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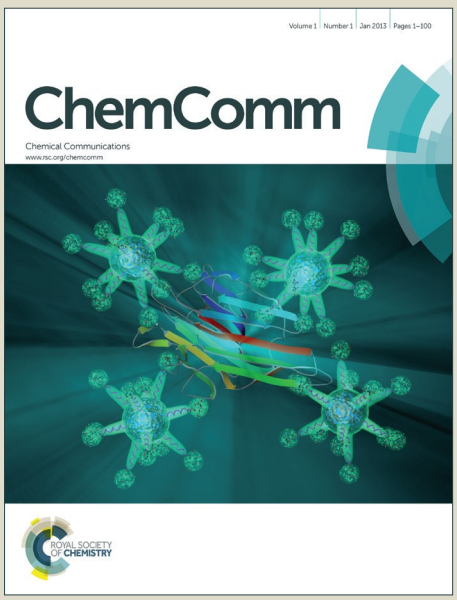

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ARTICLE TYPE

Unveiling the uncatalyzed reaction of alkynes with 1,2-dipoles for the room temperature synthesis of cyclobutenes

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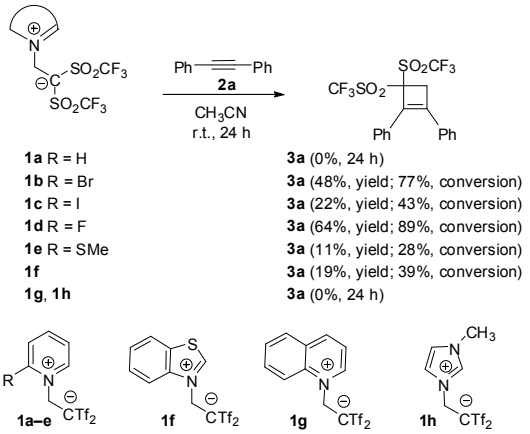
2-(Pyridinium-1-yl)-1,1-bis(triflyl)ethanides have been used as 1,2-dipole precursors in a metal-free direct [2+2] cycloaddition reaction of alkynes. Starting from stable zwitterionic pyridinium salts, the electron deficient olefin 1,1-bis(trifluoromethylsulfonyl)ethene is generated in situ and immediately reacted at room temperature with an alkyne to afford substituted cyclobutenes. Remarkably, this mild and facile uncatalyzed protocol does require neither irradiation nor heating.

Cyclobutene derivatives are attractive compounds both as target molecules as well as useful building blocks for the construction of more complex structures.[1–7] The most popular method for cyclobutene preparation in a single step is the [2+2] cycloaddition reaction of alkynes with unsaturated systems.[8] The [2+2] cycloaddition of alkynes with alkenes has been studied both under photochemical or thermal conditions as well as by transition-metal catalysis. Because the thermal [π2s + π2s] transformation is a forbidden process according to the Woodward–Hoffmann orbital symmetry principles,[9] in most cases the occurrence of discrete diradical or ionic intermediates has been suggested for both thermal and photoinitiated [2+2] reactions. Despite that, these traditional protocols present serious drawbacks because: a) modest yields are usually encountered; and b) either photochemical or strong thermal conditions are required, which may be incompatible with selectivity control as well as sensitive functional groups. Although metal-catalyzed strategies have merged recently, their widespread use in cyclobutene synthesis is precluded due to the narrow substrate scope and moderate selectivity,[10–13] or because of the use of environmentally unsafe or expensive transition-metal salts.[14–17]

Alkynes are useful starting materials for the preparation of a variety of different compounds,[18,19] and when used as reactants in 1,3-dipolar cycloaddition reactions they typically afford five-membered cycles. By analogy, the reaction of alkynes with 1,2-dipoles through a 1,2-dipolar cycloaddition reaction may be a possible solution to produce cyclobutenes with high reaction efficiency.[20] However, this synthetic achievement has not yet been accomplished mainly due to the lack of synthetic methods allowing the facile access to 1,2-dipoles. We describe herein the uncatalyzed reaction of alkynes with the 1,2-dipole 1,1-bis(trifluoromethylsulfonyl)ethene, as a straightforward route towards cyclobutenes at room temperature.

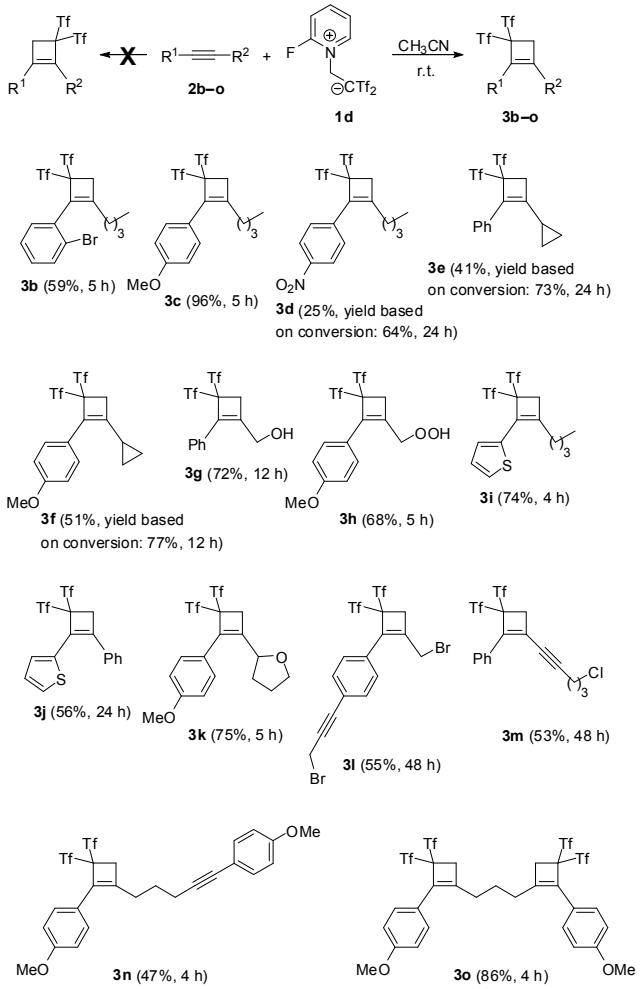
In order to achieve a practical and convenient synthesis of cyclobutenes from alkynes, a facile access to the 1,2-dipole partner, namely, the highly polarized $Tf_2C{=}CH_2$ reagent is required. Noticeably, azolium salts **1a–h** (Scheme 1) have been identified as stable precursors of the 1,1-bis(trifluoromethylsulfonyl)ethene species.[21]



Scheme 1 Room temperature uncatalyzed synthesis of diphenyl cyclobutene **3a** using differently substituted zwitterions **1**.

1,2-Diphenylethyne **2a** was then selected to test the cyclobutene formation through its reaction with 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanide **1a**. Disappointingly, the cyclobutene was not formed in the event. Much to our delight, modification of the electronic nature of the derivative **1** by using differently substituted pyridinium and azolium salts was highly beneficial, because the bromoderivative **1b** gave the cyclobutene **3a** in a fair 48% isolated yield. Even better result (64% yield) was obtained with the fluoropyridinium **1d** (Scheme 1). Worthy of note, the formation of cyclobutene **3a** was successfully carried out at room temperature with no requirements for catalyst, light or heating sources. The formal [2+2] cycloadditon reaction was optimized in the absence of any additive by systematically changing several reaction parameters. On changing the solvent polarity, the efficiency of the reaction changed slightly. Lower reaction yields and recovery of the starting material were observed using DMSO, DMF or THF. It was found that the reaction in the initially selected solvent acetonitrile gave the best results. Among all the temperatures examined, room temperature proved to be the best choice, affording cyclobutene **3a** in a reasonable 64% yield.

Finally as observed, the optimal reaction conditions for the cyclobutene formation turned out to be 2-(2-fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **1d** (1 equiv) with the appropriate alkyne (1 equiv), at room temperature in acetonitrile.

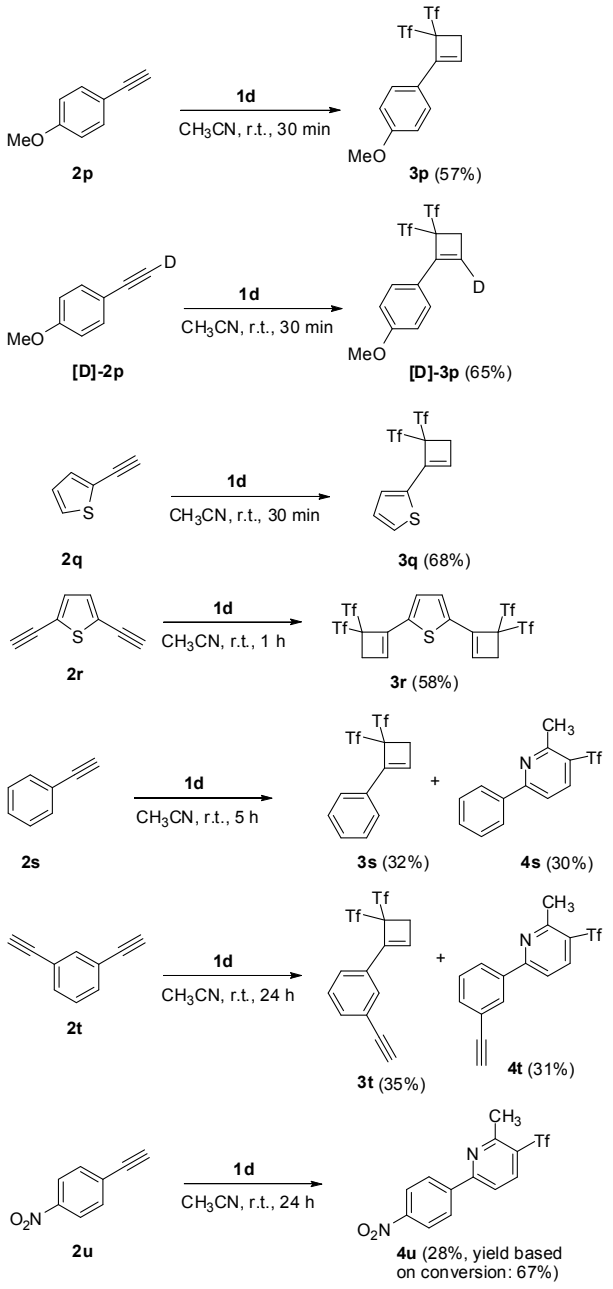


Scheme 2 Room temperature uncatalyzed synthesis of cyclobutenes **3b–o** from differently substituted alkynes **2**.

Having identified the optimized reaction conditions we proceeded to study the alkyne scope to further expand the synthetic utility of the process (Scheme 2). A variety of aliphatic, aromatic, and heteroaromatic substituents were well tolerated. Furthermore, non-symmetrical disubstituted alkynes could be successfully used in this intermolecular cyclization reaction. The steric properties of the substituents in the acetylenic moiety did not affect significantly the yield, with 2-aryl functionalized alkyne **2b** performing well in the cyclobutene **3b** formation. The electronic nature of the substituents did appear to have an influence on the course of the reaction. Compared to alkynes having electron-withdrawing substituents, alkynes bearing electron-donating groups gave us better results as far as conversions are concerned. Thus, the electronically-rich methoxy derivative **2c** afforded the corresponding cyclobutene **3c** in much better isolated yield than its nitro counterpart (e. g. **2d**). Notably, the regioselectivity was perfect, provided that the substituents at both alkynic sides were different. When a strained cyclopropyl substituent was introduced at the alkyne, the desired cyclobutene were still formed (e. g. **3e** and **3f**). Interestingly, the mildness of the protocol allows the reaction of internal alkynes phenylprop-2-yn-1-ol **2g** and 1-(3-hydroperoxyprop-1-ynyl)-4-methoxybenzene **2h** bearing sensitive functionalities to be converted into functionalized cyclobutenes **3g** and **3h** in good yields (Scheme 2). Besides alkynes possessing arylacetylene moieties, substrates with heteroaromatic substituents were also investigated. Substrates having a π-excedent heterocycle (e. g. **2i** and **2j**) provided the desired cyclobutene (e. g. **3i** and **3j**) in good yields (Scheme 2); however, when the thiophene ring was replaced with a π-deficient heterocycle (e. g. pyridine), the corresponding cyclobutene was not formed. This phenomenon could be readily understood by considering that an alkyne bearing an electron-rich substituent is more nucleophilic than an alkyne bearing an electron-poor substituent and hence the former is more prone to attack intermolecularly to the nascent zwitterion 1,1-bis(trifluoromethylsulfonyl)ethene. 2-[2-(Aryl)cyclobut-1-enyl]tetrahydrofuran **3k** was also obtained in an efficient manner from alkyne **2k** (Scheme 2). The selective monofunctionalization of diynes **2l–n** into cyclobutenes **3l–n** as well as the two-fold reaction to form bis(cyclobutene) **3o** from diyne **2n** were also successfully developed (Scheme 2). Interestingly, the mildness of the protocol allows the control of both the mono and the double reaction of diyne **2n** (Scheme 2). As shown in Scheme 2, the above process in a one-pot operation from readily available alkynes and 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides serves as general approach to polysubstituted cyclobutenes. Besides, cyclobutenes **3b–o** could be obtained in good yields and with total regioselectivity. Because cyclobutenes are of high synthetic utility, it was desirable to scale-up the procedure in order to obtain gram quantities. Worthy of note, when we performed a 5 mmol-scale reaction starting from alkyne **2g**, cyclobutene **3g** was isolated in a yield of 77%, which is slightly higher than that achieved at a smaller scale during the scope study. For conclusive assessment of the structure of compounds **3** the X-ray crystallographic analysis of the crystals of cyclobutene **3c** was undertaken (Figure S1, see ESI†).[22]

Encouraged by the results obtained in our above method, we focused our attention as well on terminal alkynes, which are generally less reactive. Terminal aliphatic alkynes failed to react and the starting material was recovered unchanged under these conditions. However, 1-ethynyl-4-methoxybenzene **2p** and 1-(ethynyl-*d*)-4-methoxybenzene [D]-**2p** were subjected to the optimized conditions and the corresponding cyclobutenes **3p** and [D]-**3p** were smoothly formed in satisfactory yields (Scheme 3). Nicely, the presence of a deuterium atom at the terminal end of the alkyne does not affect the efficiency of the reaction, which may allow the synthesis of deuterated cyclobutenes. In a similar manner 2-ethynylthiophene **2q** and 2,5-diethynylthiophene **2r** reacted with 1,1-bis(triflyl)ethanide **1d** to produce cyclobutene **3q** and bis(cyclobutene) **3r** in reasonable yields (Scheme 3). For terminal alkynes, the acetylene moiety with an electron-donating group on the arene exhibited higher reactivity and required shorter time for completion than that of internal alkynes; probably due to steric reasons. The reaction of phenylacetylene **2s** also worked well and provided the product **3s** along with an

unexpected product, the pyridine **4s** (Scheme 3).



Scheme 3 Preparation of cyclobutenes **3p–t** and pyridines **4s–u** from terminal alkynes.

1,3-Diethynylbenzene **2t** bearing an extra terminal alkyne, also reacted similarly and provided cyclobutene **3t** and pyridine **4t** in a 1:1 ratio (Scheme 3). Although there is absence of chemoselectivity for alkynes **2s** and **2t**, it is worthy of note that cyclobutenes **3s,t** and pyridines **4s,t** are easily separated, thus providing readily two valuable cyclic products. Interestingly, nitroaryl substitution in the terminal alkyne did alter the reaction which exclusively yielded the pyridine adduct **4u** (Scheme 3), but considerably amounts of starting alkyne **2u** remained unaffected under the reaction conditions. The formation of pyridines **4** may be explained taking into account the participation of the solvent (acetonitrile) as coupling partner (see below). These results suggest that for terminal alkynes, the presence of an electron-donating substituent critically influences the formation of the desired cyclobutene.

Density Functional Theory (DFT) calculations were carried out at the PCM(acetonitrile)-M06-2X/6-31+G(d) level to gain more insight into the above described reaction between alkynes and azolium salts **1**.[23] To this end, we considered the reaction involving phenylacetylene (**2s**) and **1d** in the presence of MeCN which leads to the formation of cyclobutene **3s** and pyridine **4s** in ca. 1:1 ratio. The corresponding computed reaction profiles are shown in Figure 1, which gathers the relative free energies computed at 298 K (ΔG_{298}). Our calculations suggest that the process begins with the formation of 1,1-bis(trifluoromethylsulfonyl)ethene (**INT1**) from **1d**. This initial reaction step occurs via the transition state **TS1**, associated with the C···N dissociation, with an activation barrier of only 11.9 kcal/mol in a slightly endergonic transformation (ΔG_R = 4.8 kcal/mol). The 1,2-dipole nature of ethene **INT1** is confirmed by the NBO-charges computed at both carbon atoms (+0.37 and –0.70 e, respectively).[24] As a consequence, a stepwise [2+2]-cycloaddition reaction with alkyne **2s** is expected to take place. Indeed, we were able to locate on the potential energy surface the transition state **TS2**, a saddle point associated with the nucleophilic addition of the terminal carbon atom of alkyne **2s** to the positively charged carbon atom of the dipole **INT1**. This C···C bond forming process, which leads to the zwitterionic intermediate **INT2**, proceeds with an activation barrier of 17.6 kcal/mol). Interestingly, the addition involving the internal carbon atom of the alkyne proceeds via **TS2-B** with a much higher activation barrier ($\Delta G^{\ddagger}_{298}$ = 35.7 kcal/mol), which makes this alternative nucleophilic addition unfeasible at room temperature. This finding explains the extraordinary regioselectivity of the transformation experimentally observed. Finally, cyclobutene **3s** is formed through a ring-closure reaction via **TS3**. The ease of this final reaction step becomes evident from the computed high exergonicity (ΔG_R = –28.1 kcal/mol) and low activation barrier ($\Delta G^{\ddagger}_{298}$ = 3.0 kcal/mol) associated with this ring-closure.

The formation of pyridine **4s** necessarily involves the participation of the solvent MeCN as nucleophile. Thus, zwitterion **INT2** is able to react with MeCN to produce the new zwitterionic intermediate **INT3** via **TS4** ($\Delta G^{\ddagger}_{298}$ = 11.6 kcal/mol) in an exergonic transformation (ΔG_R = –20.1 kcal/mol). A subsequent ring-closure via **TS5** ($\Delta G^{\ddagger}_{298}$ = 11.6 kcal/mol) leads to the 3,4-dihydropyridine **INT4**, which rapidly evolves to the final pyridine **4s** by TfH elimination in a strongly exergonic transformation (ΔG_R = –49.0 kcal/mol). The driving-force of this process is clearly related to the gain in aromaticity associated with the pyridine formation. Despite that, from the data in Figure 1 it becomes clear that the stepwise [2+2]-cycloaddition reaction is kinetically favoured over the pyridine formation and for this reason, the exclusive formation of cyclobutenes **3** is observed experimentally in most of the reactions studied (Schemes 2 and 3).

In conclusion, 2-(pyridinium-1-yl)-1,1-bis(triflyl)ethanides have been used as 1,2-dipole precursors in a metal-free stepwise [2+2]-cycloaddition reaction of alkynes. The great advantage of this method is the easy synthesis of substituted cyclobutenes from

readily available and stable precursors in mild conditions. Remarkably, this smooth and facile uncatalyzed protocol does require neither irradiation nor heating. Besides, this protocol has successfully overcome the challenges of earlier methods regarding selectivity of the products.

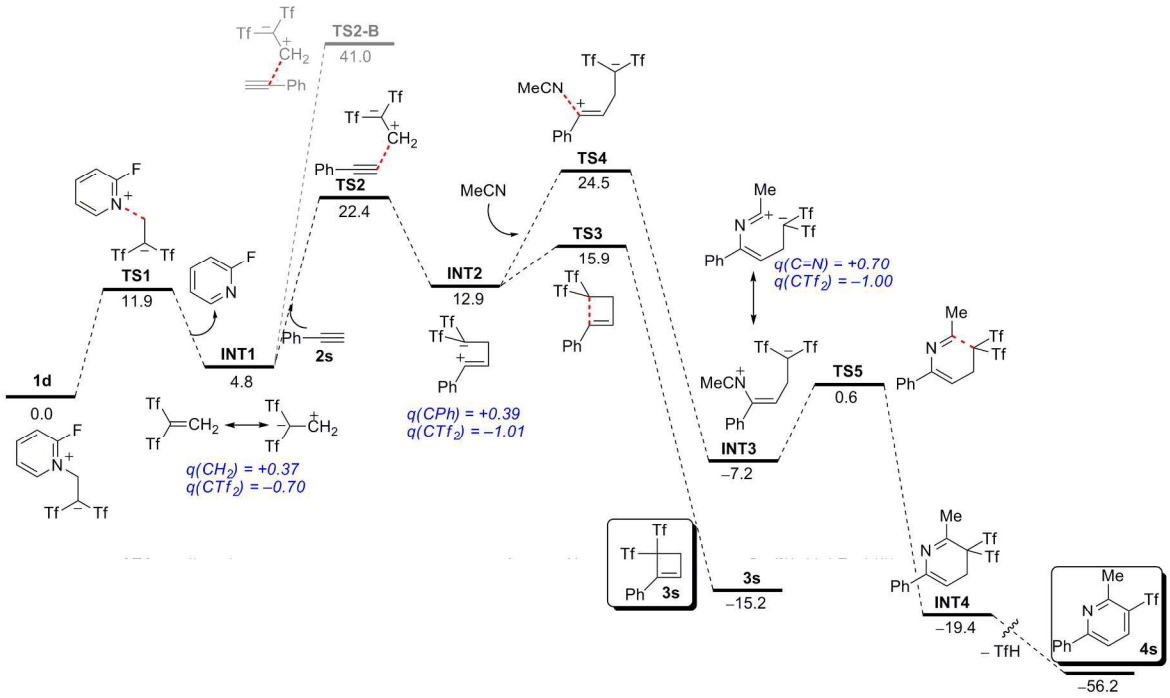


Figure 1. Computed reaction profile for the reaction between **2s** and **1d**. Relative free energies (ΔG_{298}, at 298 K) are given in kcal/mol. All data have been computed at the PCM(acetonitrile)-M06-2X/6-31+G(d) level.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds, computational details, and copies of NMR spectra. See DOI: 10.1039/b000000x/

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23 See computational details in the ESI†.

24 **INT1** is better described as a resonance hybrid between both dipolar and uncharged species.