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Regioselective Synthesis of Heteroatom-Functionalized Cyclobutene-triflones and Cyclobutenones

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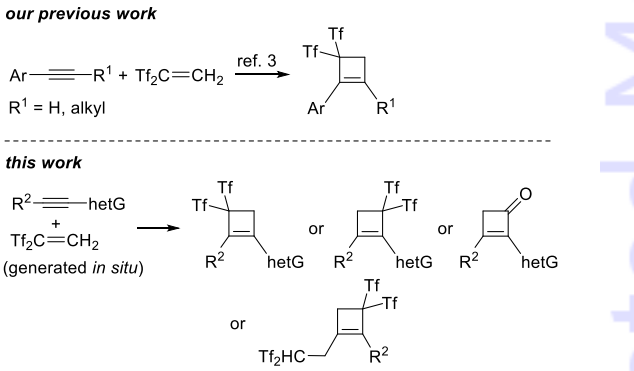
Abstract: The controlled metal-free synthesis of a vast variety of heteroatom-containing cyclobutene-triflones and cyclobutenones has been developed starting from heteroatom-substituted alkynes and a pyridinium salt (a latent $Tf_2C{=}CH_2$ source). This powerful methodology, involving cyclization reactions allows for the selective preparation of oxygen-, nitrogen-, bromine-, chlorine-, iodine-, sulphur-, selenium-, tellurium-, phosphorus-, and silicon-functionalized cyclobutene derivatives.

Keywords: alkynes; annulation; carbocycles; fluorine; synthetic methods

Introduction

The importance of the synthesis of the cyclobutene core is ever increasing in relation to its presence in natural products and biologically active substances.[1] In addition to its biological importance, this strained carbocycle serves as versatile building block and has attracted considerable attention in organic synthesis.[2] One of the most challenging issues in synthesizing cyclobutenes is how to efficiently and selectivity introduce functionality into the four-membered carbocyclic skeleton. We have recently communicated the cyclization reaction of alkynes and $Tf_2C{=}CH_2$ to afford 1-aryl-2-alkyl-4,4-bis(triflyl)cyclobutenes, but this method was restricted so far to 1-aryl-2-alkyl(aryl)substituted alkynes.[3] Due to the marked influence on the physical, chemical, and biological properties of small molecules imparted by the presence of heteroatoms, we envisaged the development of a mild method for the preparation of cyclobutene derivatives bearing an extra heteroatom directly linked to a sp^2 carbon atom of the carbocycle (Scheme 1). These heteroatom-substituted cyclobutene-triflones.[4],[5] should bring together the new properties conferred by heteroatoms and trifyl group with the exceptionally rich chemistry of cyclobutenes.



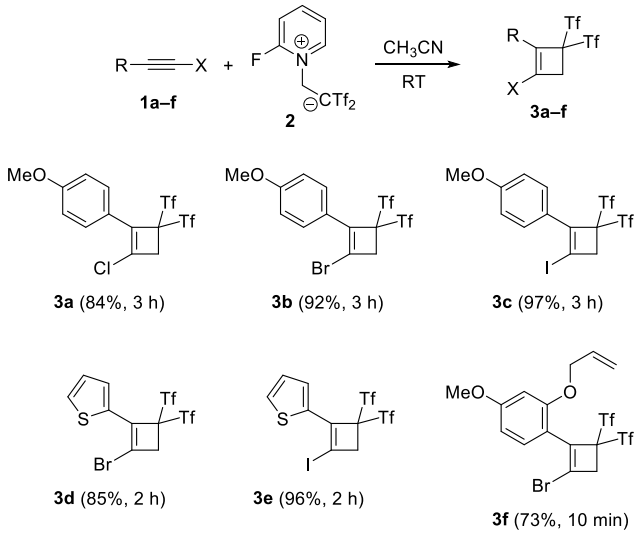
R^2 = aryl, heteroaryl, alkyl, H
hetG = Cl, Br, I, OR, SR, SOR, SO_2R, SeR, TeR, NR_2, POR_2, PSR_2, SiR_3, SnR_3

Scheme 1. Metal-free room temperature synthesis of heteroatom-substituted cyclobutene-triflones or cyclobutenones.

Results and Discussion

To explore the effect of various heteroatomic substituents on cyclobutene-triflone formation, a number of differently functionalized alkynes were selected. 1-Chloroalkyne **1a** was chosen as model substrate to optimize suitable conditions for the reaction with pyridinium salt **2**, a $Tf_2C{=}CH_2$ source. Zwitterion **2** is poorly soluble in apolar or halogenated solvents, which limited the optimization of the solvent parameter. Acetonitrile at room temperature was identified as the best choice for the reaction of 1-chloroalkyne **1a** with **2**. Notably, the reaction of **1a** with **2** led to

bis(trifluoromethylsulfonyl)chlorocyclobutene **3a**, which was obtained in good yield (84%) as single regioisomer without the requirement of any catalyst (Scheme 2). Addition of H_2O may be beneficial by enhancing the solubility of the zwitterionic reagent **2**. However, when the reaction was carried out in a mixture acetonitrile/water (1:1), chlorocyclobutene **3a** was obtained in decreased yield (70%). We further investigated the effect of different halogens on the cyclization as shown in Scheme 2. Reaction of 1-bromo(iodo)alkynes **1a–f** with $Tf_2C{=}CH_2$ afforded cycloadducts **3b–f** as sole products in 73–97% yields. Electron-rich substituents accelerated the reaction progress, as exemplified with the formation of bromocyclobutene-triflone **3f** in just 10 minutes. The structure and regiochemistry of compound **3d** was unambiguously assigned through its X-ray crystallographic analysis (Figure 1).[6]



Scheme 2. Controlled preparation of bis(trifluoromethylsulfonyl) halocyclobutenes **3**.

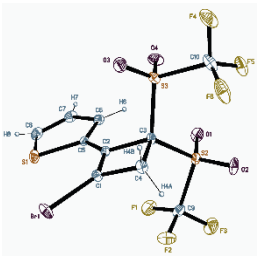
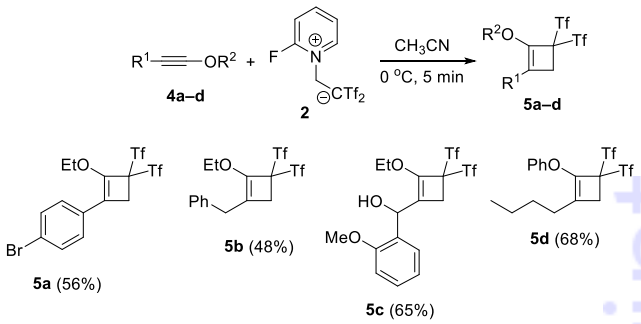


Figure 1. ORTEP drawing of bis(trifluoromethylsulfonyl)bromocyclobutene **3d**. Thermal ellipsoids shown at 50% probability.

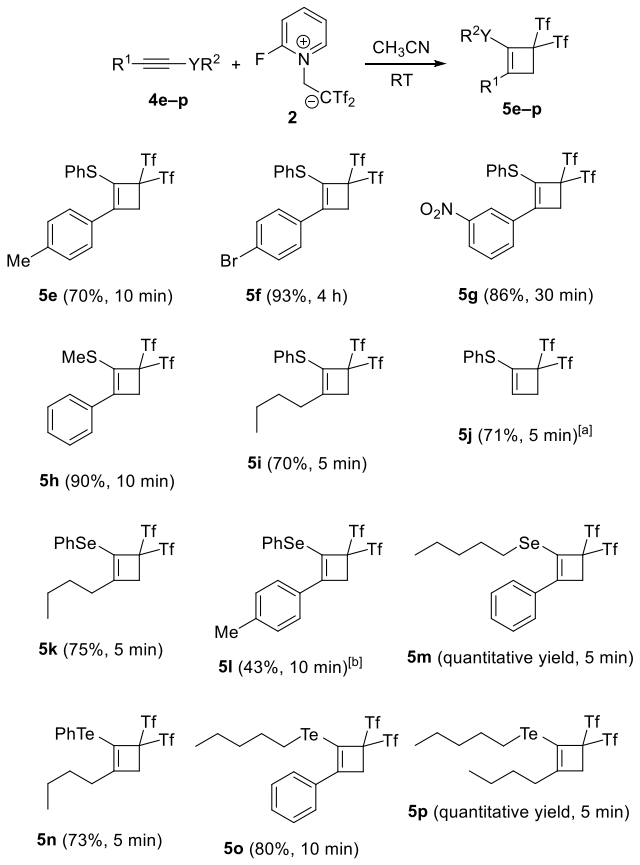
With the best halocyclobutene-triflone formation conditions identified, the scope of this transformation was then examined in alkynyl-ethers, -thioethers, -selenoethers, and -teluroethers **4**. Cyclizations adducts **5a–d** could not be obtained at RT in reasonable yield because ynol ethers **4a–d** quickly reacted in contact with zwitterion **2**, resulting in a complicated reaction. Fortunately, the reactions were more effective at 0 °C, and ynol ethers **4a–d** undergo smooth cyclization to afford cyclic enol ethers **5a–d** in reasonable yields (Scheme 3). Remarkably, the presence of OR groups instead halogens at the starting alkyne reversed the product distribution completely, implying that the choice of substituents can control the regioselectivity of the reaction.



Scheme 3. Controlled preparation of bis(trifluoromethylsulfonyl) enol ether cyclobutenes **5a–d**.

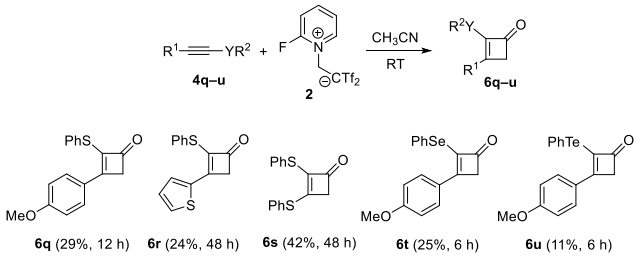
Organosulfur compounds occupy a special position in heteroatom-containing small molecules, both as bioactive compounds as well as synthetic intermediates.[7] We envisaged the preparation of cyclobutene-triflones bearing S-based groups starting from thia-alkynes. The proposed thia-cyclobutene-triflones present intringuing structures, which stability was initially of question given the supposed instability of chalcogen substituted cyclobutene-triflones. Pleasingly, when using thia-alkynes **4e–j** and pyridinium salt **2**, thia-cyclobutene-triflones **5e–j** were isolated in high yields (Scheme 4), indicating the feasibility of this type of structures. In the case of sulphur-based substrates, the same level and sense of regioselectivity as in oxygen derivatives was observed.

Cyclization precursors **4k–p** bearing Se and Te carbon chains were prepared. The standard cyclobutene formation conditions were then applied across this range of substrates. Alkynes **4k–p** efficiently formed the desired polyfunctionalized four-membered rings **5k–p**,[8] but the cyclization proved capricious for Se-derivative **5l** due to partial degradation of the final material under the chromatographic purification conditions (Scheme 4). Interestingly, in all cases the product exhibited the same regiocontrol of oxygen and sulphur derivatives.



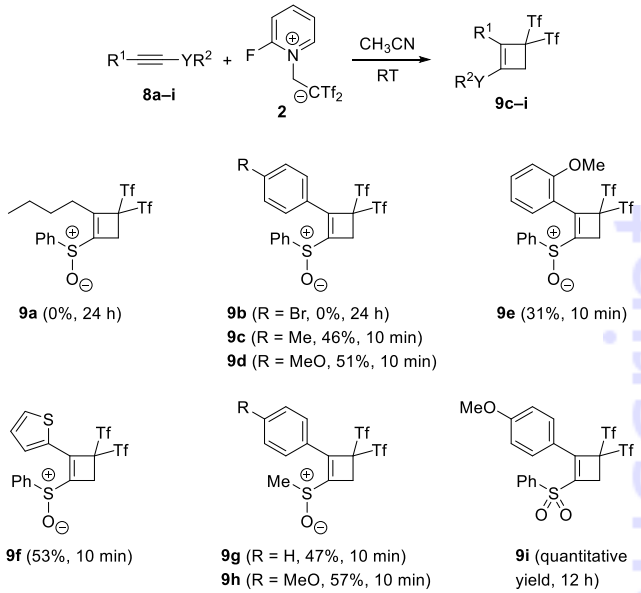
Scheme 4. Controlled preparation of bis(trifluoromethylsulfonyl) chalcogen cyclobutenes **5**. [a] The reaction was carried out at 0 °C. [b] Partial decomposition during chromatographic purification.

Chalcogen substrates **4q–u**, containing an additional electron-rich substituent at the other alkyne side, worked under the standard conditions to afford unexpected cyclobutene derivatives along with unidentified by-products. Cyclobutenones **6q–u** can be accessed from this type of substrates albeit with a lower yield (Scheme 5).



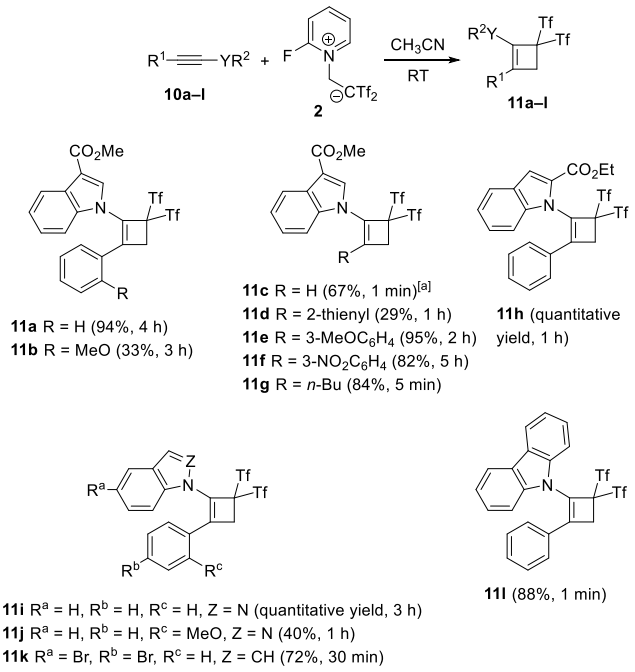
Scheme 5. Preparation of bis(trifluoromethylsulfonyl) chalcogen cyclobutenones **6**.

The influence of different sulphur oxidation states on the reactivity was also tested. In addition of thia-alkynes **4e–j** we were interested in examining sulfinyl alkynes **8a–h** and sulfonyl alkyne **8i**. Firstly, the electronic effect on the S-substituent was investigated and the result showed that substrates bearing aliphatic substituents (**8a**) or deactivated benzene rings (**8b**) did not afford the desired cyclobutenes. By contrast, neutral or electron-rich aromatic substituents can be tolerated to provide sulfinyl cyclobutenes **9c–h** and sulfonyl cyclobutene **9i** (Scheme 6). Notably, a regiochemistry reversal was observed from sulphur with oxidation number –2 such as in alkynes **4e–j** and sulphur with oxidation numbers +4 (alkynes **8c–h**) and +6 (alkyne **8i**).

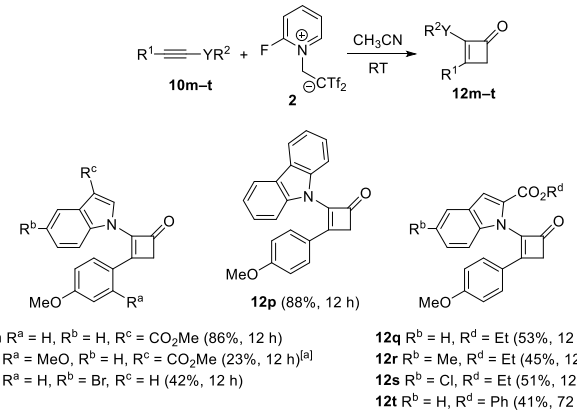


Scheme 6. Controlled preparation of bis(trifluoromethylsulfonyl) sulfinyl cyclobutenes **9d–h** and sulfonyl cyclobutene **9i**.

The effect of an amino group in the four-membered ring formation reaction was investigated with the use of indole-based ynamine derivatives **10a–l**. As in the case of OR, SR, SeR, and TeR substituents (Schemes 3–5), the regioselectivity reversal is dictated by the heteroatom. Ynamines **10a–l** afforded the corresponding cyclobutenes **11a–l** as the sole products in fair yields (Scheme 7). These examples also indicated that ynamines **11a**, **11h**, and **11i** bearing the simple phenyl ring at N1 are the best starting materials, furnishing the highest yields (quantitative or almost quantitative yields) of the appropriate cyclobutenes. Unexpectedly, results in Scheme 8 show, in all instances, that ynamines **10m–t** having electron-rich $4MeOC_6H_4$ groups furnished exclusively cyclobutenones **12m–t**.[9],[10] Cyclobutenone formation is spontaneous under the reaction conditions, but it may be facilitated by the addition of water (2 equiv) and K_2CO_3 (2 equiv) during the work-up.

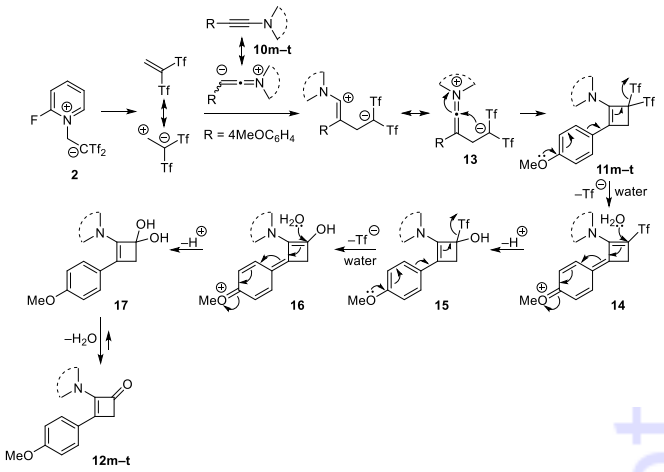


Scheme 7. Controlled preparation of bis(trifluoromethylsulfonyl) indolyl cyclobutenes **11a–l**. [a] The reaction was carried out at 0 °C.



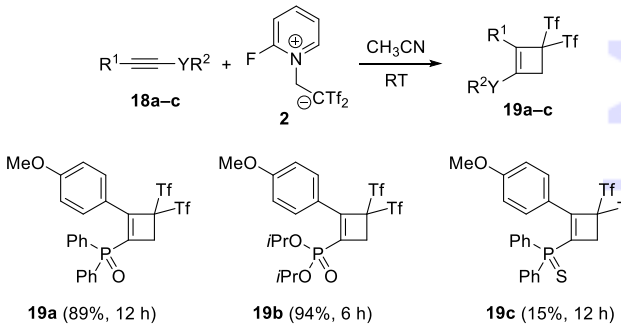
Scheme 8. Controlled preparation of bis(trifluoromethylsulfonyl) indolyl cyclobutenones **12m–t**. [a] Messy reaction.

As shown in Scheme 9, the mechanism for the cyclobutenone formation involves two main processes, namely, cyclobutene ring construction and hydrolysis. The proposal for the first process (formation of **11m–t**) is based on our previous DFT studies of 1-aryl-2-alkyl-4,4-bis(triflyl)cyclobutenes,[5] but now the regioselectivity is dictated by the electronic effects of the heterocyclic amine. Adventitious water in the reaction medium is required for the double trifluoro(hydrosulfonyl)methane (TfH) elimination, giving rise to hydrates **17**. This twofold water addition is assisted by the resonance effect of the 4-methoxy substituent in the 4-methoxyphenyl group. Finally, dehydration occurs in adducts **17** to afford cyclobutenones **12m–t**.



Scheme 9. Rationalization for the formation of cyclobutenones **12**.

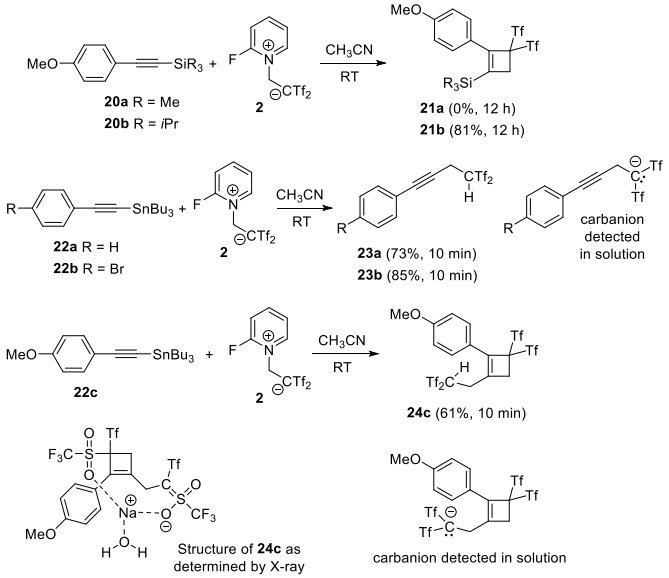
We decided to examine phosporus-substituted alkynes **18** as precursors of functionalized cyclobutenes (Scheme 10).[11] Screening of precursors **18** revealed that phosphine oxides **18a** and **18b** afforded phosphoryl cyclobutenes **19a** and **19b** in excellent yields under the usual mild conditions. However, despite that apparently thiophosphine oxide **18c** is a suitable substrate for the reaction, it produced the S=P(Ph)$_2$-cyclobutene **19c** in just 15% yield.



Scheme 10. Controlled preparation of bis(trifluoromethylsulfonyl) phosphoryl cyclobutenes **19a–c**.

Taking into account the rich chemistry of silicon and tin organoderivatives, we also became interested in the cyclobutenylation of trialkyl(ethynyl)silanes and trialkyl(ethynyl)stannanes by pyridinium salt **2** as cyclization reagent. If successfull, this reaction could afford carbon(sp^2)-linked trialkylsilyl- and trialkylstannyl-cyclobutenes. The formation of the expected TMS-cyclobutene **21a** was observed by TLC, but it could not be isolated with synthetic purposes. We were pleased to observe that the reaction of the TIPS-alkyne **20b** afforded the corresponding TIPS-cyclobutene **21b** in high yield (Scheme 11). An unexpected product was obtained starting from Bu$_3$Sn-alkyne **22a**, which identity was assigned as **23a** and resulted from the transformation of the Bu$_3$Sn group rather that the alkyne moiety. A similar behaviour was detected in the conversion of organotin derivative **22b** into adduct **23b**. Interestingly, stirring alkynyl stannane **22c** at RT in

acetonitrile with zwitterion **2** led to the formation of tetra(trifluoromethylsulfonyl)cyclobutene **24c**, in 61% isolated yield in just 10 minutes (Scheme 11). Noticeably, compounds **23a**, **23b**, and **24c** are carbon acids which in solution easily dissociate the acidic hydrogen and give rise to stable carbanions.[12] When the ^{1}H NMR spectra of **23a**, **23b**, and **24c** were performed, the signals for the hydrogen atoms of the Tf_2CH group could not be detected. Further supporting structural evidence was obtained through the X-ray crystallographic analysis of adduct **24c** (Figure 2).[13]



Scheme 11. Controlled preparation of bis(trifluoromethylsulfonyl) silacyclobutene **21b** and triflone carbanions **23a,b** and **24c**.

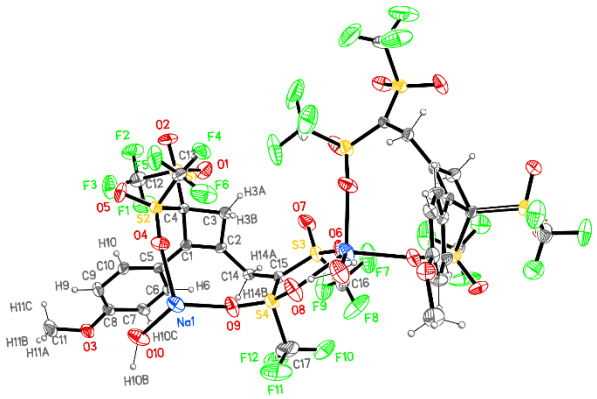
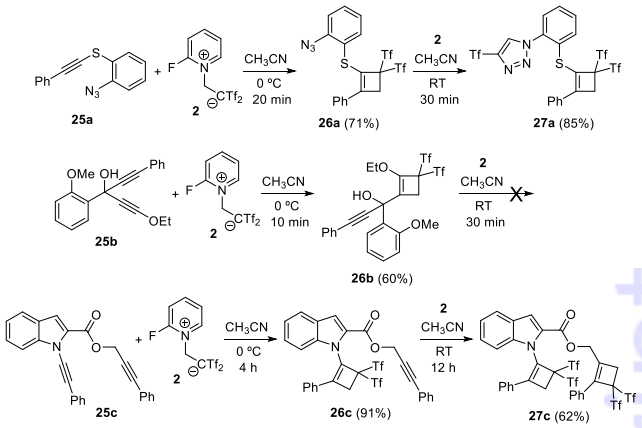


Figure 2. ORTEP drawing of tetra(trifluoromethylsulfonyl)cyclobutene **24c**. Thermal ellipsoids shown at 50% probability.

To evaluate the goal of chemoselectivity, several functionalized heteroatom-containing alkynes **25a–c** were reacted under the above standard reaction conditions. Every single reaction reached full conversion to selectively afford cyclobutenes **26a–c**, in which monocyclization towards the heteroatom-substituted alkyne was favored. Bis-functionalization of the remaining alkyne or azide functionality was achieved after the addition of a second equivalent of zwitterion **2**, suggesting that the exquisite selectivity arises from the increased reactivity imparted by the heteroatom.



Scheme 12. Chemoselective reaction of heteroatom-containing alkynes **25**.

Conclusions

In summary, we have developed a new metal-free synthesis of a vast variety of heteroatom-containing cyclobutene--triflones and cyclobutenones from the reaction of heteroatom-substituted alkynes with a pyridinium salt as a $Tf_2C{=}CH_2$ source. This powerful methodology, involving cyclization allows for the selective preparation of oxygen-, nitrogen-, bromine-, chlorine-, iodine-, sulphur-, selenium-, tellurium-, phosphorus-, and silicon-functionalized cyclobutene derivatives.

Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 76.9 ppm), or acetone-d_6 (^{1}H, 2.05 ppm; ^{13}C, 206.3 ppm), or C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm), or CD_3CN (^{1}H, 1.94 ppm; ^{13}C, 118.2 ppm), or DMSO-d_6 (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. All commercially available compounds were used without further purification.

General procedure for the reaction of heteroatom-substituted alkynes and pyridinium salt 2. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (0.2 mmol) was added at room temperature (or 0 °C) to a solution of the appropriate heteroatom-substituted alkyne **1a–f, 4a–u, 8a–i, 10a–l, 18a–c, 20a, 20b, 22a–c, 25a–c, 26a–c** (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts **3a–f, 5a–p, 6q–u, 9c–i, 11a–l, 19a–c, 21b, 23a, 23b, 24c, 26a–c, 271, 27c** follow.[14]

Bis(trifluoromethylsulfonyl)iodocyclobutene 3c. From 43 mg (0.16 mmol) of alkyne **1c**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **3c** (153 mg, 97%) as a pale yellow solid; mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.91 (m, 2H, $2CH^{Ar}$), 6.98 (m, 2H, $2CH^{Ar}$), 3.86 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.5 ($C^{Ar\text{-}q}$-OCH_3), 142.4 (*C*=C-I), 128.7 ($2CH^{Ar}$), 121.2 ($C^{Ar\text{-}q}$), 119.7 (q, J_{CF} = 331.5 Hz, $2CF_3$), 114.1 ($2CH^{Ar}$), 93.7 (C=*C*-I), 90.0 (CTf_2), 55.4 (CH_3O), 42.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.61 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1608 (C=C), 1384, 1103 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{13}H_{13}IF_6NO_5S_2$ [*M* + NH_4]$^+$: 567.9179; found: 567.9177.

Bis(trifluoromethylsulfonyl)phenoxycyclobutene 5d. From 20 mg (0.11 mmol) of alkyne **4d**, and after flash chromatography of the residue using hexanes/toluene (9:1→8:2) as eluent gave compound **5d** (36 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (m, 2H, $2CH^{Ar}$), 7.22 (m, 3H, $3CH^{Ar}$), 2.98 (s, 2H, CH_2-*cyclobutenyl*), 1.77 (t, 3H, *J* = 7.2 Hz, CH_2), 1.24 (m, 4H, $2CH_2$), 0.79 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.1 ($C^{Ar\text{-}q}$-O), 133.7 (C=*C*-O), 132.5 (*C*=C-O), 129.9 ($2CH^{Ar}$), 125.6 (CH^{Ar}), 119.7 (q, J_{CF} = 330.5 Hz, $2CF_3$), 119.0 ($2CH^{Ar}$), 86.8 (CTf_2), 30.0 (CH_2-*cyclobutenyl*), 27.8 (CH_2), 27.0 (CH_2), 22.1 (CH_2), 13.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.91 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1695 (C=C), 1383, 1106 (O=S=O), 1204 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{20}F_6NO_5S_2$ [*M* + NH_4]$^+$: 484.0682; found: 484.0671.

Bis(trifluoromethylsulfonyl)thiocyclobutene 5f. From 30 mg (0.103 mmol) of alkyne **4f**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **5f** (56 mg, 93%) as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.25 (m, 2H, $2CH^{Ar}$), 6.96 (m, 2H, $2CH^{Ar}$), 6.79 (m, 5H, $5CH^{Ar}$), 3.17 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 159.0 (C=*C*-S), 131.9 ($2CH^{Ar}$), 130.3 ($C^{Ar\text{-}q}$), 129.7 ($2CH^{Ar}$), 129.6 ($2CH^{Ar}$), 129.5 ($2CH^{Ar}$), 128.6 ($C^{Ar\text{-}q}$), 128.0 (CH^{Ar}), 126.9 ($C^{Ar\text{-}q}$), 120.3 (q, J_{CF} = 331.1 Hz, $2CF_3$), 121.0 (*C*=C-S), 89.2 (CTf_2), 34.8 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = –70.29 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1599 (C=C), 1383, 1106 (O=S=O), 1207 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{18}H_{15}BrF_6NO_4S_3$ [*M* + NH_4]$^+$: 597.9245; found: 597.9231.

Bis(trifluoromethylsulfonyl)selenocyclobutene 5m. From 30 mg (0.12 mmol) of alkyne **4m**, and after flash chromatography of the residue using hexanes→hexanes/ethyl acetate (95:5) as eluent gave compound **5m** (64 mg, quantitative yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82 (m, 2H, $2CH^{Ar}$), 7.51 (m, 3H, $3CH^{Ar}$), 3.76 (s, 2H, CH_2-*cyclobutenyl*), 3.04 (t, 2H, *J* = 7.5 Hz, CH_2), 1.73 (m, 2H, CH_2), 1.33 (m, 4H, $2CH_2$), 0.86 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 161.6 (*C*=C-Se), 131.9 (CH^{Ar}), 130.7 ($C^{Ar\text{-}q}$), 128.9 ($2CH^{Ar}$), 127.4 ($2CH^{Ar}$), 119.8 (q, J_{CF} = 331.3 Hz, $2CF_3$), 115.0 (C=*C*-Se), 87.8 (CTf_2), 36.4 (CH_2-*cyclobutenyl*), 31.7 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 22.0 (CH_2), 13.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.23 (s, 6F, $2CF_3$); ^{77}Se NMR (95 MHz, $CDCl_3$, 25 °C): δ = 245.0 (s, 1Se, Se); IR ($CHCl_3$): ν = 1381, 1106 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{22}F_6NO_4S_2Se$ [*M* + NH_4]$^+$: 562.0054; found: 562.0037.

Bis(trifluoromethylsulfonyl)telurocyclobutene 5p. From 50 mg (0.178 mmol) of alkyne **4p**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **5p** (102 mg, quantitative yield) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.62 (s, 2H, CH_2-*cyclobutenyl*), 2.90 (t, 2H, *J* = 7.6 Hz, CH_2), 2.43 (t, 2H, *J* = 7.4 Hz, CH_2), 1.82 (m, 2H, CH_2), 1.41 (m, 8H, $4CH_2$), 0.91 (m, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 178.6 (*C*=C-Te), 119.9 (q, J_{CF} = 331.1 Hz, $2CF_3$), 98.3 (C=*C*-Te), 86.5 (CTf_2), 39.8 (CH_2-*cyclobutenyl*), 33.9 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 13.9 (CH_3), 13.7 (CH_3), 10.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = –70.27 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1605 (C=C), 1380, 1107 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{15}H_{26}F_6O_4S_2Te$ [*M* + NH_4]$^+$: 592.0260; found: 592.0254.

Thiocyclobutenone 6s. From 30 mg (0.12 mmol) of alkyne **4s**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **6s** (15 mg, 42%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37 (m, 10H, $10CH^{Ar}$), 3.31 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 182.0 (C=O), 172.9 (*C*=C), 134.1 ($2CH^{Ar}$), 131.6 ($C^{Ar\text{-}q}$), 130.4 ($2CH^{Ar}$), 130.1 (CH^{Ar}), 129.6 ($C^{Ar\text{-}q}$), 129.4 ($2CH^{Ar}$), 129.0 ($2CH^{Ar}$), 128.4 (C=*C*), 127.2 (CH^{Ar}), 52.3 (CH_2); IR ($CHCl_3$): ν = 1742 (C=O) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{13}OS_2$ [*M* + H]$^+$: 285.0402; found: 285.0410.

Bis(trifluoromethylsulfonyl)sulfinylcyclobutene 9f. From 15 mg (0.064 mmol) of alkyne **8f**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1→8:2) as eluent gave compound **9f** (18 mg, 53%) as a pale yellow oil; ^{1}H NMR (700 MHz, C_6D_6, 25 °C): δ = 7.92 (d, 1H, *J* = 3.1 Hz, CH^{Ar}), 7.53 (m, 2H, $2CH^{Ar}$), 6.95 (m, 3H, $3CH^{Ar}$), 6.67 (d, 1H, *J* = 5.0 Hz, CH^{Ar}), 6.38 (t, 1H, *J* = 4.4 Hz, CH^{Ar}), 3.53 (d, 1H, *J* = 15.7 Hz, CH*H*-*cyclobutenyl*), 2.93 (d, 1H, *J* = 15.7 Hz, C*H*H-*cyclobutenyl*); ^{13}C NMR (175 MHz, C_6D_6, 25 °C): δ =

146.0 (C=*C*-S), 141.0 ($C^{Ar\text{-}q}$), 134.1 (CH^{Ar}), 132.3 (*C*=C-S), 132.2 (CH^{Ar}), 131.9 (CH^{Ar}), 129.7 ($2CH^{Ar}$), 128.7 (CH^{Ar}), 127.6 ($C^{Ar\text{-}q}$), 124.1 ($2CH^{Ar}$), 120.2 (q, J_{CF} = 331.8 Hz, CF_3), 119.9 (q, J_{CF} = 331.6 Hz, CF_3), 84.4 (CTf_2), 33.7 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.74 (s, 3F, CF_3), –71.63 (s, 3F, CF_3); IR (CH_2Cl_2): ν = 1386, 1105 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{16}H_{11}F_6O_5S_4$ [*M* + H]$^+$: 524.9388; found: 524.9400.

Bis(trifluoromethylsulfonyl)sulfonylcyclobutene 9i. From 44 mg (0.16 mmol) of alkyne **8i**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **9i** (90 mg, quantitative yield) as a colorless solid; mp 103–105 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.07 (m, 2H, $2CH^{Ar}$), 7.93 (m, 2H, $2CH^{Ar}$), 7.71 (m, 1H, CH^{Ar}), 7.59 (m, 2H, $2CH^{Ar}$), 6.97 (m, 2H, $2CH^{Ar}$), 3.88 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 163.0 ($C^{Ar\text{-}q}$-OCH_3), 141.9 (*C*=C-SO_2Ph), 139.1 (C=*C*-SO_2Ph), 137.5 ($C^{Ar\text{-}q}$), 135.0 (CH^{Ar}), 132.5 ($2CH^{Ar}$), 129.7 ($2CH^{Ar}$), 127.9 ($2CH^{Ar}$), 119.6 (q, J_{CF} = 331.5 Hz, $2CF_3$), 119.5 ($C^{Ar\text{-}q}$), 114.3 ($2CH^{Ar}$), 84.2 (CTf_2), 55.5 (OCH_3), 35.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.51 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1599 (C=C), 1386, 1101 (O=S=O), 1212 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{18}F_6NO_7S_3$ [*M* + NH_4]$^+$: 582.0144; found: 582.0155.

Bis(trifluoromethylsulfonyl)aminocyclobutene 11a. From 20 mg (0.07 mmol) of alkyne **10a**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **11a** (38 mg, 94%) as a colorless solid; mp 117–119 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 8.65 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 8.35 (s, 1H, NCH^{Ar}), 7.40 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.15 (m, 1H, CH^{Ar}), 6.98 (m, 1H, CH^{Ar}), 6.84 (m, 1H, CH^{Ar}), 6.65 (m, 4H, $4CH^{Ar}$), 3.48 (s, 3H, CH_3), 3.11 (s, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 164.0 (C=O), 152.9 (C=*C*-N), 136.4 (*C*=C-N), 132.5 (CH^{Ar}), 131.7 (CH^{Ar}), 129.1 ($2CH^{Ar}$), 128.4 ($2CH^{Ar}$), 128.2 ($C^{Ar\text{-}q}$), 126.9 ($C^{Ar\text{-}q}$), 125.0 (CH^{Ar}), 124.0 (CH^{Ar}), 123.0 (CH^{Ar}), 120.1 (q, J_{CF} = 330.8 Hz, $2CF_3$), 118.9 ($C^{Ar\text{-}q}$), 112.8 ($C^{Ar\text{-}qo}$), 112.0 (CH^{Ar}), 90.0 (CTf_2), 51.0 (CH_3), 31.1 (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 ºC): δ = –70.44 (s, 6F, $2CF_3$); IR (CH_2Cl_2): ν = 1711 (C=O), 1375, 1102 (O=S=O), 1196 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{19}F_6N_2O_6S_2$ [*M* + NH_4]$^+$: 585.0583; found: 585.0559.

Bis(trifluoromethylsulfonyl)phosphinylcyclobutene 19b. From 53 mg (0.18 mmol) of alkyne **18b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **19b** (99 mg, 94%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 8.06 (m, 2H, $2CH^{Ar}$), 6.95 (m, 2H, $2CH^{Ar}$), 4.76 (m, 2H, 2CH), 3.85 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2), 1.37 (d, 6H, *J* = 6.2 Hz, $2CH_3$), 1.27 (d, 6H, *J* = 6.2 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 162.1 ($C^{Ar\text{-}q}$-OCH_3), 145.6 (d, J_{CP} = 9.9 Hz, *C*=C-P), 136.6 (d, J_{CP} = 188.7 Hz, C=*C*-P), 131.1 ($2CH^{Ar}$), 121.5 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.6 Hz, $2CF_3$), 114.0 ($2CH^{Ar}$), 86.3 (d, J_{CP} = 35.8 Hz, CTf_2), 72.5 (d, J_{CP} = 5.6 Hz, 2CH), 55.3 (OCH_3), 36.0 (d, J_{CP} = 7.9 Hz, CH_2), 24.0 (d, J_{CP} = 4.1 Hz, $2CH_3$), 23.7 (d, J_{CP} = 5.0 Hz, $2CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.57 (s, 6F, $2CF_3$); ^{31}P NMR (121 MHz, $CDCl_3$, 25 ºC): δ = 4.48 [s, P, P=O(O^iPr)$_2$]; IR ($CHCl_3$): ν = 1605 (C=C), 1387, 1103 (O=S=O), 1206 (C–F), 988 (P=O) cm^{-1}; HRMS (ES): calcd for $C_{19}H_{23}F_6O_8PS_2Na$ [*M* + Na]$^+$: 611.0368; found: 611.0353.

Bis(trifluoromethylsulfonyl)silacyclobutene 21b. From 50 mg (0.17 mmol) of alkyne **20b**, and after flash chromatography of the residue using hexanes/ethyl acetate (99:1) as eluent gave compound **21b** (80 mg, 81%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.42 (m, 2H, $2CH^{Ar}$), 6.89 (m, 2H, $2CH^{Ar}$), 3.84 (s, 3H, OCH_3), 3.32 (s, 2H, CH_2), 1.10 (m, 21H, 3CH + $6CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 162.3 (*C*=C-Si), 160.7 ($C^{Ar\text{-}q}$-OCH_3), 149.0 (C=*C*-Si), 129.9 ($2CH^{Ar}$), 125.1 ($C^{Ar\text{-}q}$), 119.8 (q, J_{CF} = 331.1 Hz, $2CF_3$), 113.5 ($2CH^{Ar}$), 90.1 (CTf_2), 55.2 (OCH_3), 36.2 (CH_2), 18.4 ($6CH_3$), 11.5 (3CH); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.29 (s, 6F, $2CF_3$); IR ($CHCl_3$): ν = 1614 (C=C), 1379, 1106 (O=S=O), 1203 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{22}H_{31}F_6NO_5S_2Si$ [*M* + NH_4]$^+$: 598.1546; found: 598.1566.

Bis(trifluoromethylsulfonyl)bis(trifluoromethylsulfonyl)cyclobutene 24c. From 20 mg (0.047 mmol) of alkyne **22c**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound **24c** (21 mg, 61%) as a colorless solid; mp 153–155 ºC; ^{1}H NMR (300 MHz, acetone-d_6, 25 ºC): δ = 7.60 (m, 2H, $2CH^{Ar}$), 6.96 (m, 2H, $2CH^{Ar}$), 3.80 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2), 3.51 (s, 2H, CH_2-*cyclobutenyl*). The signal of C*H*Tf_2 is not visible in the ^{1}H-RMN spectrum because of its acidity; ^{13}C NMR (75 MHz, acetone-d_6, 25 ºC): δ = 161.3 ($C^{Ar\text{-}q}$-OCH_3), 156.4 (*C*=C), 130.5 (C=*C*), 130.2 ($2CH^{Ar}$), 123.5 ($C^{Ar\text{-}q}$), 122.6 (q, J_{CF} = 327.7 Hz, $2CF_3$), 120.9 (q, J_{CF} = 331.1 Hz, $2CF_3$-*cyclobutenyl*), 114.9 ($2CH^{Ar}$), 86.9 (CTf_2-*cyclobutenyl*), 61.2 (CTf_2), 55.8 (OCH_3), 37.5 (CH_2-*cyclobutenyl*), 29.6 (CH_2). The signal of *C*HTf_2 is visible in the ^{13}C-RMN spectrum as a quaternary carbon rather than as a CH because of the deprotonation; ^{19}F NMR (282 MHz, acetone-d_6, 25 ºC): δ = –72.04 (s, 6F, $2CF_3$-*cyclobutenyl*), –80.10 (s, 6F, $2CF_3$); IR (acetone): ν = 1608 (C=C), 1380, 1099 (O=S=O), 1346, 1042 (O=S=O), 1192 (C–F) cm^{-1}; HRMS (ES): calcd for $C_{17}H_{16}F_{12}NO_9S_4$ [*M* + NH_4]$^+$: 733.9511; found: 733.9513.

Bis(trifluoromethylsulfonyl)thiocyclobutene 27a. From 15 mg (0.027 mmol) of azide **26a**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **27a** (17 mg, 85%) as a yellow oil; ^{1}H NMR (700 MHz, $CDCl_3$, 25 ºC): δ = 8.80 (s, 1H, CH-*triazolyl*), 7.87 (m, 2H, $2CH^{Ar}$), 7.76 (m, 1H, CH^{Ar}), 7.63 (m, 1H, CH^{Ar}), 7.54 (m, 4H, $4CH^{Ar}$), 7.49 (m, 1H, CH^{Ar}), 3.68 (s, 2H, CH_2); ^{13}C NMR (175 MHz, $CDCl_3$, 25 ºC): δ = 165.9 (C=*C*-S), 139.5 ($C^{Ar\text{-}q}$-Tf), 136.1 (*C*=C-S), 134.5 (CH^{Ar}), 133.7 (CH^{Ar}), 133.1 (CH^{Ar}), 131.8 (CH^{Ar}), 130.1 (CH^{Ar}), 129.5 ($2CH^{Ar}$), 129.3 ($C^{Ar\text{-}q}$), 128.1 ($2CH^{Ar}$), 127.4 ($C^{Ar\text{-}q}$), 127.1 (CH^{Ar}), 119.6 (q, J_{CF} = 330.8 Hz, $2CF_3$), 119.4 (q, J_{CF} = 324.4 Hz, CF_3), 116.7 ($C^{Ar\text{-}q}$), 88.0 (CTf_2), 35.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 ºC): δ = –70.44 (s, 6F, $2CF_3$), –78.50 (s, 3F, CF_3); IR ($CHCl_3$): ν = 1385, 1104 (O=S=O), 1214 (C–F) cm^{-1};

HRMS (ES): calcd for $C_{21}H_{16}F_9N_4O_6S_4$ [M + NH_4]$^+$: 718.9803; found: 718.9797.

General procedure for the uncatalyzed reaction of heteroatom-substituted alkynes 10m–t and pyridinium salt 2. **Synthesis of cyclobutenones 12m–t.** 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (0.2 mmol) was added at room temperature to a solution of the appropriate ynamine **10m–t** (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC). Saturated potassium carbonate (2 mL) was added and the mixture was stirred for 10 minutes, before being partitioned between ethyl acetate and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts **12m–t** follow.

Aminocyclobutenone 12p. From 20 mg (0.07 mmol) of alkyne **10p**, and after flash chromatography of the residue using hexanes/ethyl acetate (85:15) as eluent gave compound **12p** (20 mg, 88%) as a colorless solid; mp 154–156 ºC; ^{1}H NMR (300 MHz, C_6D_6, 25 ºC): δ = 7.96 (d, 2H, J = 7.7 Hz, 2CH^{Ar}), 7.41 (d, 2H, J = 8.0 Hz, 2CH^{Ar}), 7.28 (m, 2H, 2CH^{Ar}), 7.21 (m, 2H, 2CH^{Ar}), 6.95 (m, 2H, 2CH^{Ar}), 6.38 (m, 2H, 2CH^{Ar}), 3.11 (s, 2H, CH_2). 3.07 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, C_6D_6, 25 ºC): δ = 183.8 (C=O), 162.5 ($C^{Ar\text{-}q}$-OCH_3), 157.7 (C=C-N), 139.0 (2$C^{Ar\text{-}q}$), 132.9 (2CH^{Ar}), 128.7 (C=C-N), 126.5 (2CH^{Ar}), 124.5 (2$C^{Ar\text{-}q}$), 123.9 ($C^{Ar\text{-}q}$), 121.3 (2CH^{Ar}), 120.7 (2CH^{Ar}), 114.3 (2CH^{Ar}), 112.5 (2CH^{Ar}), 54.8 (OCH_3), 45.5 (CH_2); IR (CH_2Cl_2): ν = 1760 (C=O), 1602 (C=C), 1262 (C–O) cm^{-1}; HRMS (ES): calcd for $C_{23}H_{18}NO$ [M + H]$^+$: 340.1332; found: 340.1324.

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FULL PAPER

Regioselective Synthesis of Heteroatom-Functionalized Cyclobutene-triflones and Cyclobutenones

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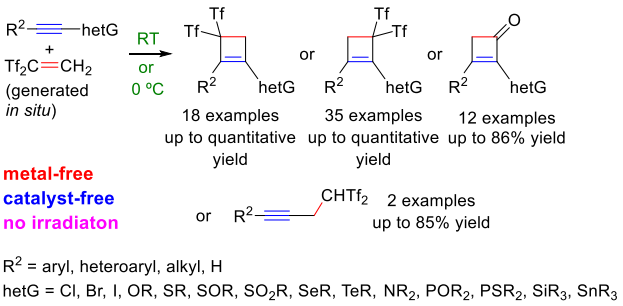

R^2 = aryl, heteroaryl, alkyl, H

hetG = Cl, Br, I, OR, SR, SOR, SO_2R, SeR, TeR, NR_2, POR_2, PSR_2, SiR_3, SnR_3