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (t, J = 7.5 Hz, 4H), 7.54 (d, J = 7.5 Hz, 2H), 7.31−7.16 (m, 8H), 4.69 (bs, 1H), 4.12−4.02 (m, 2H), 3.76 (s, 3H), 2.86−2.76 (m, 1H), 2.77−2.64 (m, 2H), 2.45 (s, 3H), 2.36−2.29 (m, 1H), 2.20 (ddd, J = 15.0, 8.0, 6.5 Hz, 1H), 2.06 (dt, J = 15.0, 7.5 Hz, 1H), 1.61−1.55 (m, 1H), 1.49−1.45 (m, 1H), 1.41−1.35 (m, 1H), 1.20−1.14 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 170.0, 168.6, 143.1, 142.6, 142.0, 137.0, 129.5, 127.9, 127.8, 127.2, 127.2, 127.0, 126.9, 126.1, 90.3, 88.7, 64.0, 52.6, 39.1, 35.9, 34.4, 28.8, 21.5, 16.7, 16.5; LCMS (ES + APCI) m/z = 586.3 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{31}H_{33}NNaO_7S$ 586.1875, found 586.1873.

*Methyl 1-(5-(2-((4-Methylphenyl)sulphonamide)ethyl)-6,6-diphenyl-2,7,8-trioxabicyclo[3.2.1]octan-1-yl)cyclopropane-1-carboxylate (**31**):* IR (ATR)/cm^{-1} 2954, 1723, 1328, 1161, 1040; ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 2H), 7.41−7.37 (m, 2H), 7.32−7.21 (m, 8H), 5.14 (dd, J = 7.3, 3.2 Hz, 1H), 3.85 (s, 3H), 3.75−3.67 (m, 1H), 3.58 (dd, J = 11.3, 6.8 Hz, 1H), 3.14−3.07 (m, 1H), 2.99 (dt, J = 8.6, 4.2 Hz, 1H), 2.45 (s, 3H), 2.00 (td, J = 12.9, 7.0 Hz, 1H), 1.92−1.87 (m, 1H), 1.82−1.74 (m, 1H), 1.54 (dd, J = 13.6, 3.8 Hz, 1H), 1.50−1.45 (m, 1H), 1.41−1.32 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 143.3, 141.1, 139.8, 136.8, 129.7, 128.5, 127.8, 127.7, 127.7, 127.1, 118.1, 90.7, 86.1, 59.2, 52.5, 39.3, 35.1, 29.3, 29.1, 21.5, 14.6, 13.4; LCMS (ES + APCI) m/z = 586.3 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{31}H_{33}NNaO_7S$ 586.1875, found 586.1872.

General Procedure 4 (Mitsunobu Reaction). A dry three-neck flask was charged with cinnamyl alcohol (1.0 equiv), PPh_3 (1.1 equiv), and *N*-hydroxyphthalimide (1.1 equiv) in anhydrous THF (0.25 M). The solution was cooled to 0 °C, and diethyl azodicarboxylate (2.2 M in PhMe, 1.1 equiv) was added dropwise. The mixture was warmed to rt and stirred for 2.5 h. The solvent was removed by rotary evaporation before purification by silica gel flash column chromatography with hexane/EtOAc mixtures to afford the target compound.

2-(Cinnamyloxy)isoindoline-1,3-dione.[35] Cinnamyl alcohol (2.2 g, 16.0 mmol), PPh_3 (4.6 g, 17.6 mmol), and *N*-hydroxyphthalimide (2.9 g, 17.6 mmol) were dissolved in anhydrous THF (64 mL) before the dropwise addition of diethyl azodicarboxylate (2.2 M in PhMe, 8.0 mL, 17.6 mmol) according to the General Procedure 4. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (4.3 g, 15.4 mmol, 96%) as a white solid: mp 148−150 °C (lit.[36] 116−118 °C); IR (ATR)/cm^{-1} 3058, 3028, 2948, 1790; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82−7.80 (m, 2H), 7.74−7.71 (m, 2H), 7.39−7.37 (m, 2H), 7.32−7.29 (m, 2H), 7.27−7.24 (m, 1H), 6.67 (d, J = 15.9 Hz, 1H), 6.47 (dt, J = 15.9, 7.1 Hz, 1H), 4.87 (d, J = 7.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 137.7, 136.0, 134.6, 129.0, 128.8, 128.6, 127.1, 123.7, 122.2, 78.8; LRMS (ES + APCI) m/z 297.0 $[M + NH_4]^+$.

(E)-2-((3-(4-Chlorophenyl)allyl)oxy)isoindoline-1,3-dione. (*E*)-3-(4-Chlorophenyl)prop-2-en-1-ol (300 mg, 1.8 mmol), PPh_3 (513 mg, 2.0 mmol), and *N*-hydroxyphthalimide (320 mg, 2.0 mmol) were dissolved in anhydrous THF (7.0 mL) before the dropwise addition of diethyl azodicarboxylate (2.2 M in PhMe, 0.9 mL, 1.96 mmol) according to General Procedure 4. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded the title compound (200 mg, 0.6 mmol, 35%) as a white solid: mp 138−140 °C; IR (ATR)/cm^{-1} 3050, 2948, 1788, 1742; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.74−7.72 (m, 2H), 7.32−7.27 (m, 4H), 6.63 (d, J = 15.9 Hz, 1H), 6.44 (dt, J = 15.9, 7.0 Hz, 1H), 4.85 (d, J = 7.0, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 136.0, 134.5, 134.3, 134.2, 128.9, 128.8, 128.1, 123.5, 122.8, 78.4; LRMS (ES + APCI) m/z 314.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}{}^{35}ClNO_3$ 314.0584, found 314.0583.

*N-(Cinnamyloxy)-4-methylbenzenesulfonamide (**33**).*[37] To a solution of 2-(cinnamyloxy)isoindoline-1,3-dione (4.5 g, 16.1 mmol) in EtOH (62 mL) was added hydrazine monohydrate (1.6 mL, 33.8 mmol) according to General Procedure 2 to give *O*-cinnamylhydroxylamine.

To a solution of crude *O*-cinnamylhydroxylamine (16.1 mmol) in CH_2Cl_2 (65 mL) was added Et_3N (27 mL, 19.3 mmol) followed by *p*-TsCl (3.4 g, 17.7 mmol) and DMAP (0.6 g, 4.8 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded title compound **33** (2.9 g, 9.6 mmol, 60%) as a white solid: mp 109−110 °C (lit.[37] 103 °C); IR (ATR)/cm^{-1} 3220, 3058, 3026, 2924, 2870; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.38−7.25 (m, 7H), 6.91 (bs, 1H), 6.63 (d, J = 15.9 Hz, 1H), 6.22 (dt, J = 15.9, 6.8 Hz, 1H), 4.61 (d, J = 6.8, 2H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 136.3, 136.0, 133.8, 129.9, 128.77, 128.75, 128.4, 126.9, 122.9, 78.1, 21.8; LRMS (ES + APCI) m/z 321.0 $[M + NH_4]^+$.

*(E)-N-((3-(4-Chlorophenyl)allyl)oxy)-4-methylbenzenesulfonamide (**35**).* To a solution of (*E*)-2-((3-(4-chlorophenyl)allyl)oxy)-isoindoline-1,3-dione (202 mg, 0.6 mmol) in EtOH (2.3 mL) was added hydrazine monohydrate (61 μL, 1.3 mmol) according to General Procedure 2 to give (*E*)-*O*-(3-(4-chlorophenyl)allyl)-hydroxylamine.

To a solution of crude (*E*)-*O*-(3-(4-chlorophenyl)allyl)-hydroxylamine(0.6 mmol) in CH_2Cl_2 (2.2 mL) was added Et_3N (120 μL, 0.8 mmol) followed by *p*-TsCl (107 mg, 0.6 mmol) and DMAP (22 mg, 0.2 mmol) according to General Procedure 2. Purification by silica gel flash column chromatography (hexane/EtOAc 8:2) afforded title compound **35** (102 mg, 0.3 mmol, 54%) as a white solid: mp 116−118 °C; IR (ATR)/cm^{-1} 3216, 3064, 2922, 2852; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.27−7.25 (s, 4H), 7.04 (bs, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.17 (dt, J = 15.9, 6.7 Hz, 1H), 4.57 (bd, J = 6.7 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 134.7, 134.4, 133.9, 133.7, 129.8, 128.8, 128.6, 127.9, 123.6, 77.6, 21.7; LRMS (ES + APCI) m/z 355.0 $[M + NH_4]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{17}{}^{35}ClNO_3S$ 338.0618, found 338.0616.

General Procedure 5. Oxidative cyclization for the synthesis of isoxazolidines. Malonoyl peroxide 1 (1.5 equiv) was added to a solution of alkene **33** or **34** (1.0 equiv) in HFIP (0.5 M). The mixture was stirred at 40 °C for 18 h before removal of the solvent by rotary evaporation. The residue was dissolved in PhMe (0.2 M) and MeOH (0.5 M) and a solution of TMS-CHN_2 in Et_2O (2.0 equiv) was added dropwise. The resulting mixture was stirred at rt for 2 h before the solvents were evaporated under reduced pressure. Purification of the crude material by silica gel flash column chromatography with petroleum ether (40−60 °C):Et_2O mixtures afforded the target compounds.

*(±)-1-(((3-Phenyl-2-tosylisoxazolidin-4-yl)oxy)carbonyl)-cyclopropane-1-carboxylic Acid (**37**).* To a solution of *N*-(cinnamyloxy)-4-methylbenzenesulfonamide **33** (151 mg, 0.50 mmol) in HFIP (1.0 mL) was added malonoyl peroxide **1** (96 mg, 0.75 mmol) according to General Procedure 5 (without the TMS-CHN_2 methyl ester formation) to give crude isoxazolidine (1:10 *cis*/*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc/AcOH 0.5%) afforded title compound **37** (178 mg, 0.41 mmol, 83%) as a white solid for characterization and X-ray analysis purposes: mp 137−139 °C; IR (ATR)/cm^{-1} 3550, 2930, 2852,1716, 1660; ^1H NMR (500 MHz, $CDCl_3$) δ 12.19 (bs, 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.44−7.34 (m, 7H), 5.61 (ddd, J = 6.0, 3.1, 0.7 Hz, 1H), 5.54 (bs, 1H), 4.44 (dd, J = 9.6, 3.1 Hz, 1H), 4.39 (dd, J = 9.6, 6.0 Hz, 1H), 2.47 (s, 3H), 2.18−2.14 (m, 1H), 2.06−2.03 (m, 1H), 1.99−1.93 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 170.0, 145.5, 136.3, 133.7, 129.9, 129.2, 129.1, 128.7, 126.5, 84.9, 74.6, 66.9, 25.6, 23.5, 23.2, 21.9; LRMS (ES + APCI) m/z 432.0 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{21}H_{20}NO_7S$ 430.0960, found 430.0954.

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*(±)-1-Methyl 1-((3R,4S)-3-Phenyl-2-tosylisoxazolidin-4-yl)-cyclopropane-1,1-dicarboxylate (**34**).* To a solution of *N*-(cinnamyloxy)-4-methylbenzenesulfonamide **33** (185 mg, 0.43 mmol) in HFIP (0.9 mL) was added malonoyl peroxide **1** (82 mg, 0.65 mmol) according to General Procedure 5 to give crude isoxazolidine (1:10 *cis*/*trans*), which was dissolved in PhMe (2.2 mL) and MeOH (0.9 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 0.43 mL, 0.86 mmol) according to General Procedure 5. Purification by silica gel flash column chromatography (petroleum ether (40−60 °C)/EtOAc 6:4) afforded title compound **34** (154 mg, 0.35 mmol, 80% over two steps) as a colorless oil: IR (ATR)/cm^{-1} 3028, 3062, 2954, 1727; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 7.3 Hz, 2H), 7.38−7.35 (m, 4H), 7.31 (t, J = 7.3 Hz, 1H), 5.52 (ddd, J = 6.1, 4.1, 1.7 Hz, 1H), 5.56 (bs, 1H), 4.38 (dd, J = 9.3, 6.1 Hz, 1H), 4.34 (dd, J = 9.3, 4.1 Hz, 1H), 3.80 (s, 3H), 2.46 (s, 3H), 1.67−1.51 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.4, 145.2, 137.3, 133.9, 129.8, 129.2, 129.0, 128.3, 126.6, 83.8, 74.4, 67.0, 53.0, 27.9, 21.9, 17.6, 17.5; LRMS (ES + APCI) m/z 463.0 $[M + NH_4]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{24}NO_7S$ 446.1273, found 446.1266.

*(±)-1-((3R,4S)-3-(4-Chlorophenyl)-2-tosylisoxazolidin-4-yl) 1-Methylcyclopropane-1,1-dicarboxylate (**36**).* To a solution of (*E*)-*N*-((3-(4-chlorophenyl)allyl)oxy)-4-methylbenzenesulfonamide **35** (66 mg, 0.20 mmol) in HFIP (0.4 mL) was added malonoyl peroxide **1** (38 mg, 0.29 mmol) according to General Procedure 5 to give crude isoxazolidine (1:7 *cis*/*trans*), which was dissolved in PhMe (1.0 mL) and MeOH (0.4 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 0.2 mL, 0.40 mmol) according to General Procedure 5. Purification by silica gel flash column chromatography (petroleum ether (40−60 °C)/EtOAc 6:4) afforded title compound **36** (80 mg, 0.17 mmol, 85% over 2 steps) as a white solid: mp 110−112 °C; IR (ATR)/cm^{-1} 3040, 2930, 2904, 1719, 1697; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 5.47−5.45 (m, 1H), 5.41 (bs, 1H), 4.35−4.34 (m, 2H), 3.79 (s, 3H), 2.46 (s, 3H), 1.66−1.52 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 169.5, 145.3, 135.8, 134.3, 133.6, 129.9, 129.2, 129.1, 128.0, 83.7, 74.2, 66.5, 53.0, 27.9, 21.9, 17.6, 17.5; LRMS (ES + APCI) m/z 497.0 $[M + NH_4]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{23}{}^{35}ClNO_7S$ 480.0889, found 480.0879.

*(±)-2-Phenyl-1-tosylpyrrolidin-3-one (**38**).*[38] (2*R*,3*S*)-2-Phenyl-1-tosylpyrrolidin-3-ol **9a** (100 mg, 0.32 mmol) was dissolved in degassed MeCN (1.6 mL). IBX (265 mg, 0.95 mmol) was added, and the mixture was stirred at 80 °C for 18 h. The mixture was filtered through Celite, and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (hexane/EtOAc 4:6) afforded title compound **38** (84 mg, 0.27 mmol, 85%) as a colorless oil: mp 124−126 °C (lit.[39] 140−141 °C); IR (ATR)/cm^{-1} 2950, 2924, 2855, 1753; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.2 Hz, 2H), 7.32−7.27 (m, 7H), 4.59 (s, 1H), 3.94 (ddd, J = 10.6, 9.0, 5.6 Hz, 1H), 3.72 (dt, J = 10.7, 8.1 Hz, 1H), 2.63−2.55 (m, 1H), 2.49−2.42 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 144.4, 135.6, 133.9, 130.0, 128.8, 128.4, 127.8, 127.0, 67.3, 44.2, 35.9, 21.7; LRMS (ES + APCI) m/z 316.1 $[M + H]^+$.

*(±)-2-Phenyl-1-tosylpyrrolidin-3-ol (**22**).*[38] To a cooled (0 °C) solution of (±)-2-phenyl-1-tosylpyrrolidin-3-one **38** (64 mg, 0.20 mmol) in THF (1 mL) was added a solution of DIBAL-H (1 M in THF, 0.3 mL, 0.30 mmol). The mixture was allowed to warm to room temperature and was stirred for 3 h, before quenching with a 2 M solution of HCl (5 mL) and diluted with EtOAc (5 mL). The organic layer was separated and further extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure affording the title compound **22** (50 mg, 0.16 mmol, 78%) as a colorless oil as a diastereomeric mixture (6:1 *cis*/*trans*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.64 (m, 2H), 7.39−7.28 (m, 7H), 4.74 (d, J = 5.6 Hz, 1H), 4.25−4.15 (m, 1H), 3.80−3.70 (m, 1H), 3.64 (ddd, J = 10.7, 7.7, 4.9 Hz, 1H), 2.43 (s, 3H), 1.89 (ddt, J = 16.3, 6.5, 4.9 Hz, 1H), 1.80−1.69 (m, 1H), 1.09 (d, J = 4.9 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00392.

NMR spectra for all compounds reported, X-ray data for **10** and **36** and DSC data for **1** (PDF)

Crystal data for **10** and **36** (CIF)

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Notes

The authors declare no competing financial interest.

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