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Trifluoromethyl Vinyl Sulfide: A Building Block for the Synthesis of CF$_3$S-Containing Isoxazolidines

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Supporting Information

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)sulfonyl group (SCF$_3$) represents a privileged substituent in agrochemicals and pharmaceuticals because of the strong electron-withdrawing effect and the large Hansch lipophilicity parameter ($

\pi = 1.44$). Cefazaflur, a first-generation cephalosporin antibiotic, toltrazuril, an antiprotozoal agent, and a losartan analogue, developed as a potential hypotensive agent, are prominent examples of biologically active compounds bearing the SCF$_3$ group (Figure 1).

Figure 1. Bioactive heterocycles containing the SCF$_3$ group.

Hence, CF$_3$S-containing compounds are considered appealing targets in the agrochemical and pharmaceutical fields, and consequently, modern research has focused on efficient (trifluoromethyl)sulfonylation methods. The main strategies that have been developed to synthesize CF$_3$S-containing compounds have focused on direct C−S bond formation and trifluoromethylation of sulfur-containing compounds. However, incorporation via simple CF$_3$S-containing building blocks is still unprecedented so that the use of a CF$_3$S-containing reagent could be an alternative strategy to construct CF$_3$S-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$_3$S-cyclohexene, and two cyclopropanation examples with organomercury reagents to yield CF$_3$S-substituted cyclopropanes.

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 to synthesize a novel group of isoxazolidines (Scheme 1).

RESULTS AND DISCUSSION

We commenced our investigations by forming alkene 2 in situ. Because of its high volatility, 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$_3$N, DBU, KO$_2$Bu, KOH and KOTMS) in the presence of various deuterated solvents (CD$_2$Cl$_2$, THF-$d_8$, CD$_3$OD and DMF-$d_7$) to eventually choose...
a solution of KO'Bu in THF-d₈ 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 parafomaldehyde as precursors for the in situ synthesis of the dipole (Table 1). The nitrone intermediates were synthesized in yields between 20 and 30% 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).

Azoxynbenzene11 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 3 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 18 nitrones (6a–r) with phenyl (containing both electron-donating and electron-withdrawing groups at the 2-, 3-, and 4-positions), heterocyclic and carbamoyl substituents in excellent yields (see the SI). We then 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).

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.

**Table 1. Synthesis of Isoxazolidines 3a–e**

<table>
<thead>
<tr>
<th>entry</th>
<th>compd</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>C₆H₄</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>3-FC₆H₄</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>3,5-FC₆H₄</td>
<td>22</td>
</tr>
<tr>
<td>4⁺</td>
<td>3d</td>
<td>C₆H₄CH₂</td>
<td>30</td>
</tr>
<tr>
<td>5⁺</td>
<td>3e</td>
<td>Cy</td>
<td>23</td>
</tr>
</tbody>
</table>

*Et₃N (1.0 equiv) was used.

**Table 2. Optimization Process for the 1,3-Dipolar Cycloaddition Reaction of Nitrones 6 with Alkene 2**

<table>
<thead>
<tr>
<th>entry</th>
<th>nitrone</th>
<th>R</th>
<th>2 (equiv)</th>
<th>T (°C)</th>
<th>scavenger</th>
<th>cis-4/trans-4</th>
<th>8° (%)</th>
<th>conv° (yield) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6c</td>
<td>4-MeC₆H₄</td>
<td>1.3</td>
<td>21</td>
<td></td>
<td>76:22</td>
<td>5</td>
<td>83 (41)⁺</td>
</tr>
<tr>
<td>2</td>
<td>6c</td>
<td>4-MeC₆H₄</td>
<td>3</td>
<td>21</td>
<td></td>
<td>79:21</td>
<td>22</td>
<td>93 (–)</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>4-MeC₆H₄</td>
<td>3</td>
<td>50</td>
<td></td>
<td>76:24</td>
<td>6</td>
<td>96 (85)⁺</td>
</tr>
<tr>
<td>4</td>
<td>6b</td>
<td>4-FC₆H₄</td>
<td>1.3</td>
<td>21</td>
<td></td>
<td>79:21</td>
<td>7</td>
<td>56 (35)⁺</td>
</tr>
<tr>
<td>5</td>
<td>6b</td>
<td>4-FC₆H₄</td>
<td>3</td>
<td>21</td>
<td></td>
<td>79:21</td>
<td>38</td>
<td>75 (–)</td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>4-FC₆H₄</td>
<td>3</td>
<td>50</td>
<td></td>
<td>77:23</td>
<td>17</td>
<td>91 (79)⁺</td>
</tr>
<tr>
<td>7</td>
<td>6b</td>
<td>4-FC₆H₄</td>
<td>3</td>
<td>50</td>
<td>galvinoxyl (3%)</td>
<td>76:24</td>
<td>0</td>
<td>100 (78)</td>
</tr>
<tr>
<td>8</td>
<td>6b</td>
<td>4-FC₆H₄</td>
<td>3</td>
<td>50</td>
<td>galvinoxyl (1%)</td>
<td>76:24</td>
<td>1</td>
<td>100 (–)</td>
</tr>
</tbody>
</table>

*Calculated by integration of the ¹H NMR signals of the crude mixtures. ⁺Isolated after column chromatography. †trans-Isomer contaminated with 7.
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 nonaromatic
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/
TZ2P14 level, using the ADF program.15 Tetrahydrofuran was
simulated using the COSMO solvation model.16 Thermochem-
ical corrections were computed using the temperature and
pressure under which the experiments were performed (see the
SI for computational details).

We focused on understanding the regioselectivity of the
cycloaddition between a simple model nitrone 9 with alkene 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
ΔΔG⧧ 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 regio-

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 ΔE(ζ) is decomposed along the
reaction coordinate ζ into the strain ΔEstrain(ζ) associated
with deforming the individual reactants plus the actual
interaction ΔEint(ζ) between the deformed reactants.

ΔE(ζ) = ΔEstrain(ζ) + ΔEint(ζ) (1)

The ΔEint(ζ) 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) model19 and is decomposed into three physically
meaningful terms:

ΔEint(ζ) = ΔVe-stat(ζ) + ΔEPauli(ζ) + ΔEoi(ζ) (2)

The ΔVe-stat(ζ) term corresponds to the classical electrostatic
interaction between unperturbed charge distributions,
ΔEPauli(ζ) is responsible for any steric repulsion, and the
ΔEoi(ζ) accounts for charge transfer (HOMO–LUMO
interactions) and polarization.

Applying the ASM along the reaction coordinate defined by
the bending of the 1,3-dipole, it is revealed that reactivity

### Table 3. Scope of the High-Pressure-Promoted 1,3-Dipolar Cycloaddition Reaction

| compd | Combined yield | cis-4o, 65% | cis-4p, 64% | 4c, 50% | dr 76:24 | 4d, 73% | dr 76:24 | 4e, 72% | cis-8f, 53% | dr 76:24 | 4g, 56% | cis-4g, 56% | dr 76:24 | 4h, 57% | cis-4h, 57% | dr 72:28 | 4i, 44% | cis-4i, 44% | dr 76:24 | 4j, 53% | cis-8j, 53% | dr 76:24 | 4k, 56% | cis-4k, 56% | dr 76:24 | 4l, 57% | cis-4l, 57% | dr 76:24 | 4m, 43% | cis-4m, 43% | dr 76:24 | 4n, 43% | cis-4n, 43% | dr 76:24 | 4o, 45% | cis-4o, 45% | dr 76:24 | 4p, 45% | cis-4p, 45% | dr 76:24 |
|-------|----------------|------------|------------|--------|----------|--------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|--------|------------|----------|
| 4a    | Combined yield | 98%        | 65%        | dr 73:27 |          | 4b      | Combined yield | 99%        | 64%        | dr 76:24 |          | 4c      | Combined yield | 85%        | 50%        | dr 76:24 |          | 4d      | Combined yield | 73%        | 64%        | dr 76:24 |          | 4e      | Combined yield | 72%        | 53%        | dr 76:24 |          | 4f      | Combined yield | 99%        | 53%        | dr 76:24 |          | 4g      | Combined yield | 99%        | 56%        | dr 76:24 |          | 4h      | Combined yield | 88%        | 57%        | dr 72:28 |          | 4i      | Combined yield | 91%        | 44%        | dr 76:24 |          | 4j      | Combined yield | 80%        | 53%        | dr 76:24 |          | 4k      | Combined yield | 95%        | 53%        | dr 76:24 |          | 4l      | Combined yield | 99%        | 57%        | dr 76:24 |          | 4m      | Combined yield | 71%        | 43%        | dr 81:19 |          | 4n      | Combined yield | 88%        | 43%        | dr 81:19 |          | 4o      | Combined yield | 65%        | 45%        | dr 81:19 |          | 4p      | Combined yield | 45%        | 45%        | dr 81:19 |          | 4q      | Combined yield | 79%        | 45%        | dr 81:19 |          | 4r      | Combined yield | 79%        | 45%        | dr 81:19 |          | 4s      | Combined yield | 79%        | 45%        | dr 81:19 |

“Combined yield. Calculated by 1H NMR of the crude. Galvinoxyl was not used in the reaction. cis-4o,p/trans-4o,p/(mixture of isomers 7).

### Scheme 3. Formation of Compounds 10 and 11

The ΔΔG⧧ between 10 and 11 (see the SI for details).

### Table 4. Computed Activation Barriers, Reaction Energies (kcal mol⁻¹), and Product Distribution Computed at the COSMO(THF)-BP86/TZ2P Level of Theory

| compd | ΔE(ΔG⧧) | ΔEint(ΔGint) | ΔErxn(ΔGrxn) | product ratio
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>12.8 (21.3)</td>
<td>−17.6 (−6.1)</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>15.0 (24.0)</td>
<td>−14.3 (−2.2)</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
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Differences in the reaction between 9 and 2 leading to 10 (blue curve) and 11 (red curve) are a result of $\Delta E_{\text{rel}}$ (Figure 2a).

$\Delta E_{\text{spin}}$ remains nearly constant for both reactions along the reaction coordinate. Next, the EDA terms were analyzed, and the $\Delta E_{\text{Pauli}}$ dominates and is chiefly responsible for the difference in the interaction energies (Figure 2b). The more favorable $\Delta V_{\text{elec}}$ and $\Delta E_{\text{ul}}$ 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$_{2}$ group far away from the CH$_{2}$ group. See the SI for an ASA and EDA analysis on 6m and 6p.

In summary, we 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. Tetrahydrofuran was used as a solvent after distillation. Potassium tert-butoxide was used as a 1.0 M solution in THF (0.40 M) under inert atmosphere and cooled to 0 °C. Then, KO'Bu (1.0 equiv, 1.0 M solution in THF) was added slowly, and the mixture was warmed to 21 °C for 90 min. This solution was used for the cycloaddition reactions of alkene 2. H NMR [400 MHz, δ (ppm), THF-d$_{8}$]: 6.54 (dd, δ = 16.5, 9.4 Hz, 1 H), 7.55–7.66 (m, 2 H). 13C NMR [101 MHz, δ (ppm), THF-d$_{8}$]: 207.3, 124.7 (q, J = 264.0 Hz). 1H NMR [400 MHz, δ (ppm), THF-d$_{8}$]: 7.23 (m, 1 H), 7.20–7.22 (m, 1 H), 7.09–7.10 (m, 1 H), 6.74–4.98 (bs, 2 H), R$_{f}$ 0.31 (CH$_{2}$Cl$_{2}$). Yield: 95%. NMR spectral data are in accordance with previously reported data. 1H NMR [500 MHz, δ (ppm), CDCl$_{3}$]: 6.93 (d, 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$_{2}$Cl$_{2}$). Yield: 89%. NMR spectral data are in accordance with previously reported data.

**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(OtBu)$_{3}$ (0.06 equiv) in dry THF (44 mM) was added to the reaction mixture. The reaction mixture was warmed to 21 °C and stirred for 16 h. 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 with MgSO$_{4}$ filtered off and concentrated in vacuo. The crude mixture was purified by column chromatography using the indicated eluent to afford isoxazolidines 3a–c.

2-Phenyl-5-[(trifluoromethyl)sulfanyl]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). 1H NMR [500 MHz, δ (ppm), CDCl$_{3}$]: 7.34–
7.27 (m, 2 H), 7.08–7.05 (m, 2 H), 7.03 (t, J = 7.3, 1.1 H, 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 (ddq, J = 13.2, 8.2, 4.0, 0.8 Hz, 1 H), 2.48–2.28 (m, 1 H).

13C NMR [126 MHz, δ (ppm), CDCl3]: 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).

19F NMR [471 MHz, δ (ppm), CDCl3]: –39.8. FTIR [\([\text{cm}^{-1}]\)]: 2860, 1599, 1491, 1295, 1109, 752, 692. HRMS (EI) m/z: [M+H]⁺ calculated for C12H1ClF4N3O2SF5: 516.0470, found 516.0459.

Yield: 80%.

**2-(3-(Trifluoromethyl)phenyl)-5-(trifluoromethyl)sulfanyl)isoazolidine (3b).** According to the general procedure, the reaction of hydroxylamine 5b (56.2 mg, 0.318 mmol) afforded isoazolidine 3b (33.5 mg, 0.071 mmol) as a colorless oil, after column chromatography (heptane/AcOEt/Et2O, 4:1). Yield: 38%.

**2-(3-(Trifluoromethyl)phenyl)-5-fluoromethyl)isoazolidine (3c).** The general procedure, the reaction of hydroxylamine 5c (29.3 mg, 0.166 mmol) afforded isoazolidine 3c (10.33 mg, 0.033 mmol) as a green oil after column chromatography (heptane/AcOEt/Et2O, 12:2:1.013). 1H NMR [500 MHz, δ (ppm), CDCl3]: 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), 2.37 (dd, J = 9.2, 8.6, 7.1 Hz, 1 H), 3.01–2.87 (m, 1 H), 2.47–2.36 (m, 1 H).

13C NMR [126 MHz, δ (ppm), CDCl3]: 151.6, 153.4, 129.7 (q, J = 307.9 Hz), 122.5, 114.2, 81.2 (q, J = 2.6 Hz), 51.6, 33.8 (q, J = 1.1 Hz). FTIR [\([\text{cm}^{-1}]\)]: 2924, 2850, 1587, 1210, 1115, 1051, 796. HRMS (EI) m/z: [M+H]⁺ calculated for C11H9F5N3OS: 249.0476, found 249.0482.

Yield: 22%.

**2-(3-Dichlorophenyl)-5-(trifluoromethyl)sulfanyl)isoazolidine (3d).** According to the general procedure, the reaction of hydroxylamine 5e (29.3 mg, 0.166 mmol) afforded isoazolidine 3e (10.33 mg, 0.033 mmol) as a green oil after column chromatography (heptane/AcOEt/Et2O, 5:1:1). 1H NMR [400 MHz, δ (ppm), CDCl3]: 8.44–8.36 (m, 2 H), 7.92 (s, 1 H), 7.81–7.74 (m, 2 H), 7.53–7.43 (m, 4 H). FTIR [\([\text{cm}^{-1}]\)]: 2956, 2925, 2855, 1593, 1490, 1328, 1210, 795, 698. HRMS (EI) m/z: [M+H]⁺ calculated for C12H1Cl2F4N3O2S: 317.0331, found 317.0325.

Yield: 2%.

**3c.** According to general procedure B, the reaction of benzaldehyde (47.0 μL, 0.458 mmol) with N-phenylhydroxylamine (50 mg, 0.458 mmol) afforded nitrene 6a (71 mg, 0.360 mmol) as a white solid, after column chromatography (heptane/AcOEt, 5:1 → 1:1). 1H NMR [400 MHz, δ (ppm), CDCl3]: 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%.

**3d.** According to general procedure B, the reaction of 4-fluorobenzaldehyde (98.0 μL, 0.916 mmol) with N-phenylhydroxylamine (100 mg, 0.916 mmol) afforded nitrene 6b (178.5 mg, 0.829 mmol) as a yellow solid. 1H NMR [400 MHz, δ (ppm), CDCl3]: 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%.

**3e.** According to general procedure B, the reaction of 4-fluoro-(E)-1-[4-(pentafluorophenyl)]phenylmethanimine oxide (6c) with N-phenylhydroxylamine (59 mg, 0.523 mmol) afforded nitrene 6d (139 mg, 0.523 mmol) as a yellow solid. 1H NMR [400 MHz, δ (ppm), CDCl3]: 8.45–8.48 (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%.

**3f.** According to general procedure A, the reaction of 4-(pentfluoro-z-sulanyl)benzaldehyde (120 mg, 0.517 mmol) with N-phenylhydroxylamine (59 mg, 0.543 mmol) afforded nitrene 6e (163.3 mg, 0.505 mmol) as a white-yellow solid. 1H NMR [400 MHz, δ (ppm), CDCl3]: 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), 7.78–7.46 (m, 3 H), 3.16–3.09 (m, 2 H), 2.30–2.18 (m, 1 H). 13C NMR [126 MHz, δ (ppm), CDCl3]: 154.5, 149.1, 133.6, 132.5, 130.7, 129.5, 128.9, 126.5 (quin, J = 4.4 Hz), 121.9. FTIR [\([\text{cm}^{-1}]\)]: 3057, 3024, 1573, 1074, 821, 810, 765. HRMS (EI) m/z: [M+H]⁺ calculated for C13H11F5N3OS: 324.0277, found 324.0282.

Yield: 98%.

**3g.** According to general procedure A, the reaction of 4-(pentfluoro-z-sulanyl)benzaldehyde (106.3 mg, 0.514 mmol) with N-phenylhydroxylamine (59 mg, 0.540 mmol) afforded nitrene 6f (110 mg, 0.484 mmol) as a yellow-brown solid, after column chromatography (CH2Cl2 → CH3Cl/MeOH, 10:0.2). 1H NMR [400 MHz, δ (ppm), CDCl3]: 8.44–8.36.
acclimatization and process 

(Z)-1-(3-Fluorophenyl)-N-phenylmethanimine Oxide (**6g**). According to 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/CH₂Cl₂/MeOH, 1:4, 10:1).

**1H NMR** ([400 MHz, CDCl₃], δ ppm): 8.34 (dd, J = 10.6, 2.6, 1 H, 7.49 (s, 1 H), 9.00 (dd, δ = 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, δ = 8.5, 1.9, 1 H), 7.17 (td, δ = 8.1, 2.6, 1 H, 1 H)

**13C NMR** (101 MHz, δ ppm, CDCl₃): 126.8 (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)-1-(3-Tolylmethyliden)-N-phenylmethanimine Oxide (**6h**). According to general procedure B, the reaction of 3-methylbenzylide (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).

**1H NMR** ([400 MHz, CDCl₃], δ ppm): 7.83 (q, J = 1.8, 0.7 Hz, 1 H), 7.81–7.75 (m, 2 H), 7.53–7.44 (m, 3 H, 7.38 (tt, J = 7.8, 1.5 Hz, 1 H), 7.32–7.27 (m, 1 H), 2.43 (s, 3 H).

**13C NMR** (101 MHz, δ ppm, CDCl₃): 194.3, 138.5, 134.9, 132.0, 130.8, 130.0, 129.4, 129.3, 128.7, 126.6, 121.9, 21.6. FTIR [v (cm⁻¹)]: 3092, 2963, 2920, 1652, 1590, 1459, 1088, 781, 692. HRMS (ESI-TOF) m/z: [M + H]+ calc 266.0789, found 266.0787. Yield: 90%.

(Z)-1-(3-Methoxyphenyl)-N-phenylmethanimine Oxide (**6i**). According to 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 (CH₂Cl₂ → CHCl₃/MeOH, 10:1).

**1H NMR** ([400 MHz, CDCl₃], δ ppm): 8.32 (tt, J = 7.9, 17.1, 12.0, 0.5 Hz, 1 H), 8.80 (tt, δ = 7.7, 0.5 Hz, 1 H, 8.13 (dd, δ = 7.9, 1.7, 12 Hz, 1 H), 8.01 (d, δ = 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).

**13C NMR** (101 MHz, δ ppm, CDCl₃): 166.5, 149.0, 133.6, 132.6, 131.6, 131.0, 130.6, 130.4, 129.3, 129.0, 121.7, 52.4. FTIR [v (cm⁻¹)]: 3064, 2942, 1718, 1434, 1278, 1072, 912, 729, 684. HRMS (ESI-TOF) m/z: [M + H]+ calc for C₁₄H₁₁F₃NO₂ 212.1070, found 212.1085. Yield: 98%.

(Z)-1-(3-Methoxyphenyl)-N-phenylmethanimine Oxide (**6j**). According to general procedure A, the reaction of methyl 3-formylbenzoate (90 mg, 0.548 mmol) with N-phenylhydroxylamine (63 mg, 0.576 mmol) afforded nitrone **6j** (112 mg, 0.439 mmol) as a yellow oil, after column chromatography (CH₂Cl₂ → CHCl₃/MeOH, 10:1).

**1H NMR** ([400 MHz, CDCl₃], δ ppm): 8.32 (tt, J = 7.9, 17.1, 12.0, 0.5 Hz, 1 H), 8.80 (tt, δ = 7.7, 0.5 Hz, 1 H, 8.13 (dd, δ = 7.9, 1.7, 12 Hz, 1 H), 8.01 (d, δ = 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).

**13C NMR** (101 MHz, δ ppm, CDCl₃): 166.5, 149.0, 133.6, 132.6, 131.6, 131.0, 130.6, 130.4, 129.3, 129.0, 121.7, 52.4. FTIR [v (cm⁻¹)]: 3064, 2942, 1718, 1434, 1278, 1072, 912, 729, 684. HRMS (ESI-TOF) m/z: [M + H]+ calc for C₁₄H₁₁F₃NO₂ 212.1070, found 212.1085. Yield: 98%.

(Z)-1-(3-Methoxyphenyl)-N-phenylmethanimine Oxide (**6k**). According to general procedure A, the reaction of methyl 3-formylbenzoate (90 mg, 0.548 mmol) with N-phenylhydroxylamine (63 mg, 0.576 mmol) afforded nitrone **6k** (112 mg, 0.439 mmol) as a yellow oil, after column chromatography (CH₂Cl₂ → CHCl₃/MeOH, 10:1).

**1H NMR** ([400 MHz, CDCl₃], δ ppm): 8.32 (tt, J = 7.9, 17.1, 12.0, 0.5 Hz, 1 H), 8.80 (tt, δ = 7.7, 0.5 Hz, 1 H, 8.13 (dd, δ = 7.9, 1.7, 12 Hz, 1 H), 8.01 (d, δ = 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).

**13C NMR** (101 MHz, δ ppm, CDCl₃): 166.5, 149.0, 133.6, 132.6, 131.6, 131.0, 130.6, 130.4, 129.3, 129.0, 121.7, 52.4. FTIR [v (cm⁻¹)]: 3064, 2942, 1718, 1434, 1278, 1072, 912, 729, 684. HRMS (ESI-TOF) m/z: [M + H]+ calc for C₁₄H₁₁F₃NO₂ 212.1070, found 212.1085. Yield: 98%.
General Procedure for the Synthesis ofIsoxazolidines 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 nitronate (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 h. Then, the reaction mixture was filtered off and the solvent was removed under vacuum. The crude mixture was purified by column chromatography (heptane/CHCl₃, 4:1) to afford isoxazolidine cis-4c (17.1 mg, 0.050 mmol, 50%) as a white solid and trans-4c (12.1 mg, 0.036 mmol, 35%) as a brown oil, contaminated with regioisomers 7c and azoxybenzene 8. Total yield: 85%.

rac-(3R,3R)-2-Phenyl-3-(4-tolyl)-5-[(trifluoromethyl)sulfonyl]isoxazolidine (3c). The solution containing alkene 2 (3 equiv) in distilled THF (500 μl) at 0 °C was added to a PTFE tube containing nitronate 6c (1.0 equiv). The tube was filled up with distilled THF, closed and brought to 15 kbar at 50 °C for 16 h. Then, the reaction mixture was filtered off and the solvent was removed under vacuum. The crude mixture was purified by column chromatography (heptane/CHCl₃, 4:1) to afford isoxazolidine cis-3c (7.0 mg, 0.018 mmol, 30%) as a white solid and regioisomers 6d (5.0 mg, 0.011 mmol, 22%) as a brown oil.

rac-(3R,3R)-2-Phenyl-3-(4-tolyl)-5-[(trifluoromethyl)sulfonyl]isoxazolidine (3d). The solution containing alkene 2 (3 equiv) in distilled THF (500 μl) at 0 °C was added to a PTFE tube containing nitronate 6d (1.0 equiv). The tube was filled up with distilled THF, closed and brought to 15 kbar at 50 °C for 16 h. Then, the reaction mixture was filtered off and the solvent was removed under vacuum. The crude mixture was purified by column chromatography (heptane/CHCl₃, 4:1) to afford isoxazolidine cis-3d (5.4 mg, 0.014 mmol, 28%) as a white solid and regioisomers 6e (3.5 mg, 0.009 mmol, 22%) as a yellow oil.
According to the general procedure, the reaction of nitrofen (6g, 0.234 mmol) and alken 2 in a 1 mL PTFE high-pressure tube afforded isoxazolidine cis-4f (46 mg, 0.136 mmol, 56%) as an off-white solid and isoxazolidine trans-4f and regioisomers 7f (26 mg, 0.077 mmol, 31%) as a yellow solid, after column chromatography (heptane/CH2Cl2, 7:3). Total yield: 88%.  

rac-(3R,5R)-2-(3-tolyl)-2-(trifluoromethyl)sulfanyl)isoxazolidine (cis-4i). H NMR [500 MHz, δ (ppm), CDCl3]: 7.31–7.28 (m, 1 H), 7.27–7.24 (m, 2 H), 7.14–7.10 (m, 1 H), 7.02–6.94 (m, 3 H), 5.98 (d, J = 8.1, 4.4 Hz, 1 H), 4.35 (d, J = 9.0, 7.2 Hz, 1 H), 3.37 (dd, J = 13.6, 9.0, 8.1, 0.9 Hz, 1 H), 2.38–2.32 (m, 1 H), 2.36 (s, 3 H). 13C NMR [126 MHz, δ (ppm), CDCl3]: 148.9, 139.7, 139.1, 130.2 (J = 307.8 Hz), 129.1, 129.1, 128.8, 127.6, 124.2, 123.6, 117.5, 80.5 (J = 2.2 Hz), 68.3, 47.2, 21.6. FTIR [v (cm⁻¹)]: 3028, 1599, 1489, 1401, 1001, 839, 737, 724, 692. HRMS (EI) m/z: [M⁺] calculated for C18H16F3NO3S 383.0805, found 383.0810. Rf: 0.41 (heptane/CH2Cl2, 4:1).  

Methyl 3-(2-phenyl-trifluoromethyl)isoxazolidin-3-yl)benzoate (4o). According to the general procedure, the reaction of nitrofen (6i) (26 mg, 0.102 mmol) and alken 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-4i and trans-4i and regioisomers 7i (18.2 mg, 0.047 mmol, 47%) as a brown-yellow solid, after column chromatography (heptane/CH2Cl2, 3:2). Total yield: 91%.  

Methyl 3-(rac-(3R,5R)-2-phenyl-2-(trifluoromethyl)sulfanyl)isoxazolidin-3-yl)benzoate (cis-4i). H NMR [500 MHz, δ (ppm), CDCl3]: 8.11 (t, J = 1.8 Hz, 1 H), 8.01 (d, J = 7.7, 1.4 Hz, 1 H), 7.76 (ddd, 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 (d, J = 8.0, 4.5 Hz, 1 H), 4.50 (d, J = 8.9, 7.0 Hz, 1 H), 3.93 (s, 3 H), 3.43 (ddd, J = 13.6, 8.9, 8.0, 0.9 Hz, 1 H), 2.42–2.30 (m, 1 H). 13C NMR [126 MHz, δ (ppm), CDCl3]: 166.8, 146.8, 140.2, 136.1, 131.1, 130.0 (J = 307.7 Hz), 129.6, 128.3, 124.0, 117.6, 80.4 (J = 2.5 Hz), 76.9, 52.4, 46.9. 19F NMR, [471 MHz, δ (ppm), CDCl3]: −39.9. FTIR [v (cm⁻¹)]: 3015, 1729, 1598, 1489, 1301, 1247, 1114, 1025, 786, 692. HRMS (EI) m/z: [M⁺] calculated for C18H16F3NO3S 383.0803, found 383.0824. Rf: 0.27 (heptane/CH2Cl2, 3:2).  

Methyl 3-(rac-(3S,5S)-2-phenyl-2-(trifluoromethyl)sulfanyl)isoxazolidin-3-yl)benzoate (trans-4i). H NMR [500 MHz, δ (ppm), CDCl3]: 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 (d, J = 6.7, 4.0 Hz, 1 H), 2.96 (t, J = 7.7 Hz, 1 H), 3.93 (s, 3 H), 3.01–2.94 (m, 1 H), 2.91 (d, J = 13.4, 8.0 Hz, 1 H). 13C NMR [126 MHz, δ (ppm), CDCl3]: 166.8, 150.7, 140.5, 131.19, 131.14, 130.0 (J = 307.9 Hz), 129.57, 128.9, 127.8, 122.6, 115.2, 82.3 (J = 2.2 Hz), 67.6, 52.4, 46.1. 19F NMR, [471 MHz, δ (ppm), CDCl3]: −39.4. FTIR [v (cm⁻¹)]: 3064, 1720, 1598, 1489, 1285, 1107, 1020, 799, 751, 692. HRMS (EI) m/z: [M⁺] calculated for C18H16F3NO3S 383.0803, found 383.0810. Rf: 0.22 (heptane/CH2Cl2, 3:2).
According to the general procedure, the reaction of nitroene 6J (49 mg, 0.234 mmol) and alkene 2 in a 1.5 mL PTFE high-pressure tube afforded isoxazolidine cis-4 (19 mg, 0.056 mmol; used for characterization as a colorless oil and mixture of isoxazolidines cis- and trans-4) (3 mg, 0.0084 mmol, 2%) as a yellow solid, after column chromatography (heptane/CH2Cl2, 7:3). Total yield: 99%.
According to the general procedure, the reaction of nitroène 6 (25 mg, 0.098 mmol) and alkene 2 in a 1 mL PTFE high-pressure tube afforded isoxazolidine cis- and trans-4. According to the general procedure, the reaction of nitroène 6 (25 mg, 0.098 mmol) and alkene 2 in a 1 mL PTFE high-pressure tube afforded isoxazolidine cis- and trans-4. According to the general procedure, the reaction of nitroène 6 (25 mg, 0.098 mmol) and alkene 2 in a 1 mL PTFE high-pressure tube afforded isoxazolidine cis- and trans-4. According to the general procedure, the reaction of nitroène 6 (25 mg, 0.098 mmol) and alkene 2 in a 1 mL PTFE high-pressure tube afforded isoxazolidine cis- and trans-4.
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**REFERENCES**


(11) For examples of 1,3-dipolar cycloaddition reactions between alkenes and nitrones, see: (a) [3].


(16) It is important to note that the assignment of the cis- and trans-diastereoisomers of 7 could not be clarified by NMR studies.


