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# Synthesis of a $CF_3$-substituted 1,3,4-oxadiazoline and its use in the generation and trapping of an α-trifluoromethyl carbene

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**This article is dedicated with profound respect and admiration to Prof. Samir Zard**

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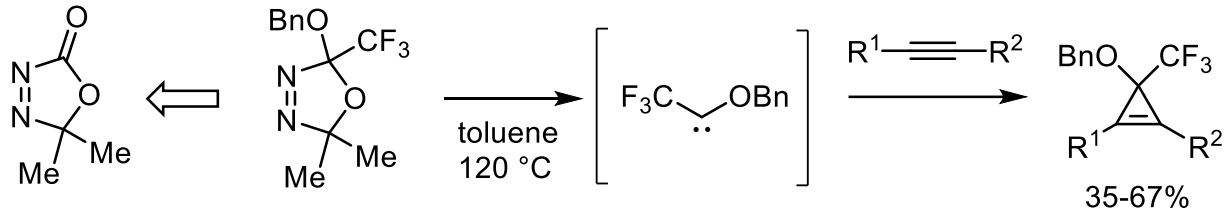
## Abstract

Among the different methods allowing the introduction of a $CF_3$ group into an organic framework, those based on the use of a fluorinated carbene intermediate are particularly useful. They can lead to the formation of structural motifs that are difficult to access by other means. We report in this article the development of a new route allowing the generation of an α-trifluoromethyl α-benzyloxy carbene from a readily accessible trifluoromethyl 1,3,4-oxadiazoline. Trapping of the carbene in the presence of various alkynes led to the formation of various protected trifluoromethyl tertiary cyclopropenols in moderate yields.




**Keywords**: (trifluoromethyl)carbene; oxadiazoline; cyclopropene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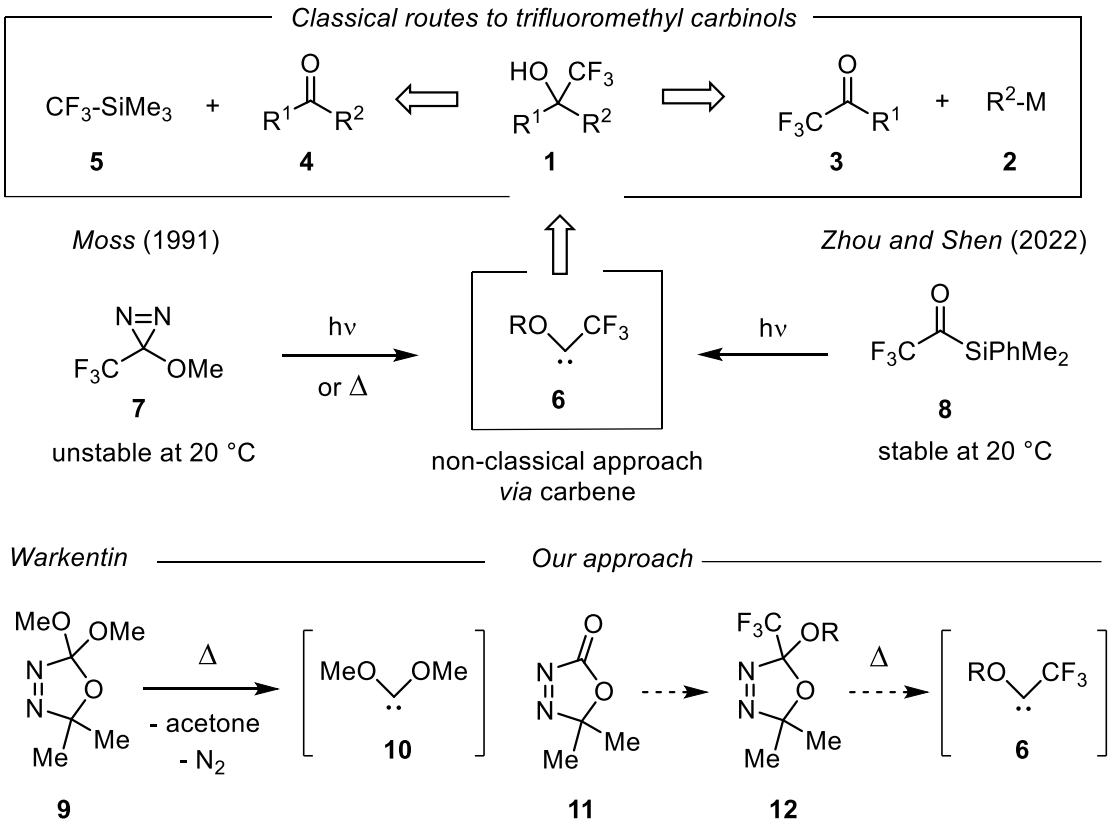
## Introduction

The introduction of a $CF_3$ group into an organic molecule, can profoundly modify its chemical, physical and biological properties.[1,2] As a result, many efforts have been devoted to the development of methods allowing its installation in an efficient and selective manner.[3-5] Trifluoromethyl carbinols **1** are very common structural motifs that are generally accessed by either nucleophilic addition of an organometallic reagent **2** to a trifluoroacyl group **3** or trifluoromethylation of a carbonyl derivative **4** with the Ruppert-Prakash reagent **5** (Scheme 1).[6]




**Scheme 1.** Classical routes to trifluoromethyl carbinols and our approach.

An alternative approach to their synthesis consists of the generation and trapping of an α-trifluoromethyl carbene **6** possessing an additional oxygen-based substituent at the α position.[7-10] While the simplest α-trifluoromethyl carbene can be easily generated from α, α, α-trifluoroethylamine,[10] access to carbenes of type **6** remain extremely limited. Seminal work by the group of Moss demonstrated that the α-methoxy α-$CF_3$ carbene **6** (R= Me) could be generated from the room temperature unstable diazirine **7** and trapped with a variety of alkenes.[9] No discrimination was observed in the reaction with electron rich or poor alkenes. An alternative and very elegant approach was recently reported by Zhou and Shen who showed that the trifluoroacylsilane **8** could be employed to generate the α-silyloxy α-$CF_3$ carbene **6** (R= $SiPhMe_2$) under mild photochemical conditions.[10] Trapping with alkynes to produce cyclopropenes was found very efficient. Looking for an alternative approach to generate and react α-trifluoromethyl carbene of type **6**, we considered 1,3,4-oxadiazolines as potential precursors. The chemistry of 1,3,4-oxadiazolines **9** has been largely studied by the group of Warkentin,[11] who showed that, under thermal conditions, they can decompose to generate

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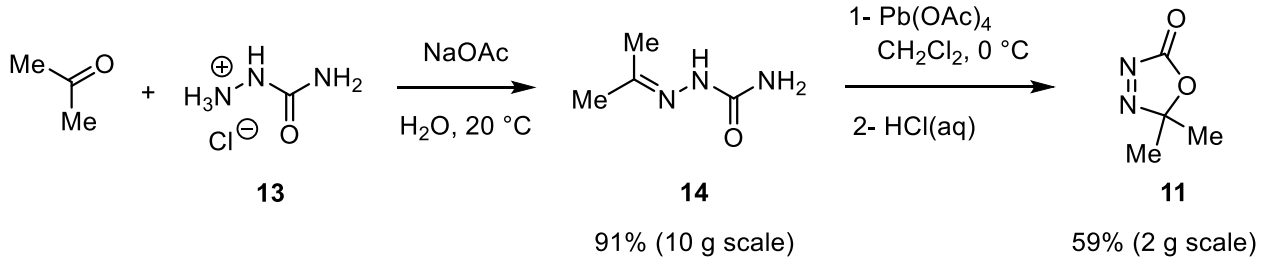
nucleophilic dialkoxycarbene **10**. Capitalizing on this reactivity, our strategy relies on the synthesis of a $CF_3$-substituted 1,3,4-oxadiazoline **12** from an oxadiazolone precursor **11**, and its degradation under thermal conditions to generate an $\alpha$-alkoxy $\alpha$-$CF_3$ carbene **6**. We report herein the results of our investigations showing the validity of this approach.

## Results and Discussion

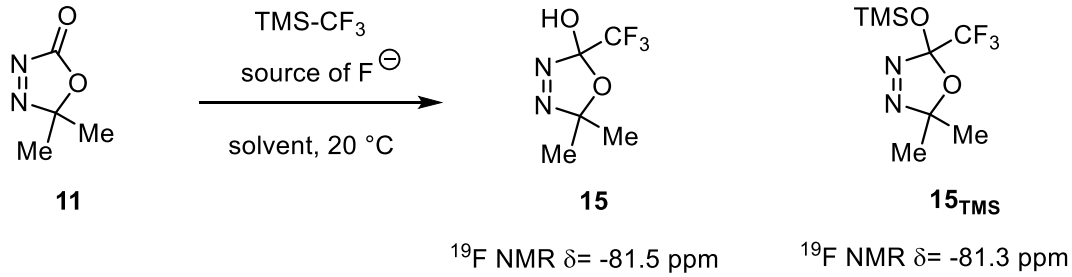
We started our investigations with the synthesis of oxadiazolone **11** following the route previously described by the group of Warkentin (Scheme 2).[12] The condensation of acetone with the hydrochloride salt of semicarbazide **13** provided intermediate **14** in an excellent 91% yield. A subsequent oxidative cyclization in the presence of $Pb(OAc)_4$ yielded oxadiazolone **11**, a potential precursor of the targeted trifluoromethylated 1,3,4-oxadiazoline **12**. This two-step procedure was straightforward and amenable to the multigram-scale synthesis of **11**. Attempts to employ $PhI(OAc)_2$ instead of $Pb(OAc)_4$, as reported by Warkentin,[13] was found less efficient (< 25%). Compound **11** could be obtained as a volatile pale yellow solid in pure form after a simple extraction.




**Scheme 2.** Synthesis of Oxadiazolone **11**

The key trifluoromethylation reaction was first attempted using a combination of the Ruppert-Prakash reagent ($TMSCF_3$) and TBAF in THF (Table 1, entry 1). After 3 hours of reaction, the crude mixture was analyzed by $^{19}F$ NMR spectroscopic analysis. Two $CF_3$-substituted compounds that could correspond to $CF_3$-oxadiazoles **15** and **$15_{TMS}$** were detected at $\delta \approx$ -81 ppm. A moderate 40% yield was determined using $\alpha,\alpha,\alpha$-trifluorobenzene as an internal reference and standard. Unfortunately, these $CF_3$-derivatives were found unstable and could not be isolated for further characterization and confirmation of their structure. Before derivatizing **15** and **$15_{TMS}$** into more stable derivatives, it was decided to optimize the experimental conditions. Using CsF in DMF instead of TBAF in THF led to minimal improvement (entry 2). Interestingly, when the loading of CsF was reduced to 10 mol%, the yield in trifluoromethylated compounds notably increased to 83% (entry 3). Doubling the amount of $TMSCF_3$ had a negative impact (entry 4).

**Table 1.** Trifluoromethylation of oxadiazolone **11**.

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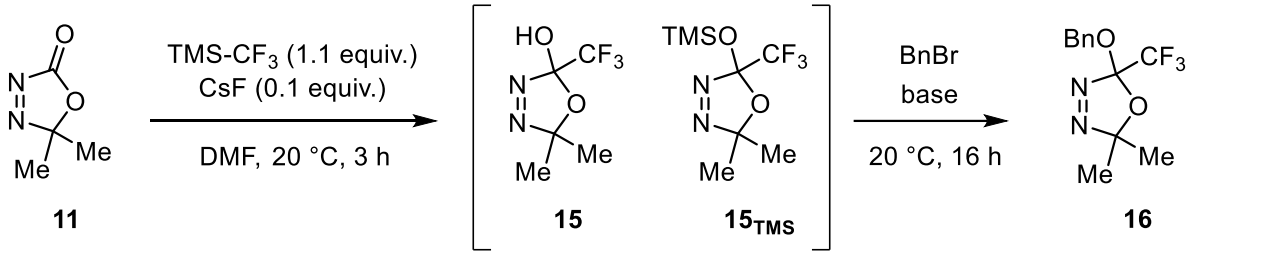
| Entry | $TMSCF_3$ (equiv.) | $F^-$ source (equiv.) | Solvent[a] | Time (h) | Yield (**15**+**15$_{TMS}$**) (%)[a] |
|---|---|---|---|---|---|
| 1 | 1.1 | TBAF (0.2) | THF | 3 | 40 |
| 2 | 1.1 | CsF (0.2) | DMF | 3 | 52 |
| 3 | 1.1 | CsF (0.1) | DMF | 3 | 83 |
| 4 | 2.0 | CsF (0.1) | DMF | 3 | 25 |
| [a] yields determined by $^{19}F$ NMR spectroscopy of the crude reaction mixture using α,α,α-trifluorobenzene as an internal reference and standard. | | | | | |

The derivatization of **15** and **15$_{TMS}$** into benzyl ether **16** was then considered (Table 2). The choice of the benzyl group was made considering its protective nature and the compatibility of the reaction conditions for its introduction with those employed for the trifluoromethylation step. A one-pot procedure was then attempted by first using additional CsF as the base for the benzylation step (entry 1). After 16 h of reaction, a new $CF_3$ derivative was detected by $^{19}F$ NMR spectroscopic analysis of the reaction mixture. This compound, which was formed in 52% yield, could be isolated. Its structure was confirmed to be that of benzyl derivative **16** thus supporting the formation of intermediates **15** and **15$_{TMS}$** during the trifluoromethylation step. While increasing both the amount of CsF and BnBr improved the yield of **16** to 75% (entries 2 and 3), these conditions were not retained. The same efficiency could be achieved by using $K_2CO_3$ in combination with a lower amount of BnBr, what was considered as an improvement in terms of cost and easiness of purification (entries 4-6). Using conditions reported in entry 6, compound **16** could be produced from **11** (2.4 g scale) in an overall 63% yield.

**Table 2.** One-pot procedure to access to $CF_3$-oxadiazoline **16**.




$^{19}F$ NMR δ= -83.0 ppm

| Entry | Base (equiv.) | BnBr (equiv.) | Yields **15**/**16** (%)[a] |
|---|---|---|---|
| 1 | CsF (1) | 1.5 | 21/52 |
| 2 | CsF (2) | 1.5 | 4/53 |
| 3 | CsF (2) | 2.5 | 3/75 |
| 4 | $K_2CO_3$ (1) | 1.5 | 0/70 |
| 5 | $K_2CO_3$ (1) | 2.5 | 0/76 |
| 6 | $K_2CO_3$ (1.6) | 1.5 | 0/75 (63% isolated) |
| [a] yields determined by $^{19}F$ NMR spectroscopy of the crude reaction mixture using α,α,α-trifluorobenzene as an internal reference and standard. | | | |

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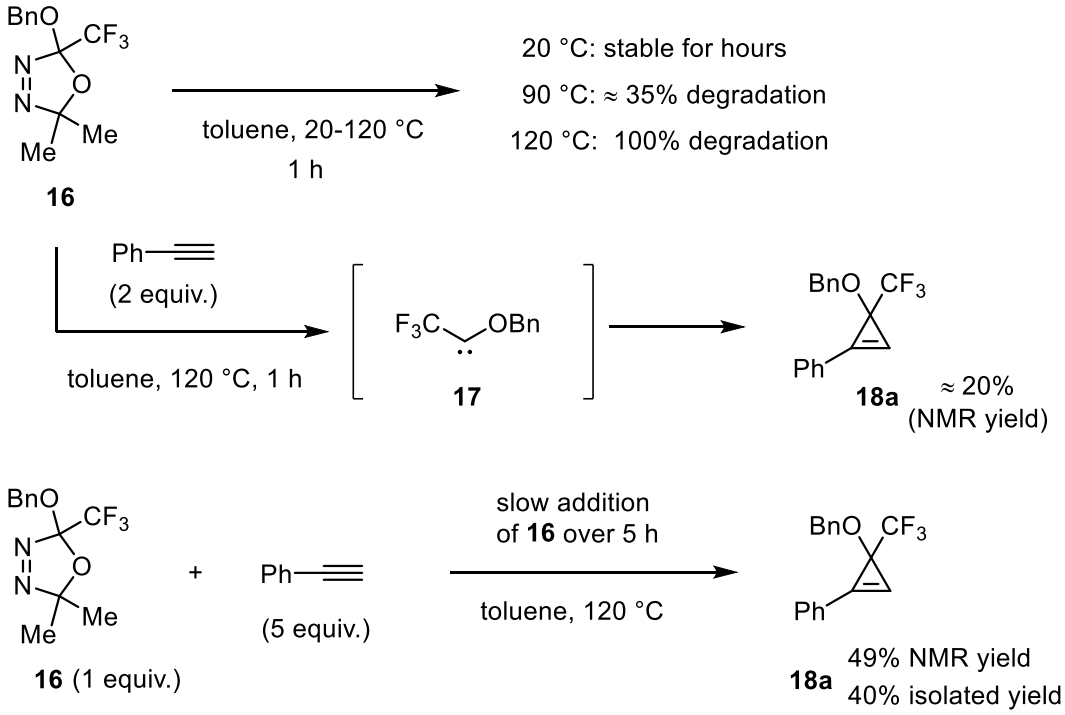
The thermal stability of oxadiazoline **16** was then evaluated (Scheme 3). It was found to be rather stable at room temperature and could be easily handled and manipulated. After 4 weeks at ≈ 5 °C, less than 5% of decomposition could be noticed. When a solution of **16** in toluene was heated at 90 °C for 1h, only partial degradation was observed (≈ 35%) thus demonstrating its relative thermal stability. At 120 °C, **16** was fully consumed after 1 h and multiple products were formed according to $^{19}F$ NMR spectroscopic analysis of the reaction mixture. Considering that **16** should thermally degrade *via* the formation of free carbene **17**, a reaction was then performed in the presence of phenyl acetylene (2 equiv.), used as a trap.[10,14,15] After 1 h at 120 °C, analysis of the crude reaction mixture showed the formation of cyclopropene **18a** in approximately 20% yield thus validating the nature of **16** as a $CF_3$-substituted carbene precursor. To favor the interception of carbene **17**, an excess of phenylacetylene (5 equiv.) was employed and the $CF_3$-oxadiazoline **16** was slowly added over a period of 5 h to the solution of phenylacetylene in toluene at 120 °C. Pleasingly, the formation of cyclopropene **18a** could be improved to 49% (40% isolated yield). Attempts to improve the yield by changing the solvent (1,4-dioxane, 1,2-dichloroethane, THF, acetonitrile, o-xylene), the concentration, the number of equivalents of the trap or the rate of addition of the oxadiazoline were unsuccessful. Notably, no product issued from the insertion of carbene **17** into the C(sp)-H bond of the terminal alkyne could be observed.




**Scheme 3.** Evaluation of the reactivity of **16** as a carbene precursor.

Cyclopropenes are useful building blocks in organic synthesis, especially for the synthesis of polysubstituted cyclopropanes.[16] A series of other alkynes could be employed as traps to produce a variety of substituted cyclopropenes (Scheme 4). However, depending on the nature of the alkyne, either an excess of the alkyne (method A) or an excess of the 1,3,4-oxadiazoline **16** (method B) was employed. The choice was made depending on the easiness of separation of the excess of alkyne by flash column chromatography or its removal prior to purification by evaporation under vacuum. While yields obtained were moderate, the method could be applied to both terminal and internal alkynes, bearing either aromatic or alkyl groups, and was tolerant to many functional groups. Notably, the reaction does not seem to be sensitive to sterics as

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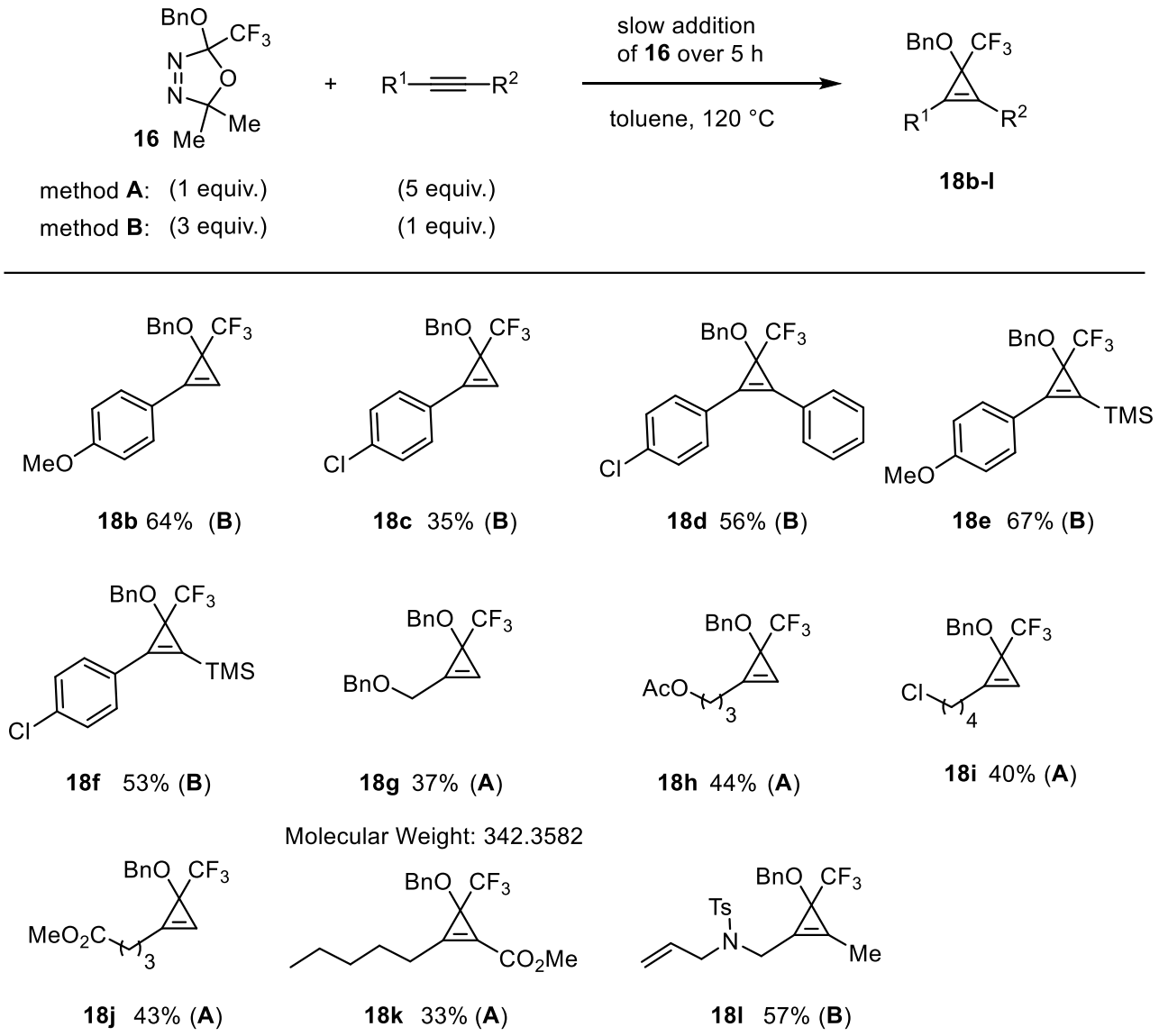
attested by the similar yields obtained for terminal versus substituted alkynes (compare **18c** and its substituted analog **18d** and **18f**). Interestingly, cyclopropene **18l** was produced selectivity with no noticeable formation of a cyclopropane product resulting from the trapping of the carbene by the alkene moiety.




**Scheme 4.** Scope for the formation of cyclopropenes.

The possibility to react carbene **17** with other trapping agents was also rapidly evaluated (Scheme 5). Under the same experimental conditions as those employed for cyclopropanation (methods A or B), alkene, aldehyde and silane were found to be viable traps. Cyclopropanation in the presence of styrene delivered **19** in a low 35% yield but as a single diastereoisomer.[9,10] Reaction of carbene **17** with benzaldehyde produced the acetophenone derivative **20** as the result of a formal insertion into the C-H bond of the aldehyde.[10] Finally, insertion into Si-H bond could be achieved with triethylsilane delivering **21** in a moderate 45% yield.[7]

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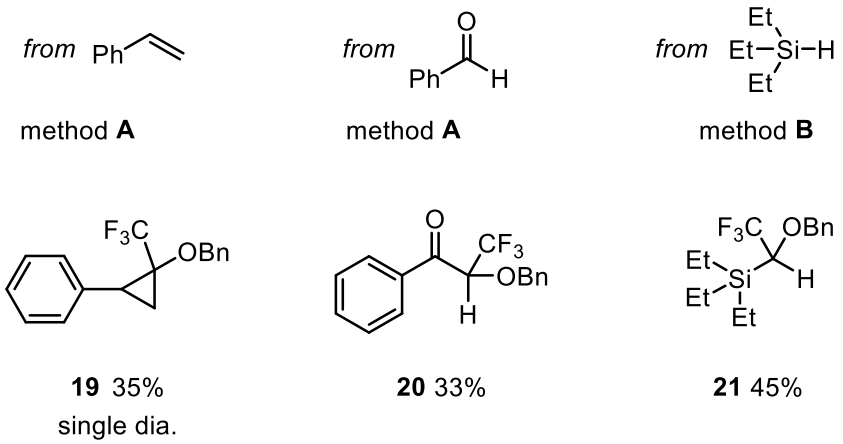


**Scheme 5.** Use of other trappings agents.

## Conclusions

On the basis of the previous work made by the group of Warkentin, we have developed an efficient synthetic route to access on a multigram scale a 1,3,4-oxadiazoline bearing both a $CF_3$ and an alkoxy group on the same carbon. This 1,3,4-oxadiazoline was found stable at room temperature, easy to handle and manipulate. At 120 °C its decomposition generates a free carbene that could be trapped by a variety of alkynes to produce cyclopropenes in moderate yields. A rapid investigation showed that carbene **17** could also react with alkene, aldehyde and silane, thus showing its general interest to access a variety of compounds possessing a trifluoromethyl carbinol moiety. Investigations aiming to improve and extend the reactivity of **17,** and accessing other $CF_3$-subtituted 1,3,4-oxadiazolines are currently ongoing.

## Experimental Section

**General.** Commercially available chemicals were used without further purification. Commercially available reagents were purchased from Sigma-Aldrich, Alfa-Aesar, Oakwood Chemicals, TCI America, Thermo Fisher Scientific, Combi-Blocks or Ambeed chemical suppliers and were used as received without further purification. Anhydrous solvents were obtained from an MB-SPS 800 or dried over 4 Å molecular sieves and kept under an inert atmosphere of nitrogen gas. Thin-layer chromatography was performed on aluminum backed TLC Silica gel 60 F254 plates (thickness: 175–225 µm) and visualized by fluorescent quenching at 254/366 nm or stained using potassium permanganate ($KMnO_4$) solution, p-anisaldehyde solution, iodine stain and ninhydrin solution followed by heating with a heat gun. Flash-column chromatography was carried out on silica gel using a forced flow of eluents with reagent-grade solvents in glass columns. Nuclear magnetic resonance (NMR) spectra were recorded at room temperature in the given deuterated solvent on 300, 400, 500, and 600 megahertz (MHz) Bruker instruments for the specified nucleus. Chemical shifts (δ) are given in parts per million (ppm) and are internally referenced to the residual $CDCl_3$ (δ 7.26 ppm 1H and δ 77.16 ppm $^{13}C$) and d6-DMSO (δ 2.50 ppm 1H and δ 39.52 ppm $^{13}C$) resonances. Coupling constants (J) are given in hertz (Hz). Signal multiplicities are depicted using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, tt = triplet of triplet, td = triplet of doublet, dq =

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doublet of quartet, qd = quartet of doublet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, dddd = doublet of doublet of doublet of doublet, and br s = broad singlet. High-resolution mass spectrometry by electron impact (HRMS-EI) was performed on a JEOL JMCGCmate II mass spectrometer and fragment signals were given in a mass per charge ratio (m/z). High-resolution mass spectrometry by electrospray ionization (HRMS-ESI) was performed on a Micromass Q-Tof II mass spectrometer and fragment signals were given in a mass per charge ratio (m/z).

**Synthesis of 14.** Prepared according to the literature.[12] A solution of semicarbazide hydrochloride (10 g, 89.7 mmol) in water (200 mL) was added acetone (10 mL, 134.6 mmol, 1.5eq) and sodium acetate (11 g, 134.6 mmol, 1.5 eq). The reaction was stirred at 20°C for 18h. The white solid was then filtered off and dried under reduced pressure to give the desired product (9.37 g, 81.4 mmol, 91%) which was directly used in the next step. Spectral data match those previously reported in the literature.[12]

**Synthesis of 11.** Prepared according to the literature.[12] To a solution of 1-(propan-2-ylidene)semicarbazide **15** (2 g, 17.4 mmol) in dry DCM (160 mL) under inert atmosphere was added at 0 °C $Pb(OAc)_4$ (8.87 g, 20.0 mmol, 1.15 eq). The reaction was stirred at the same temperature for 1.5 h before 30 mL of water and 15 mL of HCl (4M) were added at 0 °C. The reaction was then stirred for 30 min. 50 mL of water were added and the reaction mixture was extracted with DCM (2 x 50 mL). The organic phases were then washed with a saturated solution of $NaHCO_3$ (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired product as a pale-yellow solid (1.17 g, 10.3 mmol, 59%). Spectral data match those previously reported in the literature.[12] The crude product was directly used in the next step.

**Synthesis of 16.** To a solution of 5,5-dimethyl-1,3,4-oxadiazol-2(5*H*)-one **11** (2.40 g, 21.03 mmol) in dry DMF (30 mL) under inert atmosphere was added $TMSCF_3$ (3.42 mL, 23.13 mmol, 1.1 eq) and CsF (159 mg, 1.05 mmol, 0.05 eq) at room temperature. The reaction was stirred at the same temperature for 2 h and then cooled down to 0 °C. BnBr (3.75 mL, 31.55 mmol, 1.5 eq) and $K_2CO_3$ (powder, 4.65 g, 33.65 mmol, 1.6 eq) were then added. After 10 min, the ice bath was removed, and the reaction was stirred at 20 °C for 16 h. The mixture was quenched with water (120 mL) and extracted with ether (3 x 40 mL). The organic phases were washed with NaCl sat. (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (Hexanes/Eter 100:1) to afford the desired product as a pale yellow oil (3.63 g, 13.24 mmol, 63%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 4.51 (d, *J* 10.8 Hz, 1H), 4.36 (d, *J* 10.8 Hz, 1H), 1.71 (s, 3H), 1.65 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.5, 128.6, 128.4, 127.8, 126.2, 119.7 (q, *J* 284.5 Hz), 66.3, 24.3, 24.1. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -83.0. HRMS (ESI) Calculated for $C_{17}H_{20}N_2O_2$ [M]+: 284.1525; found: *m/z* 284.1490.

**General procedures (methods A and B) for the reaction of 16 with carbene trapping agents**: Method **A** (used with excess substrates that could be easily removed by evaporation or flash column chromatography): In a test tube sealed with a rubber septum, a solution of the substrate (alkene, alkyne, silane or aldehyde, 5 equiv.) in dry toluene (5 M, degassed) was heated to 120 °C. 0.2 mmol (1 equiv.) of 1,3,4-oxadiazoline **16** in solution in dry toluene (0.5 M, degassed) were added during 5 h using a syringe pump. Once the addition was complete, the mixture was heated for additional 15 min. The solvent was then removed by evaporation and the residue was directly purified by flash column chromatography. Method **B** (used with non-volatile substrates or more complex molecule): In a test tube sealed with a rubber septum, a solution of of substrate (alkene, alkyne, silane or aldehyde, 1 equiv.) in dry toluene (5 M, degassed) was heated to 120 °C. (3 equiv.) of 1,3,4-oxadiazoline **16** in solution in dry toluene (0.5 M) were added during 5 h using a syringe pump. Once the

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addition was complete, the mixture was heated for additional 15 min. Then, the solvent was then removed by evaporation and the residue was directly purified by flash column chromatography.

**Synthesis of 18a.** According to the general procedure, method **A**: phenylacetylene (0.53 mL, 4.85 mmol) and oxadiazoline **16** (265 mg, 0.97 mmol). Purification by flash chromatography with hexanes/toluene mixtures. **18a** was obtained as a pale-yellow solid (114 mg, 40%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.67-7.64 (m, 2H), 7.49-7.44 (m, 3H), 7.30-7.25 (m, 5H), 7.23 (q, *J* 1.6 Hz, 1H), 4.59 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 137.9, 131.1, 130.3, 129.1, 128.5, 127.8, 127.7, 124.8, 124.6 (q, *J* 276.4 Hz), 123.5 (q, *J* 2.3 Hz), 103.4 (q, *J* 2.8 Hz), 69.1, 60.6 (q, *J* 39.5 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.1. HRMS (EI) Calculated for $C_{16}H_{13}O$ $[M\text{-}CF_3]^+$: 221.0966; found: *m/z* 221.0979.

**Synthesis of 18b.** According to the general procedure, method **B**: 1-ethynyl-4-methoxybenzene (106 mg, 0.80 mmol) and oxadiazoline **16** (658 mg, 2.43 mmol). Purification by flash chromatography: hexanes/toluene. **18b** was obtained as a yellow solid (47 mg, 64%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.60 (dt, *J* 8.8 Hz, *J* 2.4 Hz, 2H), 7.31-7.22 (m, 5H), 7.05 (q, *J* 1.2 Hz, 1H), 6.97 (dt, *J* 8.8 Hz, *J* 2.4 Hz, 2H), 4.52 (s, 2H), 3.86 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 161.9, 138.1, 132.0, 128.4, 127.7, 127.6, 124.8 (q, *J* 276.3 Hz), 122.7 (q, *J* 2.4 Hz), 117.2, 114.6, 100.1 (q, *J* 2.9 Hz), 68.8, 60.6 (q, *J* 39.3 Hz), 55.4. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.1. HRMS (EI) Calculated for $C_{18}H_{15}F_3O_2$ $[M]^+$: 320.1024; found: *m/z* 320.1008.

**Synthesis of 18c.** According to the general procedure, method **B**: with 1-chloro-4-ethynylbenzene (109 mg, 0.80 mmol) and oxadiazoline **16** (658 mg, 2.43 mmol). Purification by flash chromatography: hexanes/toluene. **18c** was obtained as a yellow oil (90 mg, 35%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.57 (dt, *J* 8.8 Hz, *J* 2.0 Hz, 2H), 7.44 (dt, *J* 9.0 Hz, *J* 2.0 Hz, 2H), 7.31-7.22 (m, 5H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* 11.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 137.8, 137.3, 131.5, 129.5, 128.5, 127.8, 127.7, 124.5 (q, *J* 276.3 Hz), 123.2, 122.6 (q, *J* 2.5 Hz), 104.1 (q, *J* 2.9 Hz), 69.0, 60.5 (q, *J* 39.6 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.1. HRMS (EI) Calculated for $C_{17}H_{12}ClF_3O_2Si$ $[M]^+$: 324.0529; found: *m/z* 324.0544.

**Synthesis of 18d.** According to the general procedure, method **B**: with 1-chloro-4-(2-phenylethynyl)benzene (170 mg, 0.8 mmol) and oxadiazoline **16** (658 mg, 2.43 mmol). Purification by flash chromatography: hexanes/toluene. **18d** was obtained as a pale-yellow oil (181 mg, 56%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.76-7.73 (m, 2H), 7.67 (dt, *J* 8.8 Hz, *J* 2.2 Hz, 2H), 7.54-7.50 (m, 5H), 7.23-7.16 (m, 5H), 4.59 (d, *J* 11.6 Hz, 1H), 4.53 (d, *J* 11.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.5, 131.4, 130.7, 130.3, 129.5, 129.3, 128.3, 127.7, 127.6, 125.9, 124.8 (q, *J* 277.0 Hz), 124.7, 115.3 (q, *J* 2.3 Hz), 113.7 (q, *J* 2.5 Hz), 69.7, 61.5 (q, *J* 39.0 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -70.8. HRMS (EI) Calculated for $C_{23}H_{16}ClF_3O$ $[M]^+$: 400.0842; found: *m/z* 400.0849.

**Synthesis of 18e.** According to the general procedure, method **B**: with 1-(phenylethynyl)-4-(trifluoromethyl)benzene (49 mg, 0.24 mmol) and oxadiazoline **16** (165 mg, 0.60 mmol). Purification by flash chromatography: hexanes/diethyl ether. **18e** was obtained as a yellow oil (61.8 mg, 67%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* 8.4 Hz, 2H), 7.79 (d, *J* 5.7 Hz, 2H), 7.74 (d, *J* 8.5 Hz, 2H), 7.57 – 7.49 (m, 3H), 7.26 – 7.14 (m, 5H), 4.61 (d, *J* 11.5 Hz, 1H), 4.56 (d, *J* 11.5 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl3) δ 137.8, 131.8 (d, *J* 32.8 Hz), 131.1, 130.6, 130.3, 129.6, 129.4, 128.4, 127.8, 127.6, 126.2 (q, *J* 3.8 Hz), 125.7, 124.8 (q, *J* 278.3 Hz), 123.9 (q, *J* 272.4 Hz), 117.6 (q, *J* 2.6 Hz), 113.6 (q, *J* 2.3 Hz), 69.7, 61.5 (q, *J* 39.4 Hz). $^{19}$F NMR (376 MHz, CDCl3) δ -70.7, 64.0. HRMS (EI) Calculated for $C_{24}H_{16}F_6O$ [M]+: 434.1105; found: m/z 434.1096.

**Synthesis of 18f.** According to the general procedure, method **B**: with (2-(4-chlorophenyl)ethynyl)trimethylsilane (167 mg, 0.80 mmol) and oxadiazoline **16** (658 mg, 2.40 mmol). Purification by flash chromatography: hexanes/toluene. **18f** was obtained as a yellow oil (169 mg, 53%). $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.52 (dm, *J* 8.4 Hz, 2H), 7.42 (dm, *J* 8.4 Hz, 2H), 7.29-7.21 (m, 5H), 4.52 (d, *J* 11.2 Hz, 1H), 4.45 (d, *J* 11.2 Hz, 1H), 0.37 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.8, 132.6, 131.2, 129.5, 128.4,

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127.7, 127.5, 125.3 (q, *J* 276.1 Hz), 125.2, 117.9, 69.6, 62.8 (q, *J* 39.0 Hz), -1.1. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -70.9. HRMS (EI) Calculated for $C_{13}H_{13}ClF_3OSi$ [M-Bn]$^+$: 305.0376; found: *m/z* 305.0378.

**Synthesis of 18g.** According to the general procedure, method **A**: with benzyl propargyl ether (0.69 mL, 4.77 mmol) and oxadiazoline **16** (262 mg, 0.95 mmol). Purification by flash chromatography: hexanes/diethyl ether. **18g** was obtained as a yellow oil (117 mg, 37%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.39-7.25 (m, 10H), 7.14 (d, *J* 1.2 Hz, 1H), 4.57 (s, 2H), 4.55 (d, *J* 12.0 Hz, 1H), 4.48 (d, *J* 11.6 Hz, 1H), 4.45 (dd, *J* 16.0 Hz, 1.6 Hz, 1H), 4.39 (dd, *J* 16.8 Hz, 1.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 137.9, 137.2, 128.6, 128.5, 128.2, 128.0, 127.8, 127.6, 124.5 (q, *J* 2.4 Hz), 124.3 (q, *J* 276.3 Hz), 106.6 (q, *J* 2.8 Hz), 72.9, 69.0, 63.1, 61.0 (q, *J* 39.6 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.5. HRMS (ESI) Calculated for $C_{19}H_{17}F_3O_2Na$ [M+Na]$^+$: 357.1078; found: *m/z* 357.1071.

**Synthesis of 18h.** According to the general procedure, method **A**: with pent-4-ynyl acetate (606 mg, 4.80 mmol) and oxadiazoline **16** (263 mg, 0.96 mmol). Purification by flash chromatography: hexanes. **18h** was obtained as a pale-yellow oil (133 mg, 44%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 6.94 (q, *J* 1.2 Hz, 1H), 4.55 (d, *J* 11.6 Hz, 1H), 4.43 (d, *J* 11.6 Hz, 1H), 4.11 (t, *J* 6.4 Hz, 2H), 2.53 (t, *J* 6.4 Hz, 2H), 2.05 (s, 3H), 2.00-1.86 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.0, 137.9, 128.4, 127.7, 127.5, 125.9 (q, *J* 2.5 Hz), 124.6 (q, *J* 276.2 Hz), 104.4 (q, *J* 3.0 Hz), 68.5, 63.1, 60.4 (q, *J* 39.2 Hz), 25.8, 21.0, 20.8. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.3. HRMS (EI) Calculated for $C_9H_{10}F_3O_3$ [M-Bn]$^+$: 223.0582; found: *m/z* 223.0560.

**Synthesis of 18i.** According to the general procedure, method **A**: with 6-chloro-1-hexyne (0.58 mL, 4.82 mmol) and oxadiazoline **16** (264 mg, 0.96 mmol). Purification by flash chromatography: hexanes/toluene. **18i** was obtained as a pale-yellow oil (115 mg, 40%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.33-7.26 (m, 5H), 6.92 (m, 1H), 4.55 (d, *J* 11.6 Hz, 1H), 4.43 (d, *J* 11.6 Hz, 1H), 3.54 (t, *J* 6.0 Hz, 2H), 2.48 (t, *J* 6.8 Hz, 2H), 1.87-1.69 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 138.1, 128.5, 127.8, 127.6, 126.4 (q, *J* 2.3 Hz), 124.7 (q, *J* 276.3 Hz), 104.3 (q, *J* 3.0 Hz), 68.7, 60.5 (q, *J* 39.2 Hz), 44.5, 31.8, 24.1, 23.7. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.3. HRMS (EI) Calculated for $C_{14}H_{16}OCl$ [M-$CF_3$]$^+$: 235.0890; found: *m/z* 235.0869.

**Synthesis of 18j.** According to the general procedure, method **A**: with methyl-5-hexynoate (606 mg, 4.80 mmol) and oxadiazoline **16** (263 mg, 0.96 mmol). Purification by flash chromatography: hexanes/diethyl ether. **18j** was obtained as a yellow oil (130 mg, 43%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 6.93 (q, *J* 1.2 Hz, 1H), 4.53 (d, *J* 11.6 Hz, 1H), 4.43 (d, *J* 11.6 Hz, 1H), 3.68 (s, 3H), 2.52 (t, *J* 7.2 Hz, 2H), 2.39 (t, *J* 7.6 Hz, 2H),2.03-1.84 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 173.2, 138.0, 128.4, 127.7, 127.5, 126.0 (q, *J* 2.3 Hz), 124.6 (q, *J* 276.2 Hz), 104.4 (q, *J* 3.0 Hz), 68.5, 60.3 (q, *J* 39.2 Hz), 51.6, 32.9, 23.6, 22.0. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.3. HRMS (ESI) Calculated for $C_{16}H_{17}F_3O_3Na$ [M+Na]$^+$: 337.1027; found: *m/z* 337.1013.

**Synthesis of 18k.** According to the general procedure, method **A**: with methyl oct-2-ynoate (740 mg, 4.80 mmol) and oxadiazoline **16** (264 mg, 0.96 mmol). Purification by flash chromatography: then hexanes/diethyl ether. **18k** was obtained as a pale-yellow oil (108 mg, 33%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 4.73 (d, *J* 12.0 Hz, 1H), 4.53 (d, *J* 11.6 Hz, 1H), 3.85 (s, 3H), 2.61-2.48 (m, 2H), 1.74-1.58 (m, 2H), 1.38-1.25 (m, 4H), 0.90 (tm, *J* 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.7, 137.7, 136.0 (q, *J* 2.2 Hz), 128.5, 127.9, 127.6, 123.7 (q, *J* 276.9 Hz), 108.9 (q, *J* 3.0 Hz), 70.3, 62.5 (q, *J* 39.5 Hz), 52.8, 31.2, 26.2, 25.3, 22.3, 13.9. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -72.0. HRMS (ESI) Calculated for $C_{18}H_{21}F_3O_3Na$ [M+Na]$^+$: 365.1340; found: *m/z* 365.1316.

**Synthesis of 18l.** According to the general procedure, method **B**: with *N*-allyl-*N*-tosylbut-2-yn-1-amine (211 mg, 0.80 mmol) and oxadiazoline **16** (658 mg, 2.40 mmol). Purification by flash chromatography: hexanes/diethyl ether. **18l** was obtained as a pale-yellow oil (201 mg, 57%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.67 (dt, *J* 8.0 Hz, *J* 1.8 Hz, 2H), 7.37-7.26 (m, 7H), 5.70-5.60 (m, 1H), 5.16 (q, *J* 1.2 Hz, 2H), 4.46 (s, 2H), 4.22 (d, *J* 1.6 Hz, 2H), 3.85-3.58 (m, 2H), 2.41 (s, 3H), 1.68 (t, *J* 1.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 143.7, 138.0, 136.6, 131.8, 129.8, 128.5, 127.7, 127.3, 127.2, 124.5 (q, *J* 277.1 Hz), 119.9, 116.4 (q, *J* 2.6 Hz), 112.9 (q, *J* 2.5 Hz),

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69.1, 62.2 (q, *J* 38.7 Hz), 50.0, 41.3, 21.4, 8.4. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -71.3. HRMS (ESI) Calculated for $C_{23}H_{24}F_3NO_3SNa$ $[M+Na]^+$: 474.1327; found: *m/z* 474.1313.

**Synthesis of 19.** According to the general procedure, method **A**: with styrene (250 mg, 2.40 mmol) and oxadiazoline **16** (131 mg, 0.48 mmol). Purification by flash chromatography: 100 % hexanes. **19** was obtained as a colorless oil (50 mg, 35%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 7.22-7.18 (m, 3H), 6.93-6.89 (m, 2H), 4.59 (d, *J* 11.2 Hz, 1H), 4.47 (d, *J* 11.2 Hz, 1H), 2.67 (dd, *J* 10.0 Hz, *J* 8.4 Hz, 1H), 1.63-1.56 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.2, 134.2, 129.0, 128.4, 128.3, 127.8, 127.6, 127.2, 125.3 (q, *J* 276.6 Hz), 72.6, 63.6 (q, *J* 35.8 Hz), 27.0, 14.6. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -73.7. HRMS (ESI) Calculated for $C_{10}H_8F_3O$ $[M-Bn]^+$: 201.0527; found: *m/z* 201.0554.

**Synthesis of 20.** According to the general procedure, method **A**: with benzaldehyde (509 mg, 4.8 mmol) and oxadiazoline **16** (263 mg, 0.96 mmol). Purification by flash chromatography: hexanes/toluene. **20** was obtained as a colorless oil (94 mg, 33%). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.64 (tt, *J* 7.2 Hz, *J* 1.6 Hz, 1H), 7.52-7.47 (m, 2H), 7.41-7.30 (m, 5H), 6.35(q, *J* 4.0 Hz, 1H), 4.95 (d, *J* 11.6 Hz, 1H), 4.84 (d, *J* 12.0 Hz, 1H). Data match those previously reported in the literature.[17]

**Synthesis of 21.** According to the general procedure, method **B**: with triethylsilane (0.16 mL, 1.0 mmol) and oxadiazoline **16** (55 mg, 0.20 mmol). Purification by flash chromatography: hexanes/diethyl ether. **21** was obtained as a colorless oil (27 mg, 45%). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 4.90 (d, *J* 11.2 Hz, 1H), 4.48 (d, *J* 11.2 Hz, 1H), 3.57 (q, *J* 10.8 Hz, 1H), 0.96 (t, *J* 7.9 Hz, 9H), 0.68 (q, *J* 7.9 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 137.7, 128.5, 128.2, 128.0, 127.9 (d, *J* 282.7 Hz), 76.6, 70.9 (q, *J* 31.8 Hz), 7.2, 2.1. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -67.6.

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## Supplementary Material

NMR data are included in the supplementary material file associated to this manuscript.

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