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25 examples

Up to 97%

Photochemical Cyclopropenation of Alkynes with Diazirines as Carbene Precursors in Continuous Flow

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using readily available LEDs under mild reaction conditions. This new and efficient method describes the synthesis of 25 examples of 3-trifluoromethyl-3-aryl-cyclopropenes with yields *up to* 97%, achieved in continuous flow with a 5 min residence time. Control experiments highlighted that diazirines are more efficient than diazo compounds for this transformation.

iazo compounds and diazirines, despite being structural isomers, have been developed in entirely separate areas.^{1,2} Both serve as carbene precursors;^{3,4} however, diazo compounds have been regarded as essential building blocks in synthetic chemistry,^{5,6} while diazirines are distinguished as photolabeling and linking reagents.^{7,8} Trifluoromethyl diazirines, in particular, have found a home in a wide variety of applications from medicinal chemistry (i.e., as photoaffinity probes)^{9,10} to surface chemistry (i.e., for analyte immobilization),^{11,12} and polymer cross-linking.^{8,13} This divided interest has led to diazirines becoming almost forgotten as building blocks in organic synthesis despite their ability to generate carbenes.¹⁴ Hence, it is worthwhile to better develop and elaborate their utility for organic synthesis in the same sense as diazo compounds. Another factor that encourages this development is that, compared to diazo compounds, diazirines exhibit higher bench stability, less toxicity, and less explosibility.¹⁵⁻¹⁷ Diazirines are reported to generate free carbenes by the loss of nitrogen gas (N2) under ultraviolet (UV) irradiation (350-380 nm).¹⁸

Diazirines have only been studied for carbene insertion reactions, using a mercury lamp as a UV source, with alcohols; however low yields were obtained, and a limited scope was demonstrated.¹⁹ Low yields are usually associated with the high reactivity and instability of carbenes. Flow chemistry has recently emerged as a useful tool for photochemical carbene chemistry and has been gaining significant traction.^{20–22} For this, we sought to generate them in continuous flow which allows top control over reaction conditions.^{23–25} Flow chemistry has been regarded as a tool that enables a safer and more economical approach than traditional batch chemistry which is being widely adopted by industries.^{23,26–29} In addition, photochemical reactions in flow have unmatched efficiency compared to batch due to the enhanced and equal distribution of light into a reaction mixture.^{22,30}

While exploring the reactivity of trifluoromethyl diazirines in a photochemical flow setup, we found that simple purple lightemitting diodes (LED) sufficed to generate carbenes from trifluoromethyl diazirines for the formation of cyclopropenes from alkynes. So, energy-consuming, expensive, and dangerous mercury lamps could be replaced by simple LED lamps to access cyclopropenes. Cyclopropenes are essential building blocks in organic synthesis and are also valuable to the pharmaceutical sector in drug discovery.³¹ However, studies covering the synthesis of trifluoromethyl cyclopropenes have only been recently reported via the cyclopropenation reaction of alkynes using diazo compounds catalyzed by transition metals.^{32–35}

Catalyst free

Affordable LEDs

Only two reports on metal-free cyclopropenation have been disclosed (Figure 1). The first involves the reaction of tosyl hydrazones with a base to generate the diazo compound *in situ* which is then decomposed thermally into the carbene species for cyclopropenation in C_6F_6 .³⁶ The other uses diazo compounds under blue LED irradiation which is applied for the synthesis of a single example of a trifluoromethyl cyclopropene.^{21,37} Hence, we disclose a new method that will allow access toward versatile trifluoromethyl cyclopropene motifs from diazirines in a straightforward, metal-free, green, and scalable manner (Figure 1).

During screening and optimization of the cyclopropenation reaction (see Supporting Information (SI), p S-17) of 3-([1,1'-biphenyl]-4-yl)-3-(trifluoromethyl)-3H-diazirine 1a with diphenyl acetylene in continuous flow, we found that visible-

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light-emitting diodes (LEDs), purple LEDs (420 nm) in particular, result in yields as high as 93% of the corresponding cyclopropene **2a**. Optimal flow reaction conditions required a residence time of 5 min (10 mL reactor volume, 2 mL/min flow rate) at 25 °C with reactants injected in a 0.4 M concentration of diazirine **1a** in CH_2Cl_2 (Scheme 1). Using lamps with higher irradiation energies led to decreased yields (see SI, pp S-17–18). So, irradiating at 420 nm targets the lowest energy tail of the diazirine's absorption peak (see SI, p S-16).

Scheme 1. Optimized Reaction Conditions for the Cyclopropenation of Diazirine 1a with Diphenyl Acetylene



This means that the lowest energy lamp capable of decomposing the diazirine results in better selectivity toward the desired cyclopropenation reaction. Hence, this results in the slow generation of the carbene species and thus mimics slow addition in batch which is common practice in carbene chemistry. The low yields could also be attributed to an inner filter effect deriving from the cyclopropene product and could be a reasonable explanation for the high yields with purple LEDs. Control experiments involving the irradiation of pure cyclopropene under 420 and 365 nm show no decomposition (see SI p S34), and its UV–vis spectra show no absorbance (see SI page S17). Also, an excess of the alkyne (10 equiv) was required to achieve higher yields, but the remaining alkyne (9 equiv) was easily recovered (up to 98%).³⁸

The cyclopropenation of 3-([1,1'-biphenyl]-4-yl)-3-(trifluoromethyl)-3H-diazirine**1a**was then studied with variousalkynes (Scheme 2). Using internal aromatic alkynes, yields $ranged between 62% and 84% with alkynes bearing <math>-NO_2$, $-CF_3$, or -F substituents on the Ar group (Scheme 2, 2ab, 2ad-2ae). When using an aliphatic alkyne, octan-4-yne led to high yields (97%) of cyclopropene 2af. Then, in the case of terminal alkynes, yields decreased overall as a result of carbene insertion into the terminal C-H bond of the alkyne, but this did significantly change with the type of substitution on the alkyne (Scheme 2, 2ag-2ak). A detailed study by Koenigs et al. showed the particularity of electron-rich diaryl carbenes, generated by blue light irradiation of their diazo precursor, in C-H insertion with terminal alkynes.³⁹ However, in the case of the donor-acceptor carbenes generated here, this C-H

Scheme 2. Scope of Alkyne Substrates⁴



"Reaction conditions: 3-([1,1'-biphenyl]-4-yl)-3-(trifluoromethyl)-3H-diazirine 1a (0.1 mmol) and the alkyne (1 mmol) in CH₂Cl₂ (0.25 mL) is injected through a 6-way valve (0.25 mL injection loop) at 2 mL/min into the photoreactor (10 mL) equipped with 420 nm light source set to 25 °C and 6 bar. Isolated yields. "Yield determined by ¹⁹F NMR using 3-fluoro-4-nitrotoluene as an internal standard.

insertion could be detected in the crude reaction mixture albeit in low yields. When employing bis-alkynes 1,3-diethynylbenzene and 1,4-diethynylbenzene, monocyclopropenes **2al** and **2am** were obtained in 53% and 14% yield, respectively, along with products resulting from C–H insertion which was isolated in the case of **2al**'. In these cases, no bis-cyclopropenes were obtained contrary to a previous report with trifluoromethyl metal carbenes.³³

The scope of trifluoromethyl diazirine substrates was investigated with diphenyl acetylene (Scheme 3). The reaction of 3-(naphthalen-2-yl)-3-(trifluoromethyl)-3H-diazirine 1b and 3-(4-(benzyloxy)phenyl)-3-(trifluoromethyl)-3H-diazirine 1c under irradiation at 420 nm resulted in cyclopropenes 2b and 2c in 78% and 79% yield, respectively. In addition, the bisdiazirine 1d yielded a separable mixture of both the monocyclopropene diazirine 2d (30%) and the bis-cyclopropene 2d' (54%). However, when 20 equiv of diphenyl acetylene were used instead of 10 equiv, the yield of monocyclopropene 2d decreased to 18% while that of biscyclopropene 2d' increased to 64%.

Afterward, we sought to compare the effect of flow and batch conditions on this reaction. The cyclopropenation reaction of diphenylacetylene using 1a-1d was attempted in batch under the same optimized conditions, but even after 24 h, the reaction remained incomplete due to reduced light penetration. Batch conditions were found to be inefficient in producing the cyclopropene in yields close to those obtained under flow conditions, where they ranged between 42% and <1% of 2a-2d. This emphasizes the utility of flow conditions and their importance in achieving an efficient photochemical cyclopropenation reaction with diazirines. These flow conditions are superior to batch in terms of not only yields but also reaction time which is shortened to 5 min instead of >24 h and thus a higher output of cyclopropenes per hour. To

Scheme 3. Scope of Trifluoromethyl Diazirines^a



^{*a*}Reaction conditions: 3-(trifluoromethyl)-3*H*-diazirine **1a-1n** (0.1 mmol) and the diphenyl acetylene (1 mmol) in CH_2Cl_2 (0.25 mL) is injected through a 6-way valve (0.25 mL injection loop) at 2 mL/min into the photoreactor (10 mL) equipped with the light source set to 25 °C and 6 bar. Yields are isolated. ^{*b*}Yields determined by ¹⁹F NMR using 3-fluoro-4-nitrotoluene as an internal standard. ^{*c*}Twenty equiv (2 mmol) of diphenyl acetylene were used.

demonstrate the ease of scale up with this method, cyclopropene 2a was formed on a 10 mmol scale in 73% yield within less than an hour (50 min).

Phenyl-3-(trifluoromethyl)-3H-diazirines with a -Me, -tBu, or -OMe group in the *para* position of the aryl ring (1e-1g)did not decompose under 420 nm (complete recovery of the diazirine species), which was not surprising due to the absence of any absorbance in that UV-vis region (see SI, p S-16). So, a higher energy lamp was required. Using a 405 nm purple LED, the corresponding cyclopropenes were obtained in moderate vields (50-57%) (Scheme 3, 2e-2g). For 3-phenyl-3-(trifluoromethyl)-3H-diazirine 1h and phenyl-3-(trifluoromethyl)-3H-diazirines substituted with a $-F_1$, $-Br_2$, or $-CF_3$ group in either the para or meta position, an even higher energy LED wavelength was required where a UV wavelength of 380 nm allowed the decomposition of diazirines 1h-1l to give the desired cyclopropenes, albeit in moderate and poor yields (Scheme 3, 2h-2l). The low yields in cyclopropenes (i.e., 12-51%) in these cases are due to side reactions of the carbene intermediate under such high-energy irradiation. So, even though these cyclopropenes are obtained in low yields, it is a matter of the characteristic absorbance of their diazirine precursors which necessitate harsher conditions, i.e., high energy irradiation wavelengths. Then, when using 3-(2methoxyphenyl)-3-(trifluoromethyl)-3H-diazirine 1m and 3-(2-fluoro)-3-(trifluoromethyl)-3H-diazirine 1n, even at 380 nm, the diazirine remained intact. This emphasizes the significant influence of the decomposition of these diazirines by electronic and steric factors.

Photochemical cyclopropenation reactions of alkynes have been reported to occur with diazo compounds using blue LEDs (470 nm) but are limited to diazo esters.^{21,37,39} So, to evaluate the usefulness of choosing to do a photochemical cyclopropenation with diazirines instead of diazo compounds, we compared the reactivity of the diazirine substrate **1a** and its linear isomer diazo substrate **1a'** under the same reaction conditions in flow (Scheme 4a). We observed that at 420 nm the cyclopropene is obtained in only 5% yield which is

Scheme 4. Competition and Control Experiments





(b) Intermolecular competition study between an internal and teminal alkyne:



(c) Intermolecular competition between cyclopropenation and cyclopropanation







significantly less than the yields obtained with the diazirine substrate (93%). Then, when the energy of the irradiation was lowered to better accommodate the diazo, the yields of the cyclopropene **2a** from the diazo substrate did slightly increase to 12% and 14% when using LEDs at 450 and 470 nm, respectively, while those derived from the diazirine remained high, except at 470 nm where no diazirine decomposition was observed. Thus, diazirines are, by far, better candidates as carbene precursors for accessing trifluoromethyl cyclopropenes by LED irradiation.

In a competition experiment for the cyclopropenation of internal vs terminal alkynes (Scheme 4b), it was observed that when using 5 equiv of each, cyclopropenes 2a and 2aj were obtained in a 1:1 ratio (15%) with the major product being the C-H insertion product from the terminal alkyne (1:1:2).

Then when looking at the preference of the reaction conditions toward a cyclopropenation vs a cyclopropanation reaction by using 5 equiv of diphenyl acetylene and 5 equiv of (E)-1,2-diphenylethene under the optimized conditions (Scheme 4c), the corresponding cyclopropene 2a was obtained in 45% yield while the cyclopropane 2a' was obtained in 36% yield (i.e., 2a/2a' = 1.25:1 ratio). Using propargyl alcohols with the diazirine, the cyclopropene was never observed and

the major products were the corresponding ethers after O–H insertion (Scheme 4d). 4-(2,2,2-Trifluoro-1-(pent-4-yn-1-yloxy)ethyl)-1,1'-biphenyl 3a was obtained in 58% yield, and <math>4-(2,2,2-trifluoro-1-(prop-2-yn-1-yloxy)ethyl)-1,1'-biphenyl 3b, in 70% yield. Then, as a proof of concept, the TMS-cyclopropene 2ak was deprotected using TBAF (1 equiv) which occurred in 70% yield after 18 h at room temperature.

To gain better insight into the mechanism of the LEDmediated cyclopropenation of alkynes using trifluoromethyl diazirines, the reaction was monitored in real time using IR spectroscopy (see SI-31). The intermediate formation of the linear isomer, i.e. the diazo compound, was detected in traces (characteristic peak at 2093 cm⁻¹) in addition to the cyclopropene (at 1499 cm⁻¹). So, it is most likely that, upon irradiation, the diazirine generates both the carbene species and traces of the diazo compound which in turn generates the carbene. This observation is consistent with previous reports with UV irradiation of diazirines.^{2,18,19,40}

In conclusion, we have developed a streamlined approach for the synthesis of new trifluoromethyl cyclopropenes starting from diazirines as carbene precursors. This method proceeds more efficiently under continuous flow conditions, and the wavelength of irradiation needed depends on the diazirine substrate. The generality of this efficient process was shown over 25 examples. Excellent yields of 3-trifluoromethyl-3-arylcyclopropenes were obtained in continuous flow with a 5 min residence time. *In situ* reaction monitoring revealed that isomerization of the diazirine into the diazo compound occurs to some extent. This method adds to the examples of efficient combination of photochemistry and flow chemistry which is attracting the interest of both academics and industries.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01750.

Experimental procedures, characterization data of starting material and target compounds, and copies of ¹H, ¹³C, and ¹⁹F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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