



Photocatalysis Hot Paper

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Photocatalytic gem-Difluoroolefination Reactions by a Formal C–C Coupling/Defluorination Reaction with Diazoacetates

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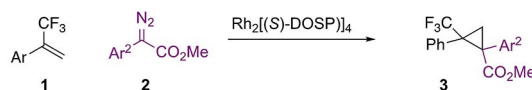
Abstract: The photolysis of diazoalkanes to conduct singlet carbene transfer reactions of colored diazoalkanes has recently attracted significant interest in organic synthesis. Herein, we describe a photocatalytic approach that allows the access of triplet carbene intermediates via energy transfer to conduct highly efficient gem-difluoroolefination reactions with α -trifluoromethyl styrenes. The use of a tertiary amines proved pivotal to unlock this unusual reaction pathway and to prevent undesired cyclopropanation pathways. The amine further facilitates the ultimate abstraction of fluoride to yield gem-difluoroolefins (43 examples, up to 88% yield), which is supported by experimental and theoretical mechanistic studies. We explored this synthesis method with a broad substrate scope, ranging from simple olefins and heterocyclic olefins towards the decoration of pharmaceutically relevant building blocks.

Diazoalkanes are key reagents in organic chemistry. They feature a reactive diazo functional group that plays a key role in dipolar cycloaddition reactions or that can undergo extrusion of nitrogen gas to liberate free or metal-bound carbene intermediate.^[1,2] Building on this fundamental reactivity of diazoalkanes, a broad spectrum of C–C or C–X bond forming reaction has been developed that is today an essential strategy for the construction of cyclopropanes (**3**), medium-sized rings, or the late-stage functionalization of drug molecules (Scheme 1a).^[1–3]

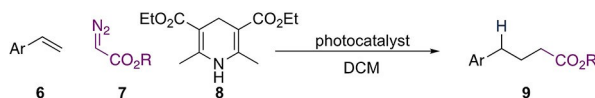
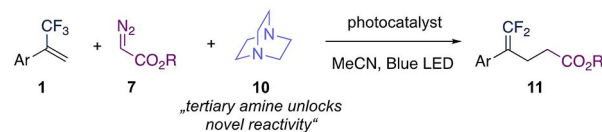
The reaction of diazoalkanes under photochemical, metal-free conditions dates back to an early report by Meerwein^[4] and recent developments build on the photochemical properties of donor-acceptor diazoalkanes **2** that absorb light in the visible spectrum and the liberation of free, reactive carbene intermediates that has recently found broad interest to conduct efficient and sustainable carbene transfer reactions,^[2,5–7] e.g. in cyclopropene synthesis (**5**, Scheme 1b).^[5c] Under photocatalytic conditions, however, the excitation of a photocatalyst can lead to fundamentally

a) metal-carbene chemistry with diazoalkanes

cyclopropanation of trifluoromethyl olefins

**b) singlet carbene reactivity via photolysis reactions**

cyclopropanation of olefins and alkyne

**c) radical reactivity in the alkylation of olefins****d) This work: triplet reactivity in gem-difluoroolefination reactions**

- photocatalytic gem-difluoroolefination reaction
- tertiary amine prevents cyclopropanation pathways
- simple reaction conditions
- broad substrate scope
- pharmaceutically relevant building blocks
- combined experimental & theoretical studies

Scheme 1. Reaction of diazoalkanes with unsaturated compounds.

different reaction pathways via single electron or energy transfer.^[8] In this context, the Gryko group reported on the proton coupled electron transfer of diazoalkanes via oxidative quenching that leads to a carbon-centered radical for downstream application in the C–H functionalization reaction of indole heterocycles.^[9] Contrarily, the Doyle group described a photocatalytic approach involving reductive quenching of a photosensitizer by Hantzsch ester **8** that allows for reductive alkylation reactions of styrenes **6** with ethyl diazoacetate **7** (Scheme 1c), or aminoalkylation when secondary amines are added.^[10] A competing reaction represents the energy transfer from the excited state of a photosensitizer that results in formation of a triplet carbene as demonstrated by the Gryko group using cobalt porphyrin catalysts.^[11]

We envisioned that the photocatalytic generation of radicals could be amenable towards the synthesis of gem-difluoro olefins **11**^[12] via radical-mediated C–C coupling—

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defluorination reaction cascades using electron-deficient α -trifluoromethyl styrenes **1** as radical acceptors (Scheme 1d). *Gem*-difluoroolefins find important application in medicinal chemistry as bioisosters of carbonyl groups, yet their synthesis remains a key challenge.^[12,13] Such radical addition strategies would overcome current synthetic challenges as readily available α -trifluoromethyl styrenes can be used as synthons of the key *gem*-difluoro olefin functional group under mild reaction conditions.

We therefore set out our investigations and examined a range of different photoredox catalysts under reductive quenching conditions (for details, see Table S1) and gratifyingly [Ir{dF(CF₃)ppy}₂(bpy)]PF₆ could be identified as the optimal catalyst to achieve this goal with only diminutive amounts of cyclopropane **12a** as by-product (Table 1, entry 1). Other photocatalysts, such as organic dyes, Ir(ppy)₃ or Ru-based dyes proved far less efficient (Table 1, entries 2–4). A survey of reaction solvents revealed that acetonitrile proved by far as the best solvent – solvents that are typically used in carbene transfer reactions, such as chlorinated solvents, proved inferior and only trace amounts of the *gem*-difluoroolefin **11a** were obtained. Instead cyclopropane **12a** was formed as an almost 1:1 mixture of diastereoisomers preferentially (Table 1 entry 5 and Table S2 in ESI). Tertiary amine bases were identified as key reagents to access the *gem*-difluoroolefin reaction product: in the absence of the tertiary amine base, or with inorganic bases *gem*-difluoroolefin **11a** was not formed, instead cyclopropane **12a** was formed in high yield (Table 1, entries 6–9). When examining Hantzsch ester **8a** as an alternative

reductive quenching agent, however, a significantly reduced yield was observed (Table 1, entry 10).

We next aimed at rationalizing this *gem*-difluoroolefination reaction by combined experimental and theoretical studies. The analysis of Stern–Volmer experiments showed fluorescence quenching of the iridium photocatalyst in the presence of DABCO (**10a**) and EDA (**7a**) near the diffusion limit (DABCO: $k_q = 8.2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, EDA: $k_q = 3.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$; for details please see Figure S7), while α -trifluoromethyl styrene **1a** did not quench the photoexcited state (Scheme 2a). This observation is further supported by cyclic voltammetry that revealed high redox potentials for EDA ($E_{\text{red}} = -1.28 \text{ V}$, vs S.C.E.) and α -trifluoromethyl styrene ($E_{\text{red}} = +2.44 \text{ V}$, vs S.C.E.).

Next, trifluoromethylated cyclopropane **12a** was subjected to the standard reaction conditions to evaluate a potential ring opening reaction. However, **12a** remained untouched under reaction conditions and the *gem*-difluoroolefin **11a** was not formed, which indicates that *gem*-difluoroolefination does not proceed via cyclopropane intermediates (Scheme 2b, I). Similarly, a cross-over experiment of a cyclopropane in the presence of a distinct α -trifluoromethyl styrene, EDA and the photocatalyst revealed that cyclopropanes do not participate in this reaction (Scheme 2b, IIa & IIb). In the presence of TEMPO or DMPO as radical scavenger, the *gem*-difluoroolefination reaction was completely inhibited and both the TEMPO adduct **13** or the DMPO adduct **14** were detected by GC-MS analysis, which is supportive of intermediates with unpaired electrons (Scheme 2c and S1 in ESI). Further experiments to probe the participation of intermediates with unpaired electrons involved the reaction of α -cyclopropyl styrene **15**, which resulted in ring opening of the cyclopropane ring and dihydronaphthalene **16** formation (Scheme 2d). We then studied 2-bromo ethyl acetate (**17**) as a reagent, which is known to easily undergo debromination and formation of a carbon-centered radical under photoredox conditions. While no reaction product was detected using DABCO a diminutive amount of the *gem*-difluoro olefin **11a** was observed when using Hantzsch ester **8a** as reductive quencher (Scheme 2e). We thus consider the direct addition of a carbon-centered radical to α -trifluoromethyl styrene seems unlikely in this reaction.^[14] However, above results are indicative of participation of intermediates with unpaired electrons in the course of the *gem*-difluoroolefination reaction.

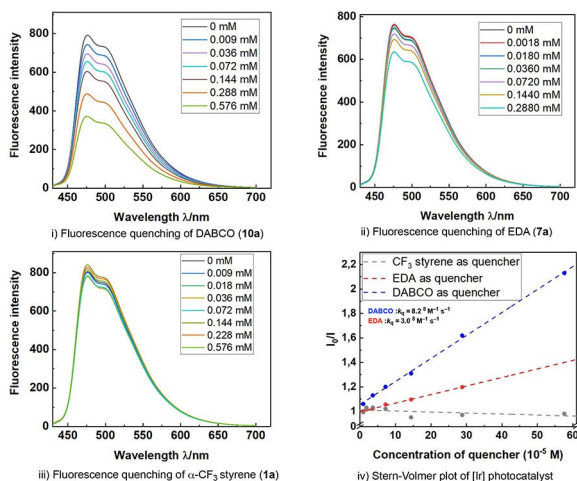
To probe the proton source in the reaction, we next examined the reaction in the presence of D₂O.^[15] First, *gem*-difluoroolefin **11a** was examined under reaction conditions in the presence of D₂O, yet no deuterium was incorporated. Second, we probed a potential deuteration of DABCO in the presence of photocatalyst and D₂O. Indeed a 16% incorporation of deuterium suggests reductive quenching of DABCO and consecutive proton/deuterium exchange reactions via a putative DABCO radical cation. Third, a potential proton exchange reaction between EDA, DABCO and D₂O was examined under catalyst-free conditions, yet no deuterium label was found (for details, please see ESI). Finally, we probed the *gem*-difluoroolefination reaction in

Table 1: Reaction Optimization.

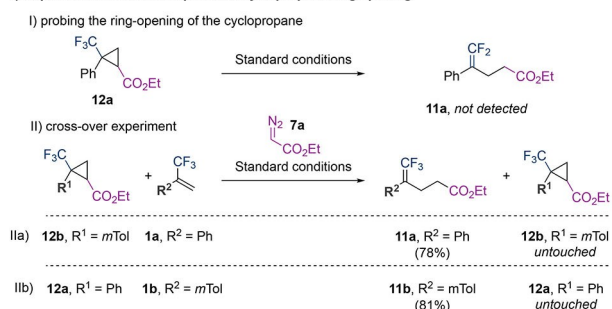
| No. ^[a] | Deviations from above | 12a | 11a |
|--------------------|---|------------|-------------------|
| 1 | None | 6 | 83 ^[b] |
| 2 | 4-CzIPN as photocatalyst | n.d. | 28 |
| 3 | Ir(ppy) ₃ as photocatalyst | 26 | n.d. |
| 4 | Ru(bpy) ₃ Cl ₂ as photocatalyst | Trace | Trace |
| 5 | DCM instead of MeCN | 39 | 7 |
| 6 | No DABCO | 95 | – |
| 7 | DIPEA instead of DABCO | n.d. | 70 |
| 8 | Ph ₂ NH instead of DABCO | 46 | 11 |
| 9 | K ₂ CO ₃ instead of DABCO | 83 | 3 |
| 10 | Hantzsch ester 8a instead of DABCO | 15 | 36 |
| 11 | No catalyst/No light | n.r./n.r. | |
| 12 | In air | 9 | 55 |

[a] Reaction conditions: trifluoromethyl styrene (0.2 mmol, 1.0 equiv), EDA (0.4 mmol, 2.0 equiv), DABCO (0.4 mmol, 2.0 equiv) and catalyst (2 mol%) were dissolved in 2.0 mL MeCN and irradiated with 25 W blue LED for 15 hours reaction time. n.d. = not detected. n.r. = no reaction. Yields by ¹⁹F NMR analysis of the crude reaction mixture. **8a** = Di-(tert.-butyl) 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate. [b] isolated yield.

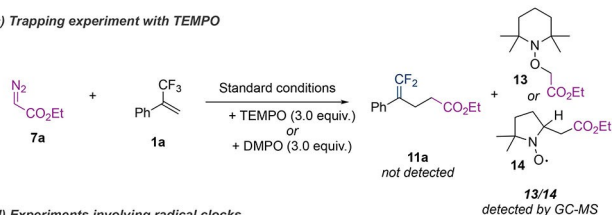
a) Stern Volmer plots



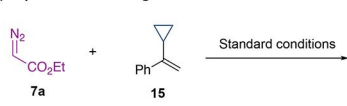
b) Experiment to examine a potential cyclopropane ring opening



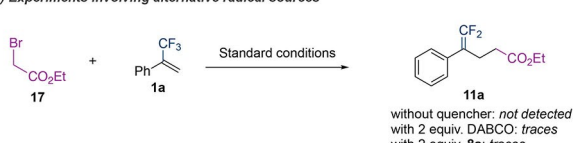
c) Trapping experiment with TEMPO



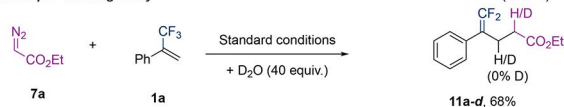
d) Experiments involving radical clocks



e) Experiments involving alternative radical sources



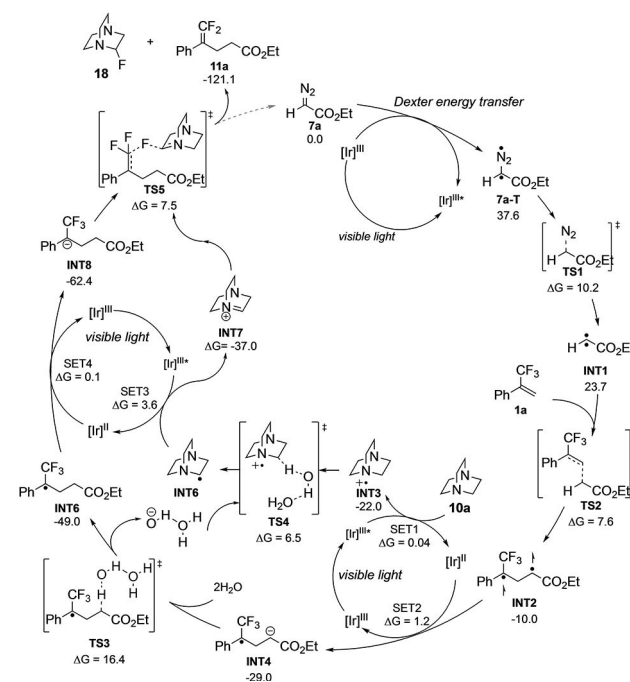
f) Isotope - labeling study



Scheme 2. Experimental studies for mechanistic support. Yields refer to isolated yields.

the presence of D₂O, and indeed the deuterium label was exclusively found in the α -position to the carbonyl group of *gem*-difluoroolefin 11a, which now provides evidence that the deuterium label is incorporated in the course of the photocatalytic reaction (Scheme 2f).

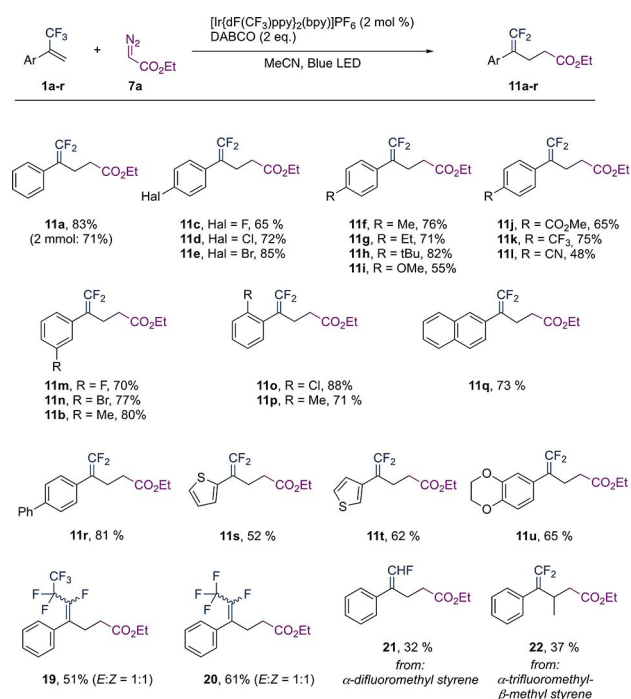
We next examined this *gem*-difluoroolefination reaction by DFT calculations (Scheme 3). These studies suggest a reaction mechanism that involves multiple photocatalytic cycles. In the first photocatalytic cycle, an energy transfer occurs to access the triplet state 7a-T of ethyl diazoacetate that can readily release the triplet carbene intermediate INT1, which is in line with the previously observed reaction outcome in the presence of TEMPO and a previous discussion of dye-sensitized reactions of ethyl diazoacetate by Gryko group on the reaction with porphyrin dyes.^[11] Examination of alternative electron transfer pathways, e.g. via reductive quenching with DABCO and subsequent formation of a diazanyl radical, revealed to be clearly feasible. However, downstream pathways to produce a potential radical intermediate, as described by Gryko and Doyle, were determined to be energetically unfavored in this case.^[9,10] Here, a simple back electron transfer from a putative diazanyl radical to DABCO⁺ radical is energetically preferred and, as a consequence, makes such electron transfer pathways unproductive (for details, please see Scheme S3). Following formation of the triplet carbene intermediate INT1, a facile addition to α -trifluoromethyl styrene occurs, giving triplet intermediate INT2.^[16] In the presence of reductive quencher DABCO, a second facile photocatalytic cycle will give radical anion INT4 with a computed SET barrier of 1.2 kcal mol⁻¹, while in the absence of DABCO, an intersystem crossing will happen and cyclize to give cyclopropane 12a. This crucial intermediate INT4 undergoes protonation in the presence of water molecules to give INT6 and rationalizes for the incorporation of deuterium. This process also leads to formation of strongly basic hydroxide ion intermediates that can explain the unusual deuterium content (see Scheme 2f). In a third photocatalytic



Scheme 3. Catalytic cycle of the *gem*-difluoroolefination reaction.

cycle, **INT6** is reduced to give carbanion intermediate **INT8**, which can finally eliminate fluoride to give the *gem*-difluoroolefin product **11a**. Reduction of DABCO radical **INT5** to the iminiumion **INT7** is necessary, as the latter acts as fluoride scavenger and facilitates the ultimate defluorination step to yield **18** as by-product.

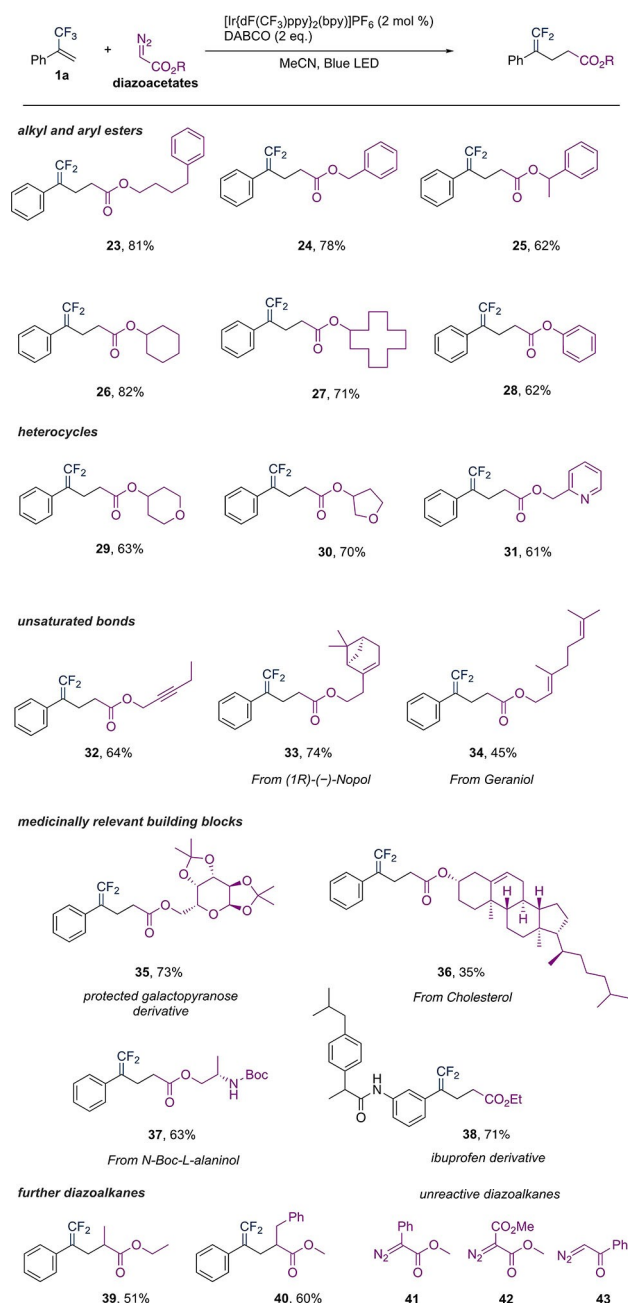
Having established conditions for the *gem*-difluoroolefin reaction of simple α -trifluoromethyl styrene, we embarked on investigations of the substrate scope (Scheme 4). We first examined different substitution patterns of the α -trifluoromethyl styrene and were delighted to observe that halogens, alkyl groups, ethers, or electron-withdrawing groups were well tolerated (**11c–i**), which could be readily scaled-up to 2 mmol scale. Similarly, substitution in all positions of the aromatic ring did not affect this *gem*-difluoroolefination reaction (**11b, m–p**), which would now enable consecutive downstream functionalization reactions of the *gem*-difluoroolefin product. Further examples include naphthalene- or biphenyl-derived α -trifluoromethyl styrene (**11q** and **11r**) and heterocyclic α -trifluoromethyl styrene, which gave the desired *gem*-difluoroolefin products in moderate to good yield. Further investigations dealt with the compatibility of α -perfluorinated styrenes. In this case, the 1-perfluoroalkyl-1-fluoro olefins **19** and **20** were obtained in good yield, however with no notable diastereoselectivity. We next examined α -difluoromethyl styrene and a trisubstituted α -trifluoromethyl olefin. In both cases the reaction proceeded smoothly, albeit only a moderate yield of the *gem*-difluoroolefin was obtained. Most importantly,



Scheme 4. Scope of different α -trifluoromethyl styrenes. Reaction conditions: **1** (0.2 mmol), **7a** (0.4 mmol), DABCO (0.4 mmol) and $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{bpy})]\text{PF}_6$ (2 mol %) were dissolved in 2.0 mL MeCN and irradiated with 25 W blue LED for 15 hours reaction time. Isolated yields.

the reaction of α -difluoromethyl styrene revealed selective defluorination and formation of the alkenyl fluoride **21** without formation of a *gem*-difluoroolefin. This observation is further supportive of the above calculations and a reaction mechanism involving fluoride abstraction.

Next, we studied the influence of the ester group of EDA in this reaction (Scheme 5). A range of different primary, secondary ester alcohols were well tolerated. Most notably, no by-products of competing intramolecular hydro-



Scheme 5. Scope of diazoacetates and investigations with medicinally relevant building blocks. Reaction conditions: **1a** (0.2 mmol), diazoacetate (0.4 mmol), DABCO (0.4 mmol) and $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{bpy})]\text{PF}_6$ (2 mol %) were dissolved in 2.0 mL MeCN and irradiated with 25 W blue LED for 15 hours reaction time. Isolated yields.

gen atom transfer were observed and selective reaction of the diazoacetate in the α -position occurred disregarding of the substitution pattern. Different heterocycles, such as furan, pyran or pyridine were well tolerated and efficient *gem*-difluoroolefination was observed. Moreover, even in the presence of double or triple bonds within the ester side-chain, no competing side-reaction from cyclopropanation was observed and the *gem*-difluoroolefin was obtained as the sole reaction product. Further studies then focussed on the application of biologically relevant small molecules. Naturally occurring (–)-Nopol or Geraniol did not alter the reaction outcome. Similarly, an example of a protected galactopyranose, an amino alcohol or other pharmaceutically relevant small molecules proofed compatible with the present reaction conditions and the desired *gem*-difluoroolefins **33–38** were obtained in good yield. We then embarked on studies of different further diazoalkanes. Diazoalkanes based on ethyl propionic acid proved compatible and *gem*-difluoroolefins **39** and **40** were obtained in good yield. We also examined aromatic donor/acceptor diazoalkanes (**41**), acceptor-acceptor diazoalkanes (**42**), and diazoketones (**43**); however, in these cases only the decomposition of the diazoalkane was observed.

In summary, we herein report on a *gem*-difluoroolefination using ethyl diazoacetate and α -trifluoromethyl styrenes. The combination of photocatalyst and tertiary amines proved vital to access an unusual reactivity of ethyl diazoacetate that can undergo C–C bond formation reaction followed by elimination of fluoride to give the *gem*-difluoroolefin product. Experimental and theoretical studies suggest a reaction mechanism that involves the participation of a triplet carbene and that the tertiary amine acts as scavenger of fluoride. Finally, the feasibility of this reaction was examined in a broad substrate scope (43 examples, up to 88% yield) showing a high functional group tolerance, including heterocycles, unsaturated bonds and biologically relevant small molecules.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: carbene · diazoalkane · DFT calculations · fluorine · photocatalysis

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- [15] The reaction in MeCN-*d*₃ revealed no incorporation of deuterium, which indicates that trace amounts of water present in the reaction solvent or reagents is the source of hydrogen.
- [16] A potential hydrogen atom abstraction from DABCO by the triplet carbene intermediate **INT1** can proceed with an activation free energy of 14.4 kcal mol⁻¹ and thus proceeds with higher activation free energy as the addition to α -trifluoromethyl styrene. Moreover, it is considered unlikely as such process would not result in deuterium incorporation in the reaction product.

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