JOC The Journal of Organic Chemistry

Article

(Trifluoromethyl) Vinyl Sulfide: a Building Block for the Synthesis of CF3S-Containing Isoxazolidines

Alejandra Riesco-Domínguez, Jeroen van de Wiel, Trevor A. Hamlin, Bas van Beek, Stephen D. Lindell, Daniel Blanco-Ania, F. Matthias Bickelhaupt, and Floris P.J.T. Rutjes

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02639 • Publication Date (Web): 10 Jan 2018

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

(Trifluoromethyl) Vinyl Sulfide: a Building Block for the Synthesis of CF_3S-Containing Isoxazolidines

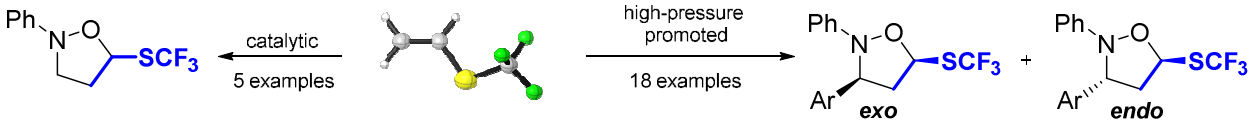
Alejandra Riesco-Domínguez,[†] Jeroen van de Wiel,[†] Trevor A. Hamlin,[§] Bas van Beek,[§] Stephen D. Lindell,[‡] Daniel Blanco-Ania,[†] F. Matthias Bickelhaupt,*[,†,§] Floris P. J. T. Rutjes*[,†]

[†]Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, 6525 AJ Nijmegen, the Netherlands

[§]Department of Theoretical Chemistry and Amsterdam Center for Multiscale Modeling (ACMM), Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, the Netherlands

[‡]Bayer CropScience AG, Industriepark Höchst, G836, 65926 Frankfurt am Main, Germany

Supporting Information Placeholder



ABSTRACT: (Trifluoromethyl) vinyl sulfide, a potential building block for pharmaceutically and agrochemically relevant products, is prepared and used for the first time in high-pressure-mediated 1,3-dipolar cycloaddition reactions with nitrones to synthesize (trifluoromethyl)sulfanyl isoxazolidines.

INTRODUCTION

The (trifluoromethyl)sulfanyl group (SCF_3) represents a privileged substituent in agrochemicals and pharmaceuticals because of the strong electron withdrawing effect and the large Hansch lipophilicity parameter (π = 1.44).[1] Cefazaflur,[2] a first-generation cephalosporin antibiotic, toltrazuril,[3] an antiprotozoal agent, and a losartan analogue,[4] developed as potential hypotensive agent, are prominent examples of biologically active compounds bearing the SCF_3 group (Figure 1).

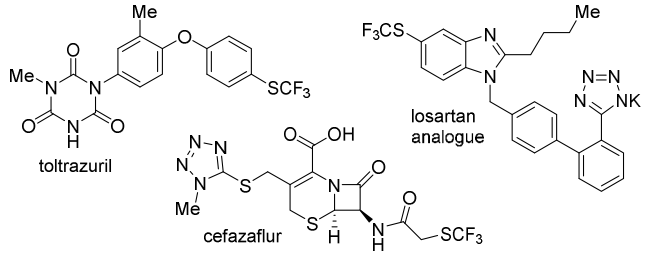


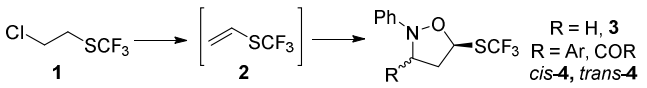
Figure 1. Bioactive heterocycles containing the SCF_3 group.

Hence, CF_3S-containing compounds are considered appealing targets in the agrochemical and pharmaceutical fields and, consequently, modern research has focused on efficient (trifluoromethyl)sulfanylation methods. The main strategies that have been developed to synthesize CF_3S-containing compounds have focused on direct C–S bond formation[5] and trifluoromethylation of sulfur-containing compounds.[6] However, incorporation via simple CF_3S-containing building blocks is still unprecedented so that the use of a CF_3S-containing reagent could be an alternative strategy to construct CF_3S-substituted heterocycles. More specifically, (trifluoromethyl) vinyl sulfide (**2**) could be an attractive building block to provide straightforward access to a wide variety of hetero- and carbocycles via cycloaddition reactions. Previously reported examples of cycloaddition reactions of alkene **2** are rather scarce: there is a single example of a Diels–Alder reaction with 2,3-dimethylbutadiene to yield the corresponding CF_3S-cyclohexene,[7] and two cyclopropanation examples with organomercury reagents to yield CF_3S-substituted cyclopropanes.[8]

The potential of this unexplored chemistry and the inherent biological attractiveness of these molecules motivated us to further study the reactivity of alkene **2** in cycloaddition reactions. Thus, we herewith present the study of the first 1,3-dipolar cycloaddition reactions of **2** with several nitrones[9] to synthesize a novel group of isoxazolidines (Scheme 1).

RESULTS AND DICSUSSION

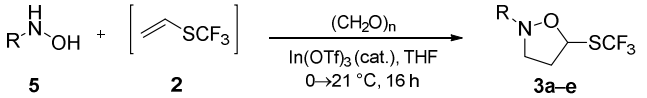
Scheme 1. Synthesis of CF_3S-containing isoxazolidines.



We commenced our investigations by forming alkene **2** in situ. Because of its high volatility,[7] we first performed the elimination reactions in deuterated solvents in order to instantly measure conversions from commercially available chloro alkane **1** into alkene **2**, with no need for further treatment or isolation of the alkene. We tested several bases (Et_3N, DBU, KO^{t}Bu, KOH and KOTMS) in the presence of various deuterated solvents (CD_2Cl_2, THF-d_8, CD_3OD and DMF-d_7; see Supporting Information [SI] for experimental details) to eventually choose a solution of KO^{t}Bu in THF-d_8 at 21 °C for 90 min as the final method for the in situ synthesis of alkene **2** with full conversion.

Initially, we focused on the synthesis of 2,5-disubstituted isoxazolidines **3** using *N*-substituted hydroxylamines **5** and paraformaldehyde as precursors for the in-situ synthesis of the dipoles (Table 1). The nitrone intermediates were used without isolation in a one-pot process with a preformed solution of alkene **2** (3 equiv) and $In(OTf)_3$ (0.06 equiv). In this manner, we obtained isoxazolidine **3a** in 22% yield after column chromatography. Increasing the concentration of **2** (6 equiv) resulted in a yield of 38% (entry 1). Isoxazolidines **3b–e** were synthesized in yields between 20–30% applying the same reaction conditions with different substrates (entries 2–5). However, yields were rather low after column chromatography in all cases (see SI for experimental details).

Table 1. Synthesis of isoxazolidines 3a–e.



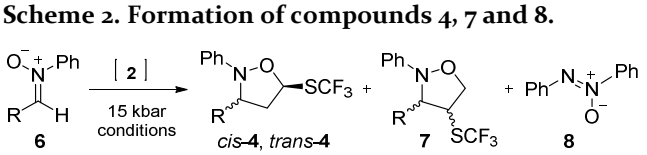
5 2 3a–e

Entry	Compound	R	Yield (%)
1	**3a**	C_6H_5	38
2	**3b**	3-$CF_3C_6H_4$	20
3	**3c**	3,5-$Cl_2C_6H_3$	22
4[a]	**3d**	$C_6H_5CH_2$	30
5[a]	**3e**	Cy	23

[a] Et_3N (1.0 equiv) was used.

With these results in hand and because of the low yields in the synthesis of **3a–e**, we changed our strategy to the synthesis of 2,3,5-trisubstituted isoxazolidines **4**, exhibiting a second (hetero)aromatic group on the 3-position and introducing consequently a second chiral center in the molecule (Scheme 2, Table 2).

Scheme 2. Formation of compounds 4, 7 and 8.



We first performed the reaction with nitrone **6a** (R = H), a catalytic amount of $In(OTf)_3$ and alkene **2** at 21 °C in THF, but no conversion into the product was observed. When applying the same conditions at 80 °C with nitrone **6c** (R = Me), less than 7% conversion into the final product was observed by ^{1}H NMR, presumably because of the low reactivity of this alkene and perhaps due to its volatility. Therefore, we decided to perform these reactions under high-pressure conditions (Table 2), which is an established and powerful tool to increase the rate of cycloaddition reactions.[10] Thus, when using 1.3 equiv of **2** at 21 °C under a 15 kbar pressure (entry 1) we gratifyingly observed an 83% conversion into isoxazolidines **4c** and **7c** (regioisomeric ratio **4c**/**7c** 13:1, diastereomeric ratio [dr] *cis*-**4c**/*trans*-**4c** 7:2). Nitrone **6b** gave only 56% conversion under the same reaction conditions (entry 4), with similar regio- and diastereoisomeric ratios. When increasing the concentration of alkene **2**, 93 and 75% conversions into compounds **4c** and **4b** were obtained, respectively (entries 2 and 5). Finally, an increase of the temperature to 50 °C gave nearly full conversion into the desired *cis*- and *trans*-products **4c** and **4b** (entries 3 and 6).

Azoxybenzene[11] **8** was formed in all reactions as a side product (Scheme 2) and could not be separated in any case from *trans*-**4** by column chromatography. Thus, we used galvinoxyl to prevent the formation of compound **8**.[12] We were pleased to see that when using three equiv of alkene **2** at 50 °C, in the presence of 1–3 mol % of galvinoxyl as radical scavenger (entries 7 and 8), not only full conversion into the desired product **4b** was obtained, but also the formation of the azoxy compound **8** was fully suppressed.

Furthermore, our reactions gave the *exo*-products as the major diastereoisomers (the *cis*-isomers), showing a 3:1 diastereomeric ratio (entries 7 and 8). Having these results in hand, the scope of nitrones in this 1,3-dipolar cycloaddition was examined by employing the conditions shown in entry 7. We first synthesized a total of eighteen nitrones (**6a–r**) with phenyl (containing both electron-donating and electron-withdrawing groups in the 2-, 3- and 4- positions), heterocyclic and carbamoyl substituents in excellent yields (see SI). Then, we studied the scope of the 1,3-dipolar cycloaddition reactions between alkene **2** and nitrones **6a–r** (Table 3).

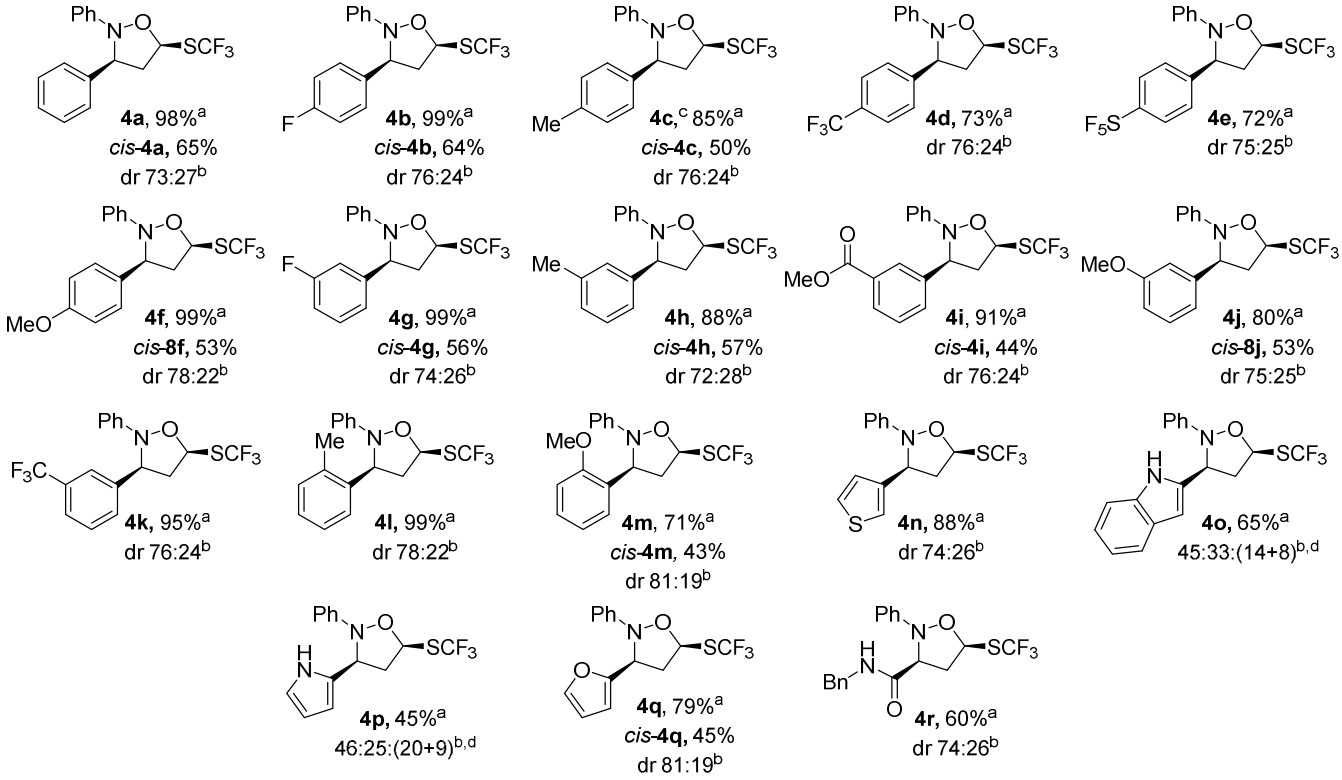
As shown in Table 3, high and excellent yields (total yields) were observed for compounds **4a–c**, **4f–i**, **4l** and **4n**. In addition, in most of the cases the major product (*cis*-**4**) was separated from the other isomers by column chromatography in good yields (*cis*-**4a–c**, *cis*-**4f–j**, *cis*-**4m** and *cis*-**4q**). Unfortunately, in a few cases the isomers **4** were obtained as a mixture that could not be separated (**4d**,**e**, **4k**,**l** and **4n**). For compounds **4o** and **4p**, the *trans*-**4** isomer and the corresponding regioisomers **7** were present as a mixture.[13] The assignment of the *cis*- and *trans*-isomers was performed by 2D NMR studies (NOESY).

Table 2. Optimization process for the 1,3-dipolar cycloaddition reaction of nitrones 6 with alkene 2.

Entry	Nitrone	R	**2** (equiv)	*t* (°C)	Scavenger	*cis*-**4**/*trans*-**4**	**8**[a]	Conversion[a] (yield)[b]
1	**6c**	4-MeC_6H_4	1.3	21	–	76:22	5%	83% (41%)[c]
2	**6c**	4-MeC_6H_4	3	21	–	79:21	22%	93% (–)
3	**6c**	4-MeC_6H_4	3	50	–	76:24	6%	96% (85%)[c]
4	**6b**	4-FC_6H_4	1.3	21	–	79:21	7%	56% (35%)[c]
5	**6b**	4-FC_6H_4	3	21	–	79:21	38%	75% (–)
6	**6b**	4-FC_6H_4	3	50	–	77:23	17%	91% (79%)[c]
7	**6b**	4-FC_6H_4	3	50	Galvinoxyl (3%)	76:24	0%	100% (78%)
8	**6b**	4-FC_6H_4	3	50	Galvinoxyl (1%)	76:24	1%	100% (–)

[a]Calculated by integration of the ^{1}H NMR signals of the crude mixtures. [b]Isolated after column chromatography. [c]*trans*-Isomer contaminated with **7**.

Table 3. Scope of the high-pressure-promoted 1,3-dipolar cycloaddition reaction.

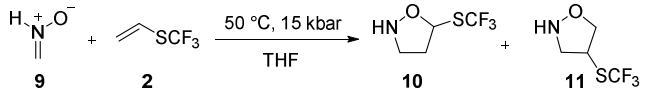


[a]Combined yield. [b]Calculated by ^{1}H NMR of the crude. [c]Galvinoxyl was not used in the reaction. [d]*cis*-**40,p**/*trans*-**40,p**/(mixture of isomers **7**).

The diastereoselectivity was lower for compounds **4o** and **4p**, which contained an indole and a pyrrole substituent, respectively. In these cases, a mixture of *cis*- and *trans*-diastereoisomers was obtained approximately in a 3:2 ratio. In addition, for compounds **4o** and **4p**, a 7:3 ratio of a mixture *cis*-**7** and *trans*-**7** from the regioisomer **7** was observed. For these two compounds (**4o** and **4p**), the total yields were significantly lower because of incomplete conversion into the products and purification problems. Finally, when using a non-aromatic nitrone, the final benzyl amide isoxazolidine **4r** was synthesized in 60% yield.

To evaluate the apparent regioselectivity of the cycloaddition, high-level DFT calculations were carried out at the BP86/TZ2P[14] level, using the ADF program.[15] Tetrahydrofuran was simulated using the COSMO solvation model.[16] Thermochemical corrections were computed using the temperature and pressure under which the experiments were performed (see SI for computational details).

Scheme 3. Formation of compounds 10 and 11.



We focused on understanding the regioselectivity of the cycloaddition between a simple model nitrone **9** with **2** (Scheme 3). This reaction proceeds in a concerted and asynchronous manner with a Gibbs free energy barrier of 21.3 and 24.0 kcal mol^{-1} for **10** and **11**, respectively (Table 4). The $\Delta\Delta G^{\ddagger}$ of 2.7 kcal mol^{-1} facilitates a high degree of regioselectivity, resulting in a calculated product ratio of 98:2 for **10**/**11**. Furthermore, the experimentally observed regioisomer **10** is more stable than **11** ($\Delta\Delta G_{rxn}$ = 3.9 kcal mol^{-1}). The calculated product ratio for the model nitrone cycloaddition is in line with experimentally observed regioselectivity of reactions involving the majority of the nitrones **6.**

Table 4. Computed activation barriers, reaction energies (kcal mol^{-1}), and product distribution computed at the COSMO(THF)-BP86/TZ2P level of theory.

Compound	$\Delta E^{\ddagger}$ ($\Delta G^{\ddagger}$)	ΔE_{rxn} (ΔG_{rxn})	Product ratio[a]
10	12.8 (21.3)	–17.6 (–6.1)	98
11	15.0 (24.0)	–14.3 (–2.2)	2

[a]Calculated at 50 °C and 15 kbar based on the $\Delta\Delta G^{\ddagger}$ between **10** and **11** (see SI for details).

Insight into why regioisomer **10** is favored over the other, **11**, is provided by the activation strain model (ASM)[17] (also known as the distortion-interaction model).[18] In this framework, the potential energy surface $\Delta E(\zeta)$ is decomposed along the reaction coordinate ζ into the strain $\Delta E_{strain}(\zeta)$ associated with deforming the individual reactants plus the actual interaction $\Delta E_{int}(\zeta)$ between the deformed reactants.

$$\Delta E^{\ddagger}(\zeta) = \Delta E_{strain}(\zeta) + \Delta E_{int}(\zeta) \quad (1)$$

The $\Delta E_{int}(\zeta)$ between the reactants is further analyzed by an energy decomposition analysis (EDA) in the conceptual framework provided by the Kohn–Sham molecular orbital (KS-MO) model[19] and is decomposed into three physically meaningful terms:

$$\Delta E_{int}(\zeta) = \Delta V_{elstat}(\zeta) + \Delta E_{Pauli}(\zeta) + \Delta E_{oi}(\zeta) \quad (2)$$

The $\Delta V_{elstat}(\zeta)$ term corresponds to the classical electrostatic interaction between unperturbed charge distributions, $\Delta E_{Pauli}(\zeta)$ is responsible for any steric repulsion, and the $\Delta E_{oi}(\zeta)$ accounts for charge transfer (HOMO–LUMO interactions) and polarization.

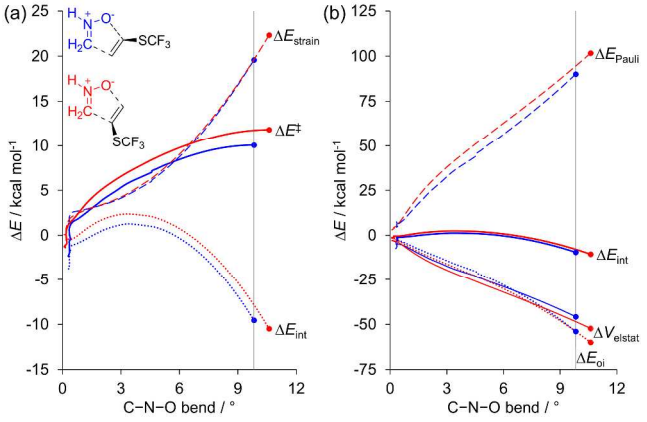


Figure 2. (a) Activation strain and (b) energy decomposition analyses of the cycloaddition reactions of nitrone **9** with dienophile **2** up to their respective TS (indicated by the dot) computed at the BP86/TZ2P level.

Applying the ASM along the reaction coordinate defined by the bending of the 1,3-dipole, it is revealed that reactivity differences in the reaction between **9** and **2** leading to **10** (blue curve) and **11** (red curve) are a result of ΔE_{int} (Figure 2a). ΔE_{strain} remains nearly constant for both reactions along the reaction coordinate. Next, the EDA terms were analyzed and the ΔE_{Pauli} dominates and is chiefly responsible for the difference in the interaction energies (Figure 2b). The more favorable ΔV_{elstat} and ΔE_{oi} curves associated with the reaction leading to **11** are unable to overcome for increased steric repulsion associated with this approach. These results highlight the fact that the reaction results from the least hindered approach, leaving the SCF_3 group far away from the CH_2 group. See SI for an ASA and EDA analysis on **6m** and **6p**.

In summary, we have developed the synthesis of a new class of 5-[(trifluoromethyl)sulfanyl]isoxazolidines. The reactions utilized for their synthesis were high-pressure-promoted 1,3-dipolar cycloaddition reactions between (trifluoromethyl) vinyl sulfide **2** and various easily synthesized nitrones. The results of our DFT computations are in harmony with experimental results and were leveraged to show that the high regioselectivity of these cycloaddition reactions originates from minimizing steric repulsion.

EXPERIMENTAL SECTION

General information. Reagents were obtained from commercial suppliers and were used without purification. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. Tetrahydrofuran was used as a solvent after distillation. Potassium *tert*-butoxide was used as a 1.0 M solution in tetrahydrofuran. The high-pressure experiments were run in a high-pressure apparatus equipped with a one-wall-piston cylinder for pressures up to 15 kbar (1.5 GPa).Reactions were performed in 1–1.5-mL PTFE ampules closed by screwed stainless steel stoppers. These ampules were inserted into the high-pressure vessel filled with 80-100 petroleum ether and transmission medium. Reactions were followed, and R_F values were obtained, using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV light, and/or by charring at ca. 150 °C after dipping into a solution of $KMnO_4$. Infrared spectra were recorded on an IR-ATR Bruker TENSOR 27 spectrometer. High-resolution mass spectra were recorded on a JEOL AccuTOF (ESI) or a MAT900 (EI, CI, and ESI) GC-TOF. NMR spectra were recorded at 298 K on a Varian Inova 400 (400 MHz), Bruker Avance III 400 MHz or Bruker Avance III 500 MHz spectrometer in the solvent indicated. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm) as internal standard for ^{1}H NMR; and $CDCl_3$ (77.16 ppm) as internal standard for ^{13}C NMR. Coupling constants are reported as *J* values in hertz (Hz). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dtdq = doublet of triplet of doublet of quartets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublets of triplets, dddd= doublet of doublets of doublets of doublets, ddquint = doublet of doublet of quintets, dddquint = doublet of doublet of doublet of quintets, quint = quintet, t = triplet, td = triplet of doublets, tt = triplet of triplets m = multiplet, b = broad), coupling constants (Hz), integration and assignment. Compounds were fully characterized by ^{1}H, ^{13}C, 2D gDQCOSY, gHSQC, gHMBC, NOESY and HOESY spectra. The characterization and assignment of isoxazolidines **4a–r** were done either from isolated compounds or mixtures of isomers. Column or flash chromatography was carried out using ACROS silica gel (0.035–0.070 mm, and 60 Å pore diameter).

General Procedure for the Synthesis of (Trifluoromethyl) Vinyl Sulfide 2. (2-Chloroethyl) (trifluoromethyl) sulfide (1.0 equiv) was dis-

solved in distilled THF (0.40 M) under inert atmosphere and cooled down to 0 °C. Then, KO^{t}Bu (1.0 equiv, 1.0 M solution in THF) was added slowly and the mixture was warmed up to 21 °C for 90 minutes. This solution was used for the cycloaddition reactions of alkene **2**. ^{1}H NMR [400 MHz, δ (ppm), THF-d_8]: 6.54 (dd, J = 16.5, 9.4 Hz, 1 H), 5.75–5.66 (m, 2 H). ^{13}C NMR [101 MHz, δ (ppm), THF-d_8]: 129.8 (q, J = 306.5 Hz), 124.4 (q, J = 1.0 Hz), 121.3 (q, J = 3.2 Hz). ^{19}F NMR [377 MHz, δ (ppm), THF-d_8]: –43.6.[7]

General Procedure for the Synthesis of Hydroxylamines 5b and 5c. The corresponding nitrobenzene (**12b** or **12c**; 1 equiv) was added to a flame-dried Schlenk tube containing a suspension of Pd/C (0.25 equiv) in dry THF (10 mL). The mixture was cooled to 0 °C and $N_2H_4{\cdot}H_2O$ (2.0 equiv) was added dropwise. The reaction was carefully monitored by TLC until the starting material disappeared. The crude mixture was diluted with THF (10 mL) and filtered over a pad of diatomaceous earth. The solvent was evaporated in vacuo and the crude mixture was purified by column chromatography using CH_2Cl_2 under a nitrogen atmosphere.

*N-[3-(Trifluoromethyl)phenyl]hydroxylamine (**5b**).* According to the general procedure, the reaction of 1-nitro-3-(trifluoromethyl)benzene **12b** (1.0 g, 5.23 mmol) afforded hydroxylamine **5b** (885 mg, 5.00 mmol) as a pale yellow oil. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.41–7.34 (m, 1 H), 7.28–7.26 (m, 1 H), 7.23–7.19 (m, 1 H), 7.15–7.10 (m, 1 H), 6.74–4.98 (bs, 2 H). R_F: 0.31 (CH_2Cl_2). Yield: 95%. NMR spectral data are in accordance with previously reported data.[20]

*N-(3,5-Dichlorophenyl)hydroxylamine (**5c**).* According to the general procedure, the reaction of 1,3-dichloro-5-nitrobenzene **12c** (1.0 g, 5.22 mmol) afforded hydroxylamine **5c** (827 mg, 4.65 mmol) as a yellow solid. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 6.93 (t, J = 1.8 Hz, 1 H), 6.88 (d, J = 1.8 Hz, 2 H), 6.79 (bs, 1 H), 5.31 (bs, 1 H). R_F: 0.33 (CH_2Cl_2). Yield: 89%. NMR spectral data are in accordance with previously reported data.[20]

General Procedure for the Synthesis of Isoxazolidines 3a–c. A solution of the corresponding hydroxylamine **5** (1 equiv) in THF (0.22 M) was added to a solution of paraformaldehyde (3 equiv) in THF (0.22 M) at 0 °C. Then, a cooled solution (0 °C) of alkene **2** (6.0 equiv) was subsequently added to the solution containing paraformaldehyde and the hydroxylamine. Finally, a solution of $In(OTf)_3$ (0.06 equiv) in dry THF (44 mM) was added to the reaction mixture. The reaction mixture was warmed up to 21 °C and stirred for 16 hours. Then, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the aqueous layer was extracted with AcOEt (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered off and concentrated in vacuo. The crude mixture was purified by column chromatography using the indicated eluent to afford isoxazolines **3a–c**.

*2-Phenyl-5-[(trifluoromethyl)sufanyl]isoxazolidine (**3a**).* According to the general procedure, the reaction of *N*-phenylhydroxylamine **5a** (17.8 mg, 0.163 mmol) afforded isoxazolidine **3a** (15.3 mg, 0.163 mmol) as a brown solid, after column chromatography (heptane/AcOEt, 19:1 → 4:1). ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.34–7.27 (m, 2 H), 7.08–7.05 (m, 2 H), 7.03 (tt, J = 7.3, 1.1 Hz, 1 H), 5.98 (dd, J = 8.1, 4.3 Hz, 1 H), 3.85–3.71 (m, 1 H), 3.24 (ddd, J = 9.3, 8.2, 7.6 Hz, 1 H), 2.91 (dtdq, J = 13.2, 8.2, 4.0, 0.8 Hz, 1 H), 2.48–2.28 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 149.8, 130.1 (q, J = 307.7 Hz), 129.0, 123.0, 116.1, 81.1 (q, J = 2.2 Hz), 52.0, 36.0 (q, J = 1.1 Hz). ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.8. FTIR [$\bar{\nu}$ (cm^{-1})]: 2860, 1599, 1491, 1295, 1109, 752, 692. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{10}H_{10}F_3NOS$ 249.0435; found 249.0458. R_F: 0.56 (heptane/AcOEt, 4:1). Yield: 38%.

*2-[3-(Trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**3b**).* According to the general procedure, the reaction of hydroxylamine **5b** (56.2 mg, 0.318 mmol) afforded isoxazolidine **3b** (23.5 mg, 0.071 mmol) as a colorless oil, after column chromatography (heptane/AcOEt/Et_3N, 12.2:1:0.13). ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.41 (ddquint, J = 8.2, 7.2, 0.8 Hz, 1 H), 7.29–7.25 (m, 2 H), 7.23–7.19 (m, 1 H), 6.01 (dd, J = 8.0, 4.2 Hz, 1 H), 3.83 (ddd, J = 9.1, 8.2, 4.3 Hz, 1 H), 3.30 (ddd, J = 9.1, 8.5, 7.4 Hz, 1 H), 3.02–2.90 (m, 1 H), 2.48–2.38 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 150.1, 131.3 (q, J = 32.3 Hz), 129.8 (q, J = 307.9 Hz), 129.4, 124.0 (q, J = 272.4 Hz), 119.2 (q, J = 3.8 Hz), 118.9, 112.3 (q, J = 4.0 Hz), 81.1 (q, J = 2.4 Hz), 51.7, 35.8 (q, J = 1.2 Hz). ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9, –62.8. FTIR [$\bar{\nu}$ (cm^{-1})]: 2956, 2925, 2855, 1593, 1328, 1120, 795, 698. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{11}H_9F_6NOS$ 317.0309; found 317.0325. R_F: 0.44 (heptane/AcOEt, 4:1). Yield: 22%.

*2-(3,5-Dichlorophenyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**3c**).* According to the general procedure, the reaction of hydroxylamine **5c** (29.3 mg, 0.166 mmol) afforded isoxazolidine **3c** (10.33 mg, 0.033 mmol) as a green oil, after column chromatography (heptane/AcOEt/Et_3N, 12.2:1:0.13). ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 6.99 (t, J = 1.8 Hz, 1 H), 6.91 (d, J = 1.8 Hz, 2 H), 5.98 (dd, J = 8.0, 4.1 Hz, 1 H), 3.75 (ddd, J = 8.9, 8.1, 4.4 Hz, 1 H), 3.27 (ddd, J = 9.2, 8.6, 7.1 Hz, 1 H), 3.01–2.87 (m, 1 H), 2.47–2.36 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 151.6, 135.4, 129.7 (q, J = 307.9 Hz), 122.5, 114.2, 81.2 (q, J = 2.6 Hz), 51.6, 35.8 (q, J = 1.1 Hz). FTIR [$\bar{\nu}$ (cm^{-1})]: 2924, 2850, 1587, 1260, 1115, 1051, 796. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{10}H_8Cl_2F_3NOS$ 316.9656; found 316.9657. R_F: 0.45 (heptane/AcOEt, 4:1). Yield: 20%.

General Procedure for the Synthesis of Isoxazolidines 3d and 3e. A solution of hydroxylamine hydrochloride **5d** or **5e** (1 equiv) in THF (0.22 M) and Et_3N (1equiv) was added to a solution of paraformaldehyde (3 equiv) in THF (0.22 M) at 0 °C. Then, a cooled solution (0 °C) of alkene **2** (6.0 equiv) was subsequently added to the solution containing paraformaldehyde and the hydroxylamine. Finally, a solution of $In(OTf)_3$ (0.06 equiv) in dry THF (22 mM) was added to the reaction mixture. The reaction mixture was warmed up to 21 °C and stirred for 16 hours. Then, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the aqueous layer was extracted with AcOEt (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered off and concentrated in vacuo. The crude mixture was purified by column chromatography using the indicated eluent to afford isoxazolines **3d** and **3e**.

*2-Benzyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**3d**).* According to the general procedure, the reaction of hydroxylamine hydrochloride **5d** (26.8 mg, 0.169 mmol) afforded isoxazolidine **3d** (13.2 mg, 0.050 mmol) as a colorless oil, after column chromatography (heptane/AcOEt/Et_3N, 9:1:0.1). ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.40–7.36 (m, 2 H), 7.35–7.30 (m, 2 H), 7.30–7.27 (m, 1 H), 5.86 (dd, J = 8.3, 4.4 Hz, 1 H), 4.35–3.82 (m, 2 H), 3.34–3.11 (m, 1 H), 3.11–2.40 (m, 1 H), 2.83 (dtd, J = 11.9, 8.0, 3.3 Hz, 1 H), 2.40–2.18 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 136.2, 130.3 (q, J = 307.9 Hz), 128.9, 128.4, 127.5, 81.3 (q, J = 2.4 Hz), 61.7, 53.3, 36.5. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 2849, 1606, 1497, 1455, 1117, 755, 698. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{11}H_{12}F_3NOS$ 263.0592; found 263.0604. R_F: 0.41 (heptane/AcOEt, 4:1). Yield: 30%.

*2-Cyclohexyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**3e**).* According to the general procedure, the reaction of hydroxylamine hydrochloride **5e** (23.1 mg, 0.152 mmol) afforded isoxazolidine **3e** (20.4 mg, 0.080 mmol) as a colorless oil, after column chromatography (heptane/AcOEt, 19:1 → 5:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 5.82 (dd, J = 8.1, 4.2 Hz, 1 H), 3.43–3.13 (m, 1 H), 2.85–2.73 (m, 1 H), 2.68–2.50 (m, 1 H), 2.68–2.18 (m, 1 H), 2.31–2.18 (m, 1 H), 1.83–1.69 (m, 2 H), 1.66–1.52 (m, 2 H), 1.39–1.13 (m, 6 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 130.4 (q, J = 308.1 Hz), 80.8 (q, J = 2.2 Hz), 65.8, 51.5, 36.6, 26.0, 24.8, 24.4. ^{19}F NMR [377 MHz, δ (ppm), $CDCl_3$]: –40.0. FTIR [$\bar{\nu}$ (cm^{-1})]: 2924, 2854, 1728, 1455, 1258, 1082, 1009, 788. R_F: 0.44 (heptane/AcOEt, 9:1). Yield: 53%.

General Procedure A for the Syntheses of Nitrones 6d–g, 6i, 6j, 6l–r. The corresponding aldehyde (1.0 equiv, dissolved in 1.5 mL of dry EtOH for solid compounds) was added to a solution of *N*-phenylhydroxylamine (1.05 equiv) in dry EtOH (1.0 mL) at 21 °C under a nitrogen atmosphere. The reaction mixture was stirred for 16–21 h and then the solvent was removed under vacuo. The crude mixture was purified by column chromatography using the indicated eluent to afford nitrones **6d–g, 6i, 6j, 6l–r**.

General Procedure B for the Syntheses of Nitrones 6a–c, 6h and 6k. The corresponding aldehyde (1.0 equiv) was added to a solution of *N*-phenylhydroxylamine (1.0 equiv) in dry EtOH (1.0 mL) and the flask was wrapped with aluminum foil. The reaction mixture was stirred at 21 °C for 16–21 h and then the solvent was removed under vacuo. The crude mixture was purified by column chromatography using the indicated eluent to afford nitrones **6a–c, 6h** and **6k**.

*(Z)-N,1-Diphenylmethanimine oxide (**6a**).*[21] According to the general procedure B, the reaction of benzaldehyde (47.0 µL, 0.458 mmol) with *N*-phenylhydroxylamine (50 mg, 0.458 mmol) afforded nitrone **6a** (71 mg, 0.360 mmol) as a white solid, after column chromatography (heptane/AcOEt, 5:1 → 1:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.44–8.36 (m, 2 H), 7.92 (s, 1 H), 7.81–7.74 (m, 2 H), 7.53–7.43 (m, 6 H). Yield: 79%.

*(Z)-1-(4-Fluorophenyl)-N-phenylmethanimine oxide (**6b**).*[22] According to the general procedure B, the reaction of 4-fluorobenzaldehyde (98.0 µL, 0.916 mmol) with *N*-phenylhydroxylamine (100 mg, 0.916 mmol) afforded nitrone **6b** (178.5 mg, 0.829 mmol) as a white solid. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.49–8.42 (m, 2 H), 7.91 (s, 1 H), 7.80–7.75 (m, 2 H), 7.55–7.44 (m, 3 H), 7.23–7.14 (m, 2 H). Yield: 91%.

*(Z)-N-Phenyl-1-(4-tolyl)methanimine oxide (**6c**).*[22] According to the general procedure B, the reaction of 4-methylbenzaldehyde (163.0 µL, 1.375 mmol) with *N*-phenylhydroxylamine (127 mg, 1.375 mmol) afforded nitrone **6c** (267.2 mg, 1.26 mmol) as yellow crystals, after column chromatography (heptane/AcOEt, 5:1 → 1:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.34–8.27 (m, 2 H), 7.89 (s, 1 H), 7.81–7.75 (m, 2 H), 7.51–7.43 (m, 3 H), 7.33–7.28 (m, 2 H), 2.42 (s, 3 H). Yield: 92%.

*(Z)-N-Phenyl-1-[4-(trifluoromethyl)phenyl]methanimine oxide (**6d**).*[23] According to the general procedure A, the reaction of 4-(trifluoromethyl)benzaldehyde (91 mg, 0.523 mmol) with *N*-phenylhydroxylamine (60 mg, 0.549 mmol) afforded nitrone **6d** (139 mg, 0.523 mmol) as a yellow solid. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.54–8.48 (m, 2 H), 8.00 (s, 1 H), 7.83–7.76 (m, 2 H), 7.76–7.70 (m, 2 H), 7.55–7.47 (m, 3 H). Yield: 99%.

*(Z)-1-[4-(Pentafluoro-λ^6-sulfanyl)phenyl]-N-phenylmethanimine oxide (**6e**).* According to the general procedure A, the reaction of 4-(pentafluoro-λ^6-sulfanyl)benzaldehyde (120 mg, 0.517 mmol) with *N*-phenylhydroxylamine (59 mg, 0.543 mmol) afforded nitrone **6e** (163.3 mg, 0.505 mmol) as a white-yellow solid. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.52–8.45 (m, 2 H), 8.00 (s, 1 H), 7.89–7.81 (m, 2 H), 7.81– 7.74 (m, 2 H), 7.58–7.46 (m, 3 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 154.5, 149.1, 133.6, 132.5, 130.7, 129.5, 128.9, 126.5 (quint, *J* = 4.4 Hz), 121.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3057, 1594, 1573, 1074, 821, 810, 765. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{13}H_{11}F_5NOS$ 324.0476; found 324.0482. R_F: 0.45 (CH_2Cl_2). Yield: 98%.

*(Z)-1-(4-Methoxyphenyl)-N-phenylmethanimine oxide (**6f**).*[24] According to the general procedure A, the reaction of 4-methoxybenzaldehyde (0.063 mL, 0.514 mmol) with *N*-phenylhydroxylamine (59 mg, 0.540 mmol) afforded nitrone **6f** (110 mg, 0.484 mmol) as a yellow-brown solid, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:0.2). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.44–8.36 (m, 2 H), 7.84 (s, 1 H), 7.79–7.72 (m, 2 H), 7.50–7.37 (m, 3 H), 7.01–6.93 (m, 2 H), 3.86 (s, 3 H). Yield: 94%.

*(Z)-1-(3-Fluorophenyl)-N-phenylmethanimine oxide (**6g**).*[25] According to the general procedure A, the reaction of 3-fluorobenzaldehyde (0.060 mL, 0.564 mmol) with *N*-phenylhydroxylamine (62 mg, 0.564 mmol) afforded nitrone **6g** (118 mg, 0.548 mmol) as a light brown solid, after column chromatography (heptane/CH_2Cl_2, 1:4 → CH_2Cl_2/MeOH, 10:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.44 (ddd, *J* = 10.6, 2.6, 1.6 Hz, 1 H), 7.94 (s, 1 H), 7.90 (ddt, *J* = 8.1, 1.6, 0.7 Hz, 1 H), 7.80–7.73 (m, 2 H), 7.54–7.47 (m, 3 H), 7.44 (td, *J* = 8.1, 5.9 Hz, 1 H), 7.17 (tdd, *J* = 8.1, 2.6, 1.0 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 162.8 (d, *J* = 245.5 Hz), 149.1, 133.5, 132.6 (d, *J* = 9.1 Hz), 130.4, 130.1 (d, *J* = 8.4 Hz), 129.4, 125.1 (d, *J* = 3.0 Hz), 121.8, 118.0 (d, *J* = 21.7 Hz), 115.3 (d, *J* = 24.7 Hz). Yield: 97%.

*(Z)-N-Phenyl-1-(3-tolyl)methanimine oxide (**6h**).*[25] According to the general procedure B, the reaction of 3-methylbenzaldehyde (42 µL, 0.458 mmol) with *N*-phenylhydroxylamine (50 mg, 0.458 mmol) afforded nitrone **6h** (95.3 mg, 0.451 mmol) as a yellow oil, after column chromatography (heptane/AcOEt, 5:1 → 1:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.32 (tq, *J* = 1.8, 0.7 Hz, 1 H), 8.12 (dddquint, *J* = 7.8, 1.8, 1.2, 0.7 Hz, 1 H), 7.89 (s, 1 H), 7.81–7.75 (m, 2 H), 7.53–7.44 (m, 3 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.32–7.27 (m, 1 H), 2.43 (s, 3 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 149.3, 138.5, 134.9, 132.0, 130.8, 130.0, 129.4, 129.3, 128.7, 126.6, 121.9, 21.6. FTIR [$\bar{\nu}$ (cm^{-1})]: 3092, 2963, 2920, 1652, 1590, 1459, 1088, 781, 692. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{14}NO$ 212.1070; found 212.1085. Yield: 98%.

*(Z)-1-[3-(Methoxycarbonyl)phenyl]-N-phenylmethanimine oxide (**6i**).* According to the general procedure A, the reaction of methyl 3-formylbenzoate (90 mg, 0.548 mmol) with *N*-phenylhydroxylamine (63 mg, 0.576 mmol) afforded nitrone **6i** (112 mg, 0.439 mmol) as a yellow oil, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.88 (dddd, *J* = 7.9, 1.7, 1.2, 0.5 Hz, 1 H), 8.80 (tt, *J* = 1.7, 0.5 Hz, 1 H), 8.13 (ddd, *J* = 7.9, 1.7, 1.2 Hz, 1 H), 8.01 (d, *J* = 0.5 Hz, 1 H), 7.83–7.75 (m, 2 H), 7.59 (tt, *J* = 7.9, 0.5 Hz, 1 H), 7.54–7.46 (m, 3 H), 3.95 (s, 3 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 166.5, 149.0, 133.6, 132.6, 131.6, 131.0, 130.6, 130.4, 130.2, 129.3, 129.0, 121.7, 52.4. FTIR [$\bar{\nu}$ (cm^{-1})]: 3064, 2952, 1718, 1434, 1278, 1187, 1072, 912, 729, 684. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{15}H_{14}NO_3$ 256.0968; found 256.0984. R_F: 0.07 (CH_2Cl_2). Yield: 80%.

*(Z)-1-(3-Methoxyphenyl)-N-phenylmethanimine oxide (**6j**).* According to the general procedure A, the reaction of 3-methoxybenzaldehyde (0.063 mL, 0.514 mmol) with *N*-phenylhydroxylamine (59 mg, 0.540 mmol) afforded nitrone **6j** (115 mg, 0.506 mmol) as a yellow oil, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:0.2). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.38 (dd, *J* = 2.7, 1.5 Hz, 1 H), 7.92 (s, 1 H), 7.81–7.75 (m, 2 H), 7.66 (dddd, *J* = 7.7, 1.5, 1.0, 0.5 Hz, 1 H), 7.52–7.44 (m, 3 H), 7.38 (dd, *J* = 8.3, 7.7 Hz, 1 H), 7.05 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 159.7, 149.1, 134.7, 131.9, 130.0, 129.5, 129.2, 122.3, 121.8, 118.1, 112.7, 55.4. FTIR [$\bar{\nu}$ (cm^{-1})]: 3060, 2834, 1553, 1270, 1025, 769, 684. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{14}H_{13}NO_2Na$ 250.0839; found 250.0857. R_F: 0.06 (CH_2Cl_2). Yield: 98%.

*(Z)-N-Phenyl-1-[3-(trifluoromethyl)phenyl]methanimine oxide (**6k**).*[25] According to the general procedure B, the reaction of 3-(trifluoromethyl)benzaldehyde (61 µL, 0.458 mmol) with *N*-phenylhydroxylamine (50 mg, 0.458 mmol) afforded nitrone **6k** (116 mg, 0.437 mmol) as a white solid, after column chromatography (heptane/AcOEt, 5:1 → 1:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.70 (dq, *J* = 2.3, 1.0 Hz, 1 H), 8.59 (dddd, *J* = 7.9, 1.7, 1.2, 0.6 Hz, 1 H), 8.01 (s, 1 H), 7.84–7.75 (m, 2 H), 7.72 (dq, *J* = 8.5, 1.1 Hz, 1 H), 7.61 (t, *J* = 7.9 Hz, 1 H), 7.55–7.48 (m, 3 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 149.1, 133.1, 131.8 (q, *J* = 1.0 Hz), 131.5, 131.5, 130.5, 129.5, 129.3, 127.3 (q, *J* = 3.7 Hz), 125.7 (q, *J* = 3.9 Hz), 122.6, 121.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3124, 1604, 1330, 1120, 1068, 770, 692. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{11}F_3NO$ 266.0787; found 266.0799. R_F: 0.35 (CH_2Cl_2). Yield: 95%.

*(Z)-N-Phenyl-1-(2-tolyl)methanimine oxide (**6l**).*[26] According to the general procedure A, the reaction of 2-methylbenzaldehyde (0.061 mL, 0.524 mmol) with *N*-phenylhydroxylamine (60 mg, 0.551 mmol) afforded nitrone **6l** (107 mg, 0.508 mmol) as a yellow-brown solid, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:0.2). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.42–9.32 (m, 1 H), 8.07 (s, 1 H), 7.81–7.73 (m, 2 H), 7.53–7.44 (m, 3 H), 7.39–7.33 (m, 2 H), 7.28–7.23 (m, 1 H), 2.46 (s, 3 H). Yield: 97%.

*(Z)-1-(2-Methoxyphenyl)-N-phenylmethanimine oxide (**6m**).*[25] According to the general procedure A, the reaction of 2-methoxybenzaldehyde (70 mg, 0.514 mmol) with *N*-phenylhydroxylamine (59 mg, 0.540 mmol) afforded nitrone **6m** (106 mg, 0.464 mmol) as an orange-brown solid, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:0.2). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.48 (dd, *J* = 7.9, 1.7 Hz, 1 H), 8.40 (s, 1 H), 7.85–7.73 (m, 2 H), 7.53–7.39 (m, 4 H), 7.13–7.06 (m, 1 H), 6.93 (dd, *J* = 8.4, 1.1 Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 157.6, 149.8, 132.3, 129.8, 129.4, 129.2, 128.9, 122.0, 121.0, 120.1, 110.0, 55.8. FTIR [$\bar{\nu}$ (cm^{-1})]: 3058, 1577, 1288, 1046, 746, 691, 611. R_F: 0.07 (CH_2Cl_2). Yield: 90%.

*(Z)-N-Phenyl-1-(thiophen-3-yl)methanimine oxide (**6n**).*[27] According to the general procedure A, the reaction of thiophene-3-carbaldehyde (0.047 mL, 0.535 mmol) with *N*-phenylhydroxylamine (61 mg, 0.562 mmol) afforded nitrone **6n** (109 mg, 0.535 mmol) as a white-yellow solid, after column chromatography (heptane/CH_2Cl_2, 1:1 → heptane/CH_2Cl_2, 0:1). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.16 (ddd, *J* = 3.1, 1.2, 0.7 Hz, 1 H), 8.06 (d, *J* = 0.6 Hz, 1 H), 7.82–7.76 (m, 2 H), 7.52–7.46 (m, 3 H), 7.45 (dd, *J* = 5.2, 1.2 Hz, 1 H), 7.39 (dd, *J* = 5.1, 3.0 Hz, 1 H). Yield: 99%.

*(Z)-1-(1H-Indol-2-yl)-N-phenylmethanimine oxide (**6o**).* According to the general procedure A, the reaction of 1*H*-indole-2-carbaldehyde (80 mg, 0.551 mmol) with *N*-phenylhydroxylamine (63 mg, 0.579 mmol) afforded nitrone **6o** (130 mg, 0.551 mmol) as a yellow-brown solid. ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 11.69 (s, 1 H), 8.14 (s, 1 H), 7.87–7.80 (m, 2 H), 7.67 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.55–7.45 (m, 4 H), 7.32 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1 H), 7.16 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1 H), 6.94 (s, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 147.4, 136.0, 130.2, 129.9, 129.4, 127.6, 126.8, 125.2, 121.3, 120.8, 112.3, 108.6. FTIR [$\bar{\nu}$ (cm^{-1})]: 3315, 3067, 1593, 1502, 1345, 1234, 818, 733. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{15}H_{12}N_2ONa$ 259.0842; found 259.0858. R_F: 0.13 (CH_2Cl_2). Yield: 99%.

*(Z)-N-Phenyl-1-(1H-pyrrol-2-yl)methanimine oxide (**6p**).* According to the general procedure A, the reaction of 1*H*-pyrrole-2-carbaldehyde (52 mg, 0.547 mmol) with *N*-phenylhydroxylamine (60 mg, 0.550 mmol) afforded nitrone **6p** (62 mg, 0.333 mmol) as a dark brown solid, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:0.1). ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 12.21 (s, 1 H), 7.95 (s, 1 H), 7.81–7.73 (m, 2 H), 7.52–7.38 (m, 3 H), 7.07 (td, *J* = 2.7, 1.3 Hz, 1 H), 6.70 (dt, *J* = 3.6, 1.6 Hz, 1 H), 6.40 (dt, *J* = 3.9, 2.5 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 147.1, 129.5, 129.3, 126.1, 125.3, 121.3, 121.0, 115.9, 111.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3317, 3062, 1580, 1403, 1294, 1074, 1045, 740, 686. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{11}H_{11}N_2O$ 187.0866; found 187.0885. R_F: 0.45 (heptane/AcOEt, 1:1). Yield: 61%.

*(Z)-1-(Furan-2-yl)-N-phenylmethanimine oxide (**6q**).*[28] According to the general procedure A, the reaction of furan-2-carbaldehyde (0.043 mL, 0.520 mmol) with *N*-phenylhydroxylamine (60 mg, 0.546 mmol) afforded nitrone **6q** (97 mg, 0.520 mmol) as a light brown solid, after column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH, 10:0.2). ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.16 (s, 1 H), 8.01 (dt, *J* = 3.5, 0.7 Hz, 1 H), 7.83–7.77 (m, 2 H), 7.58 (dd, *J* = 1.8, 0.7 Hz, 1 H), 7.52–7.44 (m, 3 H), 6.65 (dd, *J* = 3.6, 1.8 Hz, 1 H). Yield: 99%.

*(Z)-2-(Benzylamino)-2-oxo-N-phenylethan-1-imine oxide (**6r**).* According to the general procedure A, the reaction of *N*-benzyl-2-oxoacetamide (56 mg, 0.343 mmol) with *N*-phenylhydroxylamine (26 mg, 0.240 mmol) afforded nitrone **6r** (34.5 mg, 0.135 mmol) as a white solid. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 10.39 (s, 1 H), 7.72–7.67 (m, 2 H), 7.66 (s, 1 H), 7.58–7.46 (m, 3 H), 7.40–7.27 (m, 5 H), 4.64 (d, *J* = 5.9 Hz, 2 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 160.8, 147.5, 137.8, 131.7, 130.3, 129.7, 128.9, 128.0, 127.7, 121.6, 43.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3255, 3121, 2945, 1634, 1516, 1059, 768, 751, 683. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_2Na$ 277.0948; found 277.0956. R_F: 0.68 (CH_2Cl_2/MeOH, 10:0.2). Yield: 39%.

General Procedure for the Synthesis of Isoxazolidines 4a, 4b, 4d–r. The solution containing alkene **2** in distilled THF (3 equiv, 1.48 M) at 0 °C was added to a PTFE tube containing the corresponding nitrone **6** (1 equiv) and galvinoxyl (0.03 equiv). The tube was filled up with distilled THF, closed and brought to 15 kbar at 50 °C for 16 hours. Then, the reaction mixture was filtered off and the solvent was removed under vacuo. The crude mixture was purified by column chromatography using the indicated eluent to afford isoxazolidines **4a**, **4b**, **4d–r**.

*2,3-Diphenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4a**).* According to the general procedure, the reaction of nitrone **6a** (26 mg, 0.119 mmol) and alkene **2** in a 1 mL PTFE high-pressure tube afforded *cis*-**4a** (24.9 mg, 0.77 mmol, 65%) as a white solid and a mixture of *cis*- and *trans*-**4a** and regioisomers **7a** (12.6 mg, 0.039 mmol, 33%) as a yellow oil, after column chromatography (heptane/CH_2Cl_2, 9:1). Total yield: 98%.

*rac-(3R,5R)-2,3-Diphenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4a**).*
^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.52–7.47 (m, 2 H), 7.43–7.37 (m, 2 H), 7.35–7.30 (m, 1 H), 7.24–7.18 (m, 2 H), 7.04–6.99, (m, 1 H), 6.99–6.95 (m, 2 H), 6.01 (dd, *J* = 8.1, 4.4 Hz, 1 H), 4.41 (dd, *J* = 9.0, 7.1 Hz, 1 H), 3.41 (dddq, *J* = 13.6, 9.0, 8.1, 0.9 Hz, 1 H), 2.44–2.31 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.8, 139.8, 130.2 (q, *J* = 307.7 Hz), 129.3, 128.8, 128.3, 127.2, 123.8, 117.6, 80.5 (q, *J* = 2.5 Hz), 68.3, 47.2. FTIR [$\bar{\nu}$ (cm^{-1})]: 3070, 2963, 1598, 1489, 1258, 1114, 1031, 966, 928, 752, 700. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{16}H_{14}F_3NOS$ 325.0748; found 325.0765. R_F: 0.20 (heptane/CH_2Cl_2, 9:1).

*rac-(3R,5S)-2,3-Diphenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4a**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.50–7.45 (m, 2 H), 7.41–7.36 (m, 2 H), 7.35–7.30 (1 H), 7.25–7.18 (m, 2 H), 7.04–6.98 (m, 2 H), 6.98–6.93 (m, 1 H), 6.07 (dd, *J* = 6.8, 3.8 Hz, 1 H), 4.90 (t, *J* = 7.3 Hz, 1 H), 3.02–2.92 (m, 1 H), 2.88 (ddd, *J* = 13.3, 7.3, 3.8 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 151.0, 139.9, 129.9 (q, *J* = 307.8 Hz), 129.2, 128.8, 128.2, 126.7, 122.4, 115.2, 82.3 (q, *J* = 2.0 Hz), 68.1, 46.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3065, 1598, 1489, 1206, 1108, 1049, 842, 796, 665. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{16}H_{14}F_3NOS$ 325.0748; found 325.0750 . R_F: 0.11 (heptane/CH_2Cl_2, 9:1).

*3-(4-Fluorophenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4b**).* According to the general procedure, the reaction of nitrone **6b** (27 mg, 0.125 mmol) and alkene **2** in a 1 mL PTFE high-pressure tube afforded *cis*-**4b** (27.6 mg, 0.080 mmol, 64%) as a white solid, a mixture of *cis*- and *trans*-**4b** and regioisomers **7b** (13.1 mg, 0.038 mmol, 27%) as a yellow oil and *trans*-**4b** (3.5 mg, 0.010 mmol, 8%) as a pale yellow oil, after column chromatography (heptane/CH_2Cl_2, 9:1). Total yield: 99%.

*rac-(3R,5R)-3-(4-Fluorophenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4b**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.49–7.43 (m, 2 H), 7.25–7.19 (m, 2 H), 7.11–7.05 (m, 2 H), 7.05–7.01 (m, 1 H), 6.99–6.93 (m, 2 H), 6.01 (dd, *J* = 8.1, 4.3 Hz, 1 H), 4.40 (dd, *J* = 9.0, 7.0 Hz, 1 H), 3.39 (dddq, *J* = 13.7, 9.0, 8.1, 0.9 Hz, 1 H), 2.39–2.28 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 162.6 (d, *J* = 247.0 Hz), 148.6, 135.4 (d, *J* = 3.1 Hz), 130.1 (q, *J* = 307.8 Hz), 128.92, 128.91 (d, *J* = 7.2 Hz), 124.0, 117.7, 116.2 (d, *J* = 21.6 Hz), 80.5 (q, *J* = 2.3 Hz), 67.7, 47.1. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3071, 1597, 1455, 1256, 1226, 1110, 1029, 905, 804, 754. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{16}H_{13}F_4NOS$ 343.0654; found 343.0650. R_F: 0.26 (heptane/CH_2Cl_2, 17:3).

*rac-(3R,5S)-3-(4-Fluorophenyl)-2-phenyl-5-[(trifluoromethyl]sulfanyl]isoxazolidine (trans-**4b**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.44–7.40 (m, 2 H), 7.25–7.20 (m, 2 H), 7.10–7.04 (m, 2 H), 6.99–6.92 (m, 3 H), 6.05 (dd, *J* = 6.8, 3.9 Hz, 1 H), 4.88 (t, *J* = 7.2 Hz, 1 H), 2.98–2.90 (m, 1 H), 2.87 (ddd, *J* = 13.3, 7.3, 3.9 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 162.3 (d, *J* = 242.3 Hz), 150.7, 135.6, 128.9, 128.4 (d, *J* = 8.3 Hz), 122.6, 116.2 (d, *J* = 21.7 Hz), 115.3, 81.2, 67.4, 46.2. The carbon signal of SCF_3 was not observed. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.4. FTIR [$\bar{\nu}$ (cm^{-1})]: 3071, 1686, 1598, 1154, 1052, 937, 693. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{16}H_{13}F_4NOS$ 343.0654; found 343.0676. R_F: 0.21 (heptane/CH_2Cl_2, 17:3).

*2-Phenyl-3-(4-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4c**).* The solution containing alkene **2** (3.0 equiv) in distilled THF (500 µL) at 0 °C was added to a PTFE tube containing nitrone **6c** (1.0 equiv). The tube was filled up with distilled THF, closed and brought to 15 kbar at 50 °C for 16 hours. Then, the reaction mixture was filtered off and the solvent was removed under vacuo. The crude mixture was purified by column chromatography (heptane/CH_2Cl_2, 4:1) to afford isoxazolidine *cis*-**4c** (17.1 mg, 0.050 mmol, 50%) as white solid and *trans*-**4c** (12.1 mg, 0.36 mmol, 35%) as a brown oil, contaminated with regioisomers **7c** and azoxybenzene **8**. Total yield: 85%.

*rac-(3R,5R)-2-Phenyl-3-(4-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4c**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.40–7.34 (m, 2 H), 7.23–7.16 (m, 4 H), 7.03–6.95 (m, 3 H), 6.00 (dd, *J* = 8.1, 4.3 Hz, 1 H), 4.36 (dd, *J* = 9.0, 7.2 Hz, 1 H), 3.38 (dddq, *J* = 13.7, 9.0, 8.1, 0.9 Hz, 1 H), 2.39–2.32 (m, 1 H), 2.36 (s, 3 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.9, 138.1, 136.6, 130.2 (q, *J* = 307.7 Hz), 130.0, 128.8, 127.1, 123.7, 117.6, 80.5 (q, *J* = 2.2 Hz), 68.1, 47.3, 21.3. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3056, 2962, 1597, 1489, 1257, 1107, 752, 691. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{17}H_{16}F_3NOS$ 339.0905; found 339.0890. R_F: 0.21 (heptane/CH_2Cl_2, 4:1).

*rac-(3R,5S)-2-Phenyl-3-(4-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4c**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.36–7.33 (m, 2 H), 7.25–7.16 (m, 4 H), 7.02–6.98 (m, 2 H), 6.97–6.92 (m, 1 H), 6.06 (dd, *J* = 6.8, 3.8 Hz, 1 H), 4.85 (t, *J* = 7.2 Hz, 1 H), 2.95 (dddq, *J* = 13.2, 7.6, 6.8, 0.9 Hz, 1 H), 2.85 (ddd, *J* = 13.2, 7.2, 3.8 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 151.0, 137.9, 136.9, 130.1 (q, *J* = 307.7 Hz), 129.8, 128.8, 126.6, 122.2, 115.2, 82.3 (q, *J* = 2.2 Hz), 67.9, 46.4, 21.3. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3063, 2925, 1599, 1487, 1152, 1053, 756, 686. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{17}H_{16}F_3NOS$ 339.0905; found 339.0924. R_F: 0.13 (heptane/CH_2Cl_2, 4:1).

*2-Phenyl-3-[4-(trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4d**).* According to the general procedure, the reaction of nitrone **6d** (50 mg, 0.190 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube, containing approximately 300 µL of glass beads, afforded a mixture of isoxazolidines *cis*- and *trans*-**4d** and regioisomers **7d** (53.1 mg, 0.137 mmol, 73%) as a pale yellow solid oil, after column chromatography (heptane/CH_2Cl_2, 17:3). FTIR [$\bar{\nu}$ (cm^{-1})]: 1597, 1490, 1325, 1104, 1051, 850, 754, 692. HRMS (EI) *m*/*z*: [M$^{+\bullet}$] calcd for $C_{17}H_{13}F_6NOS$ 393.0622; found 393.0624. R_F: 0.20 (heptane/CH_2Cl_2, 17:3). Total yield: 73%.

*rac-(3R,5R)-2-Phenyl-3-[4-(trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4d**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.72–7.55 (m, 4 H), 7.25–7.18 (m, 2 H), 7.05–7.00 (m, 1 H), 6.97–6.93 (m, 2 H), 6.00 (dd, *J* = 8.0, 4.3 Hz, 1 H), 4.50 (dd, *J* = 9.1, 6.7, 1 H), 3.43 (dddq, *J* = 13.7, 9.1, 8.0, 0.9, 1 H), 2.33 (ddd, *J* = 13.7, 6.7, 4.3 Hz, 1

H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.4, 144.1, 130.6 (q, *J* = 32.6 Hz), 130.0 (q, *J* = 307.8 Hz), 129.0, 127.4, 126.3 (q, *J* = 3.8 Hz), 124.09 (q, *J* = 272.1 Hz), 124.05, 117.4, 80.4 (q, *J* = 2.2 Hz), 67.5, 46.9.

*rac-(3R,5S)-2-Phenyl-3-[4-(trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4d**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.70–7.56 (m, 4 H), 7.27–7.18 (m, 2 H), 7.00–6.96 (m, 3 H), 6.04 (dd, *J* = 6.3, 4.6 Hz, 1 H), 4.97 (t, *J* = 7.1 Hz, 1 H), 3.01–2.83 (m, 2 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 150.5, 144.1, 130.5 (q, *J* = 32.5 Hz), 130.0 (q, *J* = 307.8 Hz), 129.0, 127.0, 126.2 (q, *J* = 3.9 Hz), 122.7, 115.1, 82.2 (q, *J* = 2.1 Hz), 67.5, 45.9.

*3-[4-(Pentafluoro-λ^6-sulfanyl)phenyl]-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4e**).* According to the general procedure, the reaction of nitrone **6e** (37.8 mg, 0.143 mmol) and alkene **2** in a 1 mL PTFE high-pressure tube afforded a mixture of isoxazolidines *cis*- and *trans*-**4e** and regioisomers **7e** (41 mg, 0.091 mmol, 72%) as a white solid, after column chromatography (heptane/CH_2Cl_2, 17:3). FTIR [$\bar{\nu}$ (cm^{-1})]: 2963, 1670, 1585, 1261, 1120, 1104, 817, 753, 584. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{16}H_{13}F_8NOS_2$ 451.0311; found 451.0318. R_F: 0.21 (heptane/CH_2Cl_2, 17:3). Total yield: 72%.

*rac-(3R,5R)-3-[4-(Pentafluoro-λ^6-sulfanyl)phenyl]-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4e**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.85–7.72 (m, 2 H), 7.64–7.55 (m, 2 H), 7.30–7.21 (m, 2 H), 7.09–7.02 (m, 1 H), 7.02–6.92 (m, 2 H), 6.00 (dd, *J* = 8.0, 4.3 Hz, 1 H), 4.52 (dd, *J* = 9.2, 6.6, 1 H), 3.43 (dt, *J* = 13.7, 8.6, 1 H), 2.32 (ddd, *J* = 13.7, 6.6, 4.3 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 153.7–153.4 (m), 148.3, 144.0, 130.0 (q, *J* = 307.9 Hz), 129.1, 127.3, 127.0, 124.2, 117.3, 80.4 (q, *J* = 2.3 Hz), 67.1, 46.7.

*rac-(3R,5S)-3-[4-(Pentafluoro-λ^6-sulfanyl)phenyl]-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4e**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.80–7.74 (m, 2 H), 7.60–7.56 (m, 2 H), 7.28–7.21 (m, 2 H), 7.01–6.97 (m, 3 H), 6.03 (dd, *J* = 5.9, 5.0, 1 H), 4.97 (t, *J* = 7.1 Hz, 1 H), 3.01–2.80 (m, 2 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 153.7–153.4 (m), 150.4, 143.9, 130.0 (q, *J* = 307.9 Hz), 129.0, 127.1, 127.0, 122.8, 115.1, 82.2 (q, *J* = 2.2 Hz), 67.1, 45.8.

*3-(4-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4f**).* According to the general procedure, the reaction of nitrone **6f** (54 mg, 0.238 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4f** (44.3 mg, 0.125 mmol, 53%), a mixture of isoxazolidines *cis*- and *trans*-**4f** (27.3 mg, 0.077 mmol, 32%) and isoxazolidine *trans*-**4f** mixed with *cis*-**4f** and regioisomers **7f** (12.4 mg, 0.035 mmol, 15%) as yellow oils, after column chromatography (heptane/CH_2Cl_2, 7:3). Total yield: 99%.

*rac-(3R,5R)-3-(4-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4f**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.43–7.35 (m, 2 H), 7.23–7.18 (m, 2 H), 7.04–6.99 (m, 1 H), 6.99–6.95 (m, 2 H), 6.94–6.90 (m, 2 H), 6.01 (dd, *J* = 8.1, 4.3 Hz, 1 H), 4.34 (dd, *J* = 8.9, 7.3 Hz, 1 H), 3.82 (s, 3 H), 3.37 (dddq, *J* = 13.8, 8.9, 8.2, 0.9 Hz, 1 H), 2.46–2.25 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 159.6, 148.8, 131.4, 130.2 (q, *J* = 307.8 Hz), 128.8, 128.4, 123.8, 117.8, 114.6, 80.5 (q, *J* = 2.2 Hz), 68.0, 55.4, 47.2. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3003, 1614, 1515, 1298, 1103, 1031, 816, 773. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{17}H_{16}F_3NO_2S$ 355.0854; found 355.0861. R_F: 0.15 (heptane/CH_2Cl_2, 4:1).

*rac-(3R,5S)-3-(4-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4f**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.38–7.35 (m, 2 H), 7.22–7.18 (m, 2 H), 7.01–6.98 (m, 2 H), 6.97–6.93 (m, 1 H), 6.92–6.89 (m, 2 H), 6.06 (dd, *J* = 6.8, 3.7 Hz, 1 H), 4.87–4.77 (m, 1 H), 3.81 (s, 3 H), 3.00–2.90 (m, 1 H), 2.84 (ddd, *J* = 13.2, 7.2, 3.7 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 159.5, 151.0, 131.8, 130.0 (q, *J* = 307.8 Hz), 128.8, 127.9, 122.4, 115.4, 114.5, 82.3 (q, *J* = 2.3 Hz), 67.7, 55.5, 46.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3002, 1512, 1489, 1248, 1109, 1030, 794, 693. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{17}H_{16}F_3NO_2S$ 355.0854; found 355.0855. R_F: 0.10 (heptane/CH_2Cl_2, 4:1).

*3-(3-Fluorophenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4g**).* According to the general procedure, the reaction of nitrone **6g** (52 mg, 0.242 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4g** (46.6 mg, 0.136 mmol, 56%) as a white solid, a mixture of *cis*- and *trans*-**6g** (27.8 mg, 0.081, 34%) as a yellow oil, and isoxazolidine *trans*-**6g** mixed with *cis*-**6g** and regioisomers **7g** (8.5 mg, 0.025 mmol, 10%) as a yellow solid, after column chromatography (heptane/CH_2Cl_2, 9:1). Total yield: 99%.

*rac-(3R,5R)-3-(3-Fluorophenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4g**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.34 (td, *J* = 8.1, 5.9 Hz, 1 H), 7.28–7.18 (m, 4 H), 7.06–6.98 (m, 2 H), 6.98–6.93 (m, 2 H), 5.98 (dd, *J* = 8.1, 4.3 Hz, 1 H), 4.41 (dd, *J* = 9.1, 6.8 Hz, 1 H), 3.39 (dddq, *J* = 13.7, 9.1, 8.1, 0.9 Hz, 1 H), 2.33 (ddd, *J* = 13.7, 6.8, 4.3 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 163.4 (d, *J* = 247.0 Hz), 148.6, 142.5 (d, *J* = 7.2 Hz), 130.9 (d, *J* = 8.3 Hz), 130.1 (q, *J* = 307.9 Hz), 128.9, 123.9, 122.7 (d, *J* = 2.9 Hz), 117.4, 115.3 (d, *J* = 21.3 Hz), 114.1 (d, *J* = 22.6 Hz), 80.4 (q, *J* = 2.4 Hz), 67.5 (d, *J* = 1.9 Hz), 46.9. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3062, 1594, 1489, 1448, 1258, 1111, 1044, 915, 833, 752, 690. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{16}H_{13}F_4NOS$ 343.0654; found 343.0675. R_F: 0.22 (heptane/CH_2Cl_2, 17:3).

*rac-(3R,5S)-3-(3-Fluorophenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4g**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.35 (td, *J* = 8.1, 5.9 Hz, 1 H), 7.25–7.20 (m, 4 H), 7.04–6.94 (m, 4 H), 6.05 (dd, *J* = 6.8, 4.0 Hz, 1 H), 4.90 (t, *J* = 7.4 Hz, 1 H), 2.99–2.91 (m, 1 H), 2.33 (ddd, *J* =13.2, 7.4, 4.0 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 163.4 (d, *J* = 247.1 Hz), 150.6, 142.6 (d, *J* = 7.2 Hz), 130.7 (d, *J* = 8.3 Hz), 128.9, 122.6, 122.2 (d, *J* = 2.8 Hz), 115.2 (d, *J* = 21.6 Hz), 115.1, 113.7 (d, *J* = 22.7 Hz), 80.2 (q, *J* = 2.5 Hz), 67.4 (d, *J* =2.1 Hz), 46.0. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.4. FTIR [$\bar{\nu}$ (cm^{-1})]: 3070, 1593, 1488, 1451, 1256, 1109, 947, 787, 691. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{16}H_{13}F_4NOS$ 343.0654; found 343.0667. R_F: 0.15 (heptane/CH_2Cl_2, 17:3).

*2-Phenyl-3-(3-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4h**).* According to the general procedure, the reaction of nitrone **6h** (49 mg, 0.234 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4h** (46 mg, 0.136 mmol, 57%) as an off white solid and isoxazolidine *trans*-**4h** and regioisomers **7h** (26 mg, 0.077 mmol, 31%) as a yellow solid, after column chromatography (heptane/CH_2Cl_2, 17:3 →7:3). Total yield: 88%.

*rac-(3R,5R)-2-Phenyl-3-(3-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4h**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.31–7.28 (m, 1 H), 7.27–7.24 (m, 2 H), 7.22–7.17 (m, 2 H), 7.14–7.10 (m, 1 H), 7.02–6.94 (m, 3 H), 5.98 (dd, *J* = 8.1, 4.4 Hz, 1 H), 4.35 (dd, *J* = 9.0, 7.2 Hz, 1 H), 3.37 (dddq, *J* = 13.6, 9.0, 8.1, 0.9 Hz, 1 H), 2.38–2.32 (m, 1 H), 2.36 (s, 3 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.9, 139.7, 139.1, 130.2 (q, *J* = 307.7 Hz), 129.1, 129.1, 128.8, 127.6, 124.2, 123.6, 117.5, 80.5 (q, *J* = 2.2 Hz), 68.3, 47.2, 21.6. FTIR [$\bar{\nu}$ (cm^{-1})]: 3028, 1599, 1489, 1040, 1001, 839, 737, 724, 692. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{17}H_{16}F_3NOS$ 339.0905; found 339.0925. R_F: 0.41 (heptane/CH_2Cl_2, 4:1).

*rac-(3R,5S)-2-Phenyl-3-(3-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4h**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.31–7.18 (m, 5 H), 7.14–7.10 (m, 1 H), 7.03–6.98 (m, 2 H), 6.98–6.91 (m, 1 H), 6.06 (dd, *J* = 6.8, 3.7 Hz, 1 H), 4.85 (t, *J* = 7.3 Hz, 1 H), 2.95 (dddq, *J* = 13.2, 7.6, 6.8, 0.9 Hz, 1 H), 2.86 (ddd, *J* = 13.2, 7.3, 3.7 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 151.2, 139.9, 139.0, 130.0 (q, *J* = 307.8 Hz), 129.0, 128.9, 128.8, 127.1, 123.7, 122.3, 115.1, 82.4 (q, *J* = 2.1 Hz), 68.1, 46.4, 21.6. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3029, 1598, 1489, 1150, 1111, 1045, 785, 692. HRMS (EI) *m/z*: [$M^{+\bullet}$] calcd for $C_{17}H_{16}F_3NOS$ 339.0905; found 339.0931. R_F: 0.34 (heptane/CH_2Cl_2, 4:1).

*Methyl 3-{2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidin-3-yl}benzoate (**4i**).* According to the general procedure, the reaction of nitrone **6i** (26 mg, 0.102 mmol) and alkene **2** in a 1 mL PTFE high-pressure tube, containing approximately 150 µL of glass beads, afforded isoxazolidine *cis*-**4i** (17.3 mg, 0.045 mmol, 44%) as an off white solid and a mixture of isoxazolidines *cis*- and *trans*-**4i** and regioisomers **7i** (18.2 mg, 0.047 mmol, 47%) as a brown-yellow solid, after column chromatography (heptane/CH_2Cl_2, 3:2). Total yield: 91%.

*Methyl-3-{rac-(3R,5R)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidin-3-yl}benzoate (cis-**4i**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 8.11 (t, *J* = 1.8 Hz, 1 H), 8.01 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.76 (dddd, *J* = 7.7, 1.8, 1.2, 0.5 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 1 H), 7.24–7.19 (m, 2 H), 7.07–7.00 (m, 1 H), 6.98–6.94 (m, 2 H), 6.01 (dd, *J* = 8.0, 4.5 Hz, 1 H), 4.50 (dd, *J* = 8.9, 7.0 Hz, 1 H), 3.93 (s, 3 H), 3.43 (dddq, *J* = 13.6, 8.9, 8.0, 0.9 Hz, 1 H), 2.42–2.30 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 166.8, 148. 6, 140.4, 131.6, 131.1, 130.0 (q, *J* = 307.7 Hz), 129.6, 129.0, 128.3, 124.0, 117.6, 80.4 (q, *J* = 2.5 Hz), 67.9, 52.4, 46.9. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3015, 1729, 1598, 1489, 1301, 1247, 1114, 1025, 786, 692, 674. HRMS (EI) *m/z*:

[M$^{+\bullet}$] calcd for $C_{18}H_{16}F_3NO_3S$ 383.0803; found 383.0824. R_F: 0.27 (heptane/CH_2Cl_2, 3:2).

*Methyl-3-{rac-(3R,5S)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidin-3-yl}benzoate (trans-**4i**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 8.12 (t, *J* = 1.8 Hz, 1 H), 8.02–7.98 (m, 1 H), 7.69 (dt, *J* = 7.8, 1.6 Hz, 1 H), 7.47 (t, *J* = 7.7, 1 H), 7.26–7.18 (m, 2 H), 7.00–6.98 (m, 2 H), 6.97–6.94 (m, 1 H), 6.06 (dd, *J* = 6.7, 4.0 Hz, 1 H), 4.96 (t, *J* = 7.3 Hz, 1 H), 3.93 (s, 3 H), 3.01–2.94 (m, 1 H), 2.91 (ddd, *J* = 13.3, 7.4, 4.0 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 166.8, 150.7, 140.5, 131.19, 131.14, 130.0 (q, *J* = 307.9 Hz), 129.57, 129.55, 128.9, 127.8, 122.6, 115.2, 82.3 (q, *J* = 2.2 Hz), 67.6, 52.4, 46.1. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –39.4. FTIR [$\bar{\nu}$ (cm^{-1})]: 3064, 1720, 1598, 1489, 1285, 1107, 1020, 799, 751, 692. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{18}H_{16}F_3NO_3S$ 383.0803; found 383.0810. R_F: 0.22 (heptane/CH_2Cl_2, 3:2).

*3-(3-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4j**).* According to the general procedure, the reaction of nitrone **6j** (50 mg, 0.190 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube, containing approximately 300 µL of glass beads, afforded isoxazolidine *cis*-**4j** (33.8 mg, 0.095 mmol, 53%) as a white solid, a mixture of isoxazolidines *cis*- and *trans*-**4j** (3 mg, 0.0084 mmol, 5%) as a yellow oil and isoxazolidines *trans*-**4j** and **7j** (18.2 mg, 0.051 mmol, 22%) as a yellow oil, after column chromatography (heptane/CH_2Cl_2, 7:3). Total yield: 80%.

*rac-(3R,5R)-3-(3-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4j**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.29 (t, *J* = 7.9 Hz, 1 H), 7.24–7.17 (m, 2 H), 7.09–6.95 (m, 5 H), 6.85 (ddd, *J* = 8.3, 2.7, 1.1 Hz, 1 H), 5.99 (dd, *J* = 8.1, 4.3 Hz, 1 H), 4.37 (dd, *J* = 9.1, 7.0 Hz, 1 H), 3.81 (s, 3 H), 3.43–3.32 (m, 1 H), 2.36 (ddd, *J* = 13.7, 7.0, 4.3 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 160.4, 148.9, 141.6, 130.3, 130.2 (q, *J* = 307.7 Hz), 128.8, 123.6, 119.3, 117.3, 113.8, 112.4, 80.5 (q, *J* = 2.5 Hz), 68.0, 55.4, 47.2 (q, *J* = 1.2 Hz). ^{19}F NMR [377 MHz, δ (ppm), $CDCl_3$]: –39.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3006, 2838, 1599, 1490, 1117, 757, 694. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{17}H_{16}F_3NO_2S$ 355.0854; found 355.0868. R_F: 0.16 (heptane/CH_2Cl_2, 7:3).

*rac-(3R,5S)-3-(3-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4j**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.29 (t, *J* = 8.1 Hz, 1 H), 7.25–7.19 (m, 2 H), 7.07–6.92 (m, 5 H), 6.89–6.81 (m, 1 H), 6.06 (dd, *J* = 6.8, 3.8, 1 H), 4.86 (t, *J* = 7.4 Hz, 1 H), 3.81 (s, 3 H), 2.96 (dddq, *J* = 13.3, 7.6, 6.8, 0.9 Hz, 1 H), 2.87 (ddd, *J* = 13.3, 7.3, 3.8 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 160.3, 151.0, 141.6, 130.2, 130.0 (q, *J* = 307.8 Hz), 128.8, 122.3, 118.8, 115.1, 113.7, 112.0, 82.3 (q, *J* = 2.3 Hz), 68.0, 55.5, 46.3. ^{19}F NMR [377 MHz, δ (ppm), $CDCl_3$]: –39.3. FTIR [$\bar{\nu}$ (cm^{-1})]: 3064, 1720, 1598, 1489, 1347, 1107, 1020, 799, 750, 692. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{17}F_3NO_2S$ 356.0932; found 356.0939. R_F: 0.13 (heptane/CH_2Cl_2, 7:3).

*2-Phenyl-3-[3-(trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4k**).* According to the general procedure, the reaction of nitrone **6k** (49 mg, 0.234 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded a mixture of isoxazolidines *cis*- and *trans*-**4k** and **7k** (87.4 mg, 0.222 mmol, 95%) as a white-yellow solid, after column chromatography (heptane/CH_2Cl_2, 17:3 → 7:3). FTIR [$\bar{\nu}$ (cm^{-1})]: 2927, 1598, 1490, 1263, 1144, 1045. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{17}H_{13}F_6NOS$ 393.0622; found 393.0639. R_F: 0.38 (heptane/CH_2Cl_2, 4:1). Total yield: 95%.

*rac-(3R,5R)-2-Phenyl-3-[3-(trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4k**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.73–7.69 (m, 2 H), 7.60–7.56 (m, 1 H), 7.54–7.48 (m, 1 H), 7.26–7.20 (m, 2 H), 7.05–7.00 (m, 1 H), 6.98–6.93 (m, 2 H), 5.99 (dd, *J* = 8.0, 4.5 Hz, 1 H), 4.51 (dd, *J* = 9.0, 6.7 Hz, 1 H), 3.41 (dddq, *J* = 13.6, 9.0, 8.0, 0.8 Hz, 1 H), 2.37–2.28 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.6, 141.1, 131.6 (q, *J* = 32.4 Hz), 130.4 (q, *J* = 1.2 Hz), 129.9 (q, *J* = 308.0 Hz), 129.9, 129.0, 125.2 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.4 Hz), 124.1, 123.9 (q, *J* = 3.8 Hz), 117.4, 80.4 (q, *J* = 2.5 Hz), 67.8, 46.8.

*rac-(3R,5S)-2-Phenyl-3-[3-(trifluoromethyl)phenyl]-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4k**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.73–7.70 (m, 1 H), 7.68–7.64 (m, 1 H), 7.60–7.56 (m, 1 H), 7.53–7.48 (m, 1 H), 7.26–7.20 (m, 2 H), 6.92–6.88 (m, 3 H), 6.06–6.02 (m, 1 H), 4.96 (t, *J* = 7.2 Hz, 1 H), 2.98–2.86 (m, 2 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 150.6, 141.1, 131.6 (q, *J* = 32.4 Hz), 130.4 (q, *J* = 1.2 Hz), 129.7, 128.9, 125.1 (q, *J* = 4.0 Hz), 123.5 (q, *J* = 3.8 Hz), 122.7, 115.2, 82.3 (q, *J* = 2.4 Hz), 67.5, 46.0.

*2-Phenyl-3-(2-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4l**).* According to the general procedure, the reaction of nitrone **6l** (49 mg, 0.234 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4l** (1.9 mg, 0.0056 mmol; used for characterization) as a colorless oil and a mixture of isoxazolidines *cis*- and *trans*-**4l** (79.5 mg, 0.234 mmol, 99%) as a yellow solid, after column chromatography (heptane/CH_2Cl_2, 4:1). FTIR [$\bar{\nu}$ (cm^{-1})]: 3025, 1596, 1489, 1258, 1109, 1041, 972, 754, 695. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{17}H_{16}F_3NOS$ 339.0905; found 339.0923. R_F: 0.23 (heptane/CH_2Cl_2, 4:1). Total yield: 99%.

*rac-(3R,5R)-2-Phenyl-3-(2-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4l**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.72 (dd, *J* = 7.2, 1.7 Hz, 1 H), 7.26–7.17 (m, 5 H), 7.00 (tt, *J* = 7.4, 1.2 Hz, 1 H), 6.96–6.88 (m, 2 H), 6.01 (dd, *J* = 8.1, 4.2 Hz, 1 H), 4.61 (dd, *J* = 9.1, 7.1 Hz, 1 H), 3.44 (dddq, *J* = 13.5, 9.1, 8.1, 0.9 Hz, 1 H), 2.35 (s, 3 H), 2.25 (ddd, *J* = 13.5, 7.1, 4.2 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.9, 138.0, 134.6, 130.8, 130.1 (q, *J* = 307.4 Hz), 128.9, 127.8, 127.3, 126.6, 123.5, 117.2, 80.5 (q, *J* = 2.2 Hz), 64.5, 45.6, 19.7. ^{19}F NMR [471 MHz, δ (ppm), $CDCl_3$]: –40.0.

*rac-(3R,5S)-2-Phenyl-3-(2-tolyl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4l**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.65–7.62 (m, 1 H), 7.27–7.15 (m, 5 H), 6.97–6.93 (m, 3 H), 6.06 (dd, *J* = 6.7, 3.9 Hz, 1 H), 5.04 (t, *J* = 7.5 Hz, 1 H), 2.89 (ddd, *J* = 13.1, 7.5, 3.9 Hz, 1 H), 2.80 (dddq, *J* = 13.1, 7.5, 6.7, 0.9 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 151.1, 137.8, 134.3, 130.8, 128.7, 127.8, 127.0, 126.2, 122.1, 114.7, 82.2 (q, *J* = 2.3 Hz), 65.3, 44.6, 19.4.

*3-(2-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4m**).* According to the general procedure, the reaction of nitrone **6m** (53 mg, 0.234 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4m** (35.6 mg, 0.100 mmol, 43%) as an off white solid and a mixture of isoxazolidines *cis*- and *trans*-**4m** (29.6 mg, 0.083 mmol, 28%) as a yellow solid, after column chromatography (heptane/CH_2Cl_2, 7:3). Total yield: 71%.

*rac-(3R,5R)-3-(2-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4m**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.65 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.28 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1 H), 7.25–7.19 (m, 2 H), 7.01–6.94 (m, 4 H), 6.91 (dd, *J* = 8.3, 1.0 Hz, 1 H), 5.94 (dd, *J* = 8.0, 4.5 Hz, 1 H), 4.87 (dd, *J* = 9.1, 6.1 Hz, 1 H), 3.86 (s, 3 H), 3.40 (dddq, *J* = 13.6, 9.1, 8.0, 0.9 Hz, 1 H), 2.30–2.20 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 156.3, 149.4, 130.3 (q, *J* = 307.7 Hz), 128.9, 128.4, 127.5, 123.1, 121.3, 116.7, 110.5, 80.6 (q, *J* = 2.4 Hz), 62.1, 55.5, 45.0. FTIR [$\bar{\nu}$ (cm^{-1})]: 3075, 1599, 1490, 1243, 1106, 1027, 897, 751, 664. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{17}H_{16}F_3NO_2S$ 355.0854; found 355.0875. R_F: 0.19 (heptane/CH_2Cl_2, 7:3).

*rac-(3R,5S)-3-(2-Methoxyphenyl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4m**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.59 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.31–7.26 (m, 2 H), 7.06–7.02 (m, 2 H), 7.00–6.88 (m, 4 H), 5.99–5.96 (m, 1 H), 5.26 (dd, *J* = 7.5, 5.8 Hz, 1 H), 3.88 (s, 3 H), 2.90 (ddd, *J* = 12.7, 7.5, 5.0 Hz, 1 H), 2.84–2.76 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 156.3, 151.2, 128.9, 128.8, 128.1, 127.2, 122.0, 121.1, 114.9, 110.4, 82.4 (q, *J* = 2.2 Hz), 62.9, 55.5, 43.7. The carbon signal of SCF_3 was not observed. FTIR [$\bar{\nu}$ (cm^{-1})]: 2839, 1599, 1490, 1256, 1106, 1026, 751, 692. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{17}H_{16}F_3NO_2S$ 355.0854; found 355.0862. R_F: 0.15 (heptane/CH_2Cl_2, 7:3).

*2-Phenyl-3-(thiophen-3-yl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4n**).* According to the general procedure, the reaction of nitrone **6n** (48 mg, 0.234 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded a mixture of isoxazolidines *cis*- and *trans*-**4n** (68.4 mg, 0.206 mmol, 88%) as a yellow solid, after column chromatography (heptane/CH_2Cl_2, 3:2). FTIR [$\bar{\nu}$ (cm^{-1})]: 3095, 1598, 1489, 1257, 1163, 1110, 1031, 837, 792, 754, 692. HRMS (EI) *m/z*: [M$^{+\bullet}$] calcd for $C_{14}H_{12}F_3NOS_2$ 331.0312; found 331.0330. R_F: 0.19 (heptane/CH_2Cl_2, 17:3). Total yield: 88%.

*rac-(3R,5R)-2-Phenyl-3-(thiophen-3-yl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4n**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.36 (dd, *J* = 5.0, 3.0 Hz, 1 H), 7.30–7.27 (m, 1 H), 7.25–7.20 (m, 2 H), 7.19 (dd, *J* = 5.0, 1.3 Hz, 1 H), 7.02 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.00–6.96 (m, 2 H), 6.00 (dd, *J* = 8.2, 4.2 Hz, 1 H), 4.51 (dd, *J* = 8.8, 6.7 Hz, 1 H), 3.36–3.28 (m, 1 H), 2.38 (ddd, *J* = 13.6, 6.7, 4.2 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.9, 140.4, 130.2 (q, *J* = 307.7 Hz), 128.8, 127.3, 126.1, 123.9, 122.7, 117.5, 80.5 (q, *J* = 2.5 Hz), 64.6, 45.9.

*rac-(3R,5S)-2-Phenyl-3-(thiophen-3-yl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4n**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.32 (dd, *J* = 5.0, 3.0 Hz, 1 H), 7.30–7.27 (m, 1 H), 7.26–7.20 (m, 2 H), 7.09 (dd, *J* = 5.0, 1.4 Hz, 1 H), 7.06–6.95 (m, 3 H), 6.03 (dd, *J* = 7.2, 4.9 Hz, 1 H), 5.01 (t, *J* = 6.5 Hz, 1 H), 2.96 (dt, *J* = 13.0, 6.4 Hz, 1 H), 2.78 (ddd, *J* = 12.7, 7.3, 4.7 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 150.2, 140.6, 130.2 (q, *J* = 307.7 Hz), 128.8, 127.0, 125.8, 122.7, 122.4, 115.7, 81.9 (q, *J* = 2.2 Hz), 64.2, 44.6.

*3-(1H-Indol-2-yl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4o**).* According to the general procedure, the reaction of nitrone **6o** (56 mg, 0.237 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded isoxazolidines *cis*- and *trans*-**4o** (20.3 mg, 0.056 mmol, 24%; contaminated with **8**) as an brown-yellow oil and a mixture of isoxazolidine *trans*-**4o** and regioisomers **7o** (35.6 mg, 0.098 mmol, 41%) as a brown oil, after column chromatography (heptane/CH_2Cl_2, 11:9). FTIR [$\bar{\nu}$ (cm^{-1})] of isoxazolidines *cis*- and *trans*-**4o**: 3413, 3060, 2962, 1599, 1436, 1258, 1110, 1022, 788, 756, 684, 660. FTIR [$\bar{\nu}$ (cm^{-1})] of isoxazolidine *trans*-**4o** and regioisomers **7o**: 3406, 3059, 2963, 1597, 1455, 1231, 1107, 1014, 793, 693. Total yield: 65%.

*rac-(3R,5R)-3-(1H-Indol-2-yl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4o**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 8.67 (bs, 1 H), 7.61–7.58 (m, 1 H), 7.40–7.37 (m, 1 H), 7.25–7.18 (m, 3 H), 7.15–7.12 (m, 1 H), 7.05–7.02 (m, 3 H), 6.50 (d, *J* = 2.0 Hz, 1 H), 6.07 (dd, *J* = 8.3, 3.5 Hz, 1 H), 4.77 (dd, *J* = 9.4, 5.6 Hz, 1 H), 3.44–3.32 (m, 1 H), 2.50 (ddd, *J* = 13.8, 5.6, 3.5 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.6, 136.2, 135.6, 130.0 (q, *J* = 306.8 Hz), 129.1, 128.6, 123.9, 122.6, 120.6, 120.4, 116.7, 111.5, 100.9, 80.7 (q, *J* = 2.4 Hz), 62.2, 44.9. R_F: 0.51 (heptane/CH_2Cl_2, 1:1).

*rac-(3R,5S)-3-(1H-Indol-2-yl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4o**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 8.50 (bs, 1 H), 7.57–7.47 (m, 3 H), 7.32 (dt, *J* = 8.2, 0.9 Hz, 1 H), 7.06–7.03 (m, 1 H), 6.98–6.90 (m, 2 H), 6.86–6.82 (m, 2 H), 6.40 (d, *J* = 2.1 Hz, 1 H), 5.84 (dd, *J* = 8.3, 4.0 Hz, 1 H), 4.28 (dd, *J* = 9.4, 5.7 Hz, 1 H), 2.82 (dt, *J* = 13.7, 8.9 Hz, 1 H), 2.16–2.09 (m, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 148.5, 134.4, 132.7, 129.0, 128.6, 122.6, 122.5, 120.6, 119.5, 116.2, 111.3, 100.5, 82.1 (q, *J* = 2.4 Hz), 59.8, 44.6. R_F: 0.42 (heptane/CH_2Cl_2, 1:1).

*3-(1H-Indol-2-yl)-2-phenyl-4-[(trifluoromethyl)sulfanyl]isoxazolidine (**7o**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.64–7.59 (m, 2 H), 7.38–6.97 (m, 16 H), 6.59–6.55 (m, 2 H), 5.25 (d, *J* = 8.2 Hz, 1 H), 4.94 (d, *J* = 4.4 Hz, 1 H), 4.67–4.61 (m, 1 H), 4.61–4.56 (m, 1 H), 4.31 (q, *J* = 7.6 Hz, 1 H), 4.25–4.18 (m, 2 H), 4.11 (dd, *J* = 9.3, 6.2 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 149.3, 148.9, 135.9, 135.7, 135.5, 132.8, 129.2, 129.2, 128.5, 127.9, 123.4, 123.2, 122.7, 122.5, 120.8, 120.6, 120.3, 115.1, 115.0, 111.3, 111.2, 103.1, 100.6, 73.2, 72.7, 70.1, 65.6, 52.4, 48.1.

*2-Phenyl-3-(1H-pyrrol-2-yl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4p**).* According to the general procedure, the reaction of nitrone **6p** (44 mg, 0.234 mmol) and alkene **2** in a 1.5 mL PTFE high-pressure tube afforded a mixture of isoxazolidines *cis*- and *trans*-**4p** and **7p** (33 mg, 0.105 mmol, 45%) as a brown oil, after column chromatography (heptane/CH_2Cl_2, 4:1 → CH_2Cl_2/MeOH, 10:1). FTIR [$\bar{\nu}$ (cm^{-1})]: 3421, 2960, 1597, 1489, 1154, 1109, 1082, 1029, 756, 722. HRMS (EI) *m*/*z*: [$M^{+\bullet}$] calcd for $C_{14}H_{13}F_3N_2OS$ 314.0701; found 314.0706. R_F (unassigned mixture): 0.46, 0.30, 0.24, 0.20 (heptane/CH_2Cl_2, 1:1). Total yield: 45%.

*rac-(3R,5R)-2-Phenyl-3-(1H-pyrrol-2-yl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4p**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.65 (bs, 1 H), 7.28–7.22 (m, 2 H), 7.08–6.98 (m, 3 H), 6.81–6.77 (m, 1 H), 6.21–6.18 (m, 1 H), 6.15–6.12 (m, 1 H), 6.03 (dd, *J* = 8.3, 3.6 Hz, 1 H), 4.62 (dd, *J* = 8.9, 5.6 Hz, 1 H), 3.34–3.17 (m, 1 H), 2.48–2.36 (m, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: δ 148.9, 130.0 (q, *J* = 307.9 Hz), 129.0, 128.8, 123.8, 116.8, 115.2, 109.1, 106.7, 80.7 (q, *J* = 2.3 Hz), 62.5, 44.6.

*rac-(3R,5S)-2-Phenyl-3-(1H-pyrrol-2-yl)-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4p**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 8.57 (bs, 1 H), 7.31–6.66 (m, 7 H), 6.27–6.15 (m, 1 H), 5.97 (t, *J* = 6.4 Hz, 1 H), 5.07 (dd, *J* = 7.0, 4.4 Hz, 1 H), 3.00 (ddd, *J* = 12.2, 7.1, 4.4 Hz, 1 H), 2.68 (dt, *J* = 13.1, 6.4 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 150.0, 129.9, 128.9, 123.8, 118.0, 115.8, 107.2, 106.3, 82.1, 62.7, 43.2. The carbon signal of SCF_3 was not observed.

*2-Phenyl-3-(1H-pyrrol-2-yl)-4-[(trifluoromethyl)sulfanyl]isoxazolidine (**7p**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.65 (bs, 1 H), 7.30–7.23 (m, 2 H), 7.06–6.99 (m, 3 H), 6.81–6.77 (m, 1 H), 6.27–6.19 (m, 1 H), 6.19 (m, 1 H), 5.11 (d, *J* = 7.8 Hz, 1 H), 4.66–4.55 (m, 1 H), 4.22 (q, *J* = 7.5 Hz, 1 H), 4.15 (dd, *J* = 8.6, 6.8 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 149.2, 129.3, 126.0, 123.4, 118.8, 115.2, 109.0, 108.8, 73.5, 65.3, 48.7 (q, *J* = 1.3 Hz). The carbon signal of SCF_3 was not observed.

*2-Phenyl-3-(1H-pyrrol-2-yl)-4-[(trifluoromethyl)sulfanyl]isoxazolidine (**7p**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 8.57 (bs, 1 H), 7.31–6.66 (m, 7 H), 6.27–6.15 (m, 1 H), 4.82 (d, *J* = 4.2 Hz, 1 H), 4.65–4.50 (m, 2 H), 4.26–4.10 (m, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 149.6, 129.4, 126.0, 124.1, 118.1, 115.2, 109.1, 108.7, 70.3, 65.3, 48.7. The carbon signal of SCF_3 was not observed.

*3-(Furan-2-yl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (**4q**).* According to the general procedure, the reaction of nitrone **6q** (44 mg, 0.234 mmol) in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4q** (33.2 mg, 0.105 mmol, 45%) as an off white solid and isoxazolidines *trans*-**4q** and **7q** (24.7 mg, 0.078 mmol, 34%) as a yellow oil, after column chromatography (heptane/CH_2Cl_2, 23:2 →heptane/CH_2Cl_2, 0:1). Total yield: 79%.

*rac-(3R,5R)-3-(Furan-2-yl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (cis-**4q**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.45 (dd, *J* = 1.8, 0.9 Hz, 1 H), 7.31–7.22 (m, 2 H), 7.10–6.98 (m, 3 H), 6.37 (dd, *J* = 3.2, 1.8 Hz, 1 H), 6.35 (d, *J* = 3.2 Hz, 1 H), 6.00 (dd, *J* = 8.1, 4.5 Hz, 1 H), 4.50 (dd, *J* = 8.8, 6.5 Hz, 1 H), 3.23 (dddq, *J* = 13.5, 8.8, 8.1, 0.9 Hz, 1 H), 2.63 (ddd, *J* = 13.5, 6.5, 4.5 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 151.0, 148.7, 143.0, 130.2 (q, *J* = 307.7 Hz), 128.9, 124.2, 117.5, 110.8, 109.0, 80.5 (q, *J* = 2.6 Hz), 63.0, 42.4 (q, *J* = 1.2 Hz). FTIR [$\bar{\nu}$ (cm^{-1})]: 2922, 1489, 1453, 1254, 1106, 1037, 936, 743, 680. HRMS (EI) *m*/*z*: [$M^{+\bullet}$] calcd for $C_{14}H_{12}F_3NO_2S$ 315.0541; found 315.0538. R_F: 0.48 (heptane/CH_2Cl_2, 7:3).

*rac-(3R,5S)-3-(Furan-2-yl)-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine (trans-**4q**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.37 (dd, *J* = 1.8, 0.9 Hz, 1 H), 7.27–7.22 (m, 2 H), 7.09–7.05 (m, 2 H), 6.98 (tt, *J* = 7.3, 1.2 Hz, 1 H), 6.30 (dd, *J* = 3.3, 1.8 Hz, 1 H), 6.26 (dt, *J* = 3.3, 0.8, 1 H), 6.11 (dd, *J* = 7.4, 5.2 Hz, 1 H), 5.00 (dd, *J* = 7.7, 4.3, 1 H), 3.17 (dddq, *J* = 13.7, 7.4, 4.3, 0.8, 1 H), 2.77–2.67 (m, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 151.6, 149.2, 142.8, 130.0 (q, *J* = 307.7 Hz), 128.8, 123.0, 116.2, 110.6, 108.4, 81.8 (q, *J* = 2.5 Hz), 61.6, 41.6 (q, *J* = 1.2 Hz). FTIR [$\bar{\nu}$ (cm^{-1})]: 2872, 1599, 1490, 1262, 1118, 1046, 757, 694. HRMS (EI) *m*/*z*: [$M^{+\bullet}$] calcd for $C_{14}H_{12}F_3NO_2S$ 315.0541; found 315.0545. R_F: 0.39 (heptane/CH_2Cl_2, 7:3).

*N-Benzyl-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine-3-carboxamide (**4r**).* According to the general procedure, the reaction of nitrone **6r** (25 mg, 0.098 mmol) and alkene **2** in a 1 mL PTFE high-pressure tube afforded isoxazolidine *cis*-**4r** (3.2 mg, 0.0084 mmol, 9%; used for NMR characterization) as a white solid and a mixture of isoxazolidines *cis*- and *trans*-**4r** (16.1 mg, 0.042 mmol, 51%) as a yellow-white solid, after column chromatography (heptane/CH_2Cl_2, 17:3 → CH_2Cl_2/MeOH, 24:1). FTIR [$\bar{\nu}$ (cm^{-1})]: 3385, 3309 2930, 1668, 1597, 1454, 1161, 1029, 697. HRMS (EI) *m*/*z*: [$M^{+\bullet}$] calcd for $C_{18}H_{17}F_3N_2O_2S$ 382.0963; found 382.0964. Total yield: 60%.

*rac-(3R,5R)-N-Benzyl-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine-3-carboxamide (cis-**4r**).* ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.59–7.52 (m, 1 H), 7.37–7.27 (m, 7 H), 7.11–7.03 (m, 1 H), 7.02–6.97 (m, 2 H), 5.88 (dd, *J* = 8.1, 4.7 Hz, 1 H), 4.56 (dd, *J* = 14.8, 6.1 Hz, 1 H), 4.49 (dd, *J* = 14.8, 5.9 Hz, 1 H), 4.31 (dd, *J* = 9.6, 3.5 Hz, 1 H), 3.19–3.07 (m, 1 H), 2.75–2.65 (m, 1 H). ^{13}C NMR [101 MHz, δ (ppm), $CDCl_3$]: 169.7, 148.8, 137.6, 129.6 (q, *J* = 308.1 Hz), 129.5, 128.9, 127.9, 127.8, 123.9, 115.1, 80.3 (q, *J* = 2.5 Hz), 67.6, 43.7, 39.4.

*rac-(3R,5S)-N-Benzyl-2-phenyl-5-[(trifluoromethyl)sulfanyl]isoxazolidine-3-carboxamide (trans-**4r**).* ^{1}H NMR [500 MHz, δ (ppm), $CDCl_3$]: 7.52–7.43 (m, 1 H), 7.36–7.23 (m, 7 H), 7.11–7.02 (m, 3 H), 5.91 (t, *J* = 6.8 Hz, 1 H), 4.54–4.49 (m, 2 H), 4.46 (dd, *J* = 15.0, 5.6 Hz, 1 H), 3.29 (ddd, *J* = 13.5, 7.3, 3.9 Hz, 1 H), 2.62 (ddd, *J* = 13.9, 8.1, 6.2 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), $CDCl_3$]: 169.1, 149.4, 137.6, 129.6 (q, *J* = 308.1 Hz), 129.0, 128.8, 127.7, 127.6, 123.6, 115.1, 82.3 (q, *J* = 2.5 Hz), 67.1, 43.5, 39.0.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed optimization reaction conditions, ^{1}H NMR, ^{13}C NMR spectra (PDF), computational details, ASA and EDA of **6m** and **6p** and Cartesian coordinates.

AUTHOR INFORMATION

Corresponding Author

*E-mail: f.m.bickelhaupt@vu.nl
*E-mail: floris.rutjes@ru.nl

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work has been supported by the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012-316379) and NWO via the Planetary and Exo- Planetary Science program (PEPSci) and the Dutch Astrochemistry Network (DAN). We thank Dr. Paul B. White for his help in the assignment of the diastereo- and regioisomers.

REFERENCES

(1) (a) Xu, X. H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731–764. (b) Liu, J.; Chu, L.; Qing, F. L. *Org. Lett.* **2013**, *15*, 894–897. (c) Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782–8785. (d) Zhang, C. P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183–185. (e) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Xikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207–1216.
(2) Aswapokee. N.; Neu. H. C. *Antimicrob. Agents Chemother.* **1979**, *15*, 444–446.
(3) Pommier, P.; Keita, A.; Wessel-Robert, S.; Dellac, B.; Mundt, H. C. *Rev. Med. Vet.* **2003**, *154*, 41.
(4) Yagupolskii. L. M.; Maletina. I. I.; Petko. K. I.; Fedyuk. D. V.; Handrock. R.; Shavaran. S. S.; Klebanov. B. M.; Herzig. S. *J. Fluorine Chem.* **2001**, *109*, 87–94.
(5) (a) Jiang, L.; Qian, J.; Yi, W.; Lu, G.; Cai, C.; Zhang, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 14965–14969. (b) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460. (c) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1548–1552. (d) Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782–8785. (e) Zhang, C. P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183–185. (f) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 7312–7314.
(6) (a) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754–757. (b) Pooput, C.; Dolbier, W. R., Jr.; Médebielle, M. *J. Org. Chem.* **2006**, *71*, 3564–3568. (c) Pooput, C.; Médebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2004**, *6*, 301–303. (d) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65–68.
(7) Harris, J. F. Jr. *J. Org. Chem.* **1967**, *32*, 2063–2074.
(8) Haas, A.; Hinsken, W. *J. Fluorine Chem.* **1985**, *28*, 303–317.
(9) For examples of 1,3-dipolar cycloaddition reactions between alkenes and nitrones, see: (a) Chakraborty, B.; Luitel, G. P. *Tetrahedron Lett.* **2013**, *54*, 765–770. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449–1458. (c) Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845–3853.
(10) (a) Blanco-Ania. D.; Aben. R. W. M.; van Berkom. L. W. A.; Scheeren. H. W.; Rutjes. F. P. J. T. *Eur. J. Org. Chem.* **2017**, 3729–3737. (b) Blanco-Ania. D.; Aben. R. W. M.; van Berkom. L. W. A.; Scheeren. H. W.; Rutjes. F. P. J. T. *Eur. J. Org. Chem.* **2014**, 1438–1444. (c) Matsumoto, K.; Hamana H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033–2234. (d) Jenner, G. *Tetrahedron* **2002**, *58*, 5185–5202.
(11) Becker, A. R.; Sternson, L. A. *PNAS* **1981**, *78*, 2003–2007.
(12) Penoni A.; Volkmann, J.; Nicholas, K. M. *Org. Lett.* **2002**, *4*, 699–701.
(13) It is important to note that the assignment of the *cis*- and *trans*-diastereoisomers of **7** could not be clarified by NMR studies.
(14) (a) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098–3100. (b) Perdew, J. P. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1986**, *33*, 8822–8824. (c) Lenthe, E. V.; Baerends, E. J. *J. Comput. Chem.* **2003**, *24*, 1142–1156.
(15) (a) te Velde, G.; Bickelhaupt, F. M.; Baerends, E. J.; Fonseca Guerra, C.; van Gisbergen, S. J. A.; Snijders, J. G.; Ziegler, T. *J. Comp. Chem.* **2001**, *22*, 931–967. (b) Fonseca Guerra, C.; Snijders, J. G.;te Velde, G.; Baerends, E. J. *Theor. Chem. Acc.* **1998**, *99*, 391–403.
(16) (a) Pye, C. C.; Ziegler, T. *Theor. Chem. Acc.* **1999**, *101*, 396–408. (b) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799–805. (c) Klamt, A. *J. Phys. Chem.* **1995**, *99*, 2224–2235. (d) Klamt, A, Jonas, V. *J. Chem. Phys.* **1996**, *105*, 9972–9981.
(17) (a) Bickelhaupt, F. M.; Houk, K. N. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070–10086. (b) Wolters, L. P.; Bickelhaupt, F. M. *WIRES Comput. Mol. Sci.* **2015**, *5*, 324–343; (c) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114–128.
(18) (a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187–10198. (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647.
(19) Bickelhaupt, F. M.; Baerends, E. J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 2000; Vol. 15, pp 1–86.
(20) Ung, S.; Falguières, A.; Guy, A.; Ferroud, C. *Tetrahedron Lett.* **2005**, *46*, 5913–5917.
(21) Wheeler, O. H.; Gore, P. H.; *J. Am. Chem. Soc.* **1956**, *78*, 3363–3366.
(22) Raunak; Kumar, V.; Mukherjee, S.; Poonam; Prasad, A. K.; Olsen, C. E.; Schaeffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W.; Parmar, V. S. *Tetrahedron* **2005**, *61*, 5687–5697.
(23) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411–2413.
(24) Ito, S.; Kubota, Y.; Asami, M. *Tetrahedron Lett.* **2014**, *55*, 4930–4932.
(25) Xie, L.; Bai, H.; Li, J.; Yu, X.; Zhang, Z.; Fu, B. *Tetrahedron* **2017**, *73*, 2923–2930.
(26) Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D. K. B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2016**, *138*, 6412–6415.
(27) Dooley, B. M.; Bowles, S. E.; Storr, T.; Frank. N. L. *Org. Lett.* **2007**, *9*, 4781–4783.
(28) Andrade, M. M.; Barros, M. T.; Pinto, R. C. *Tetrahedron* **2008**, *64*, 10521–10530.