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Studies on the application of the Paternò-Büchi reaction to the synthesis of novel fluorinated scaffolds

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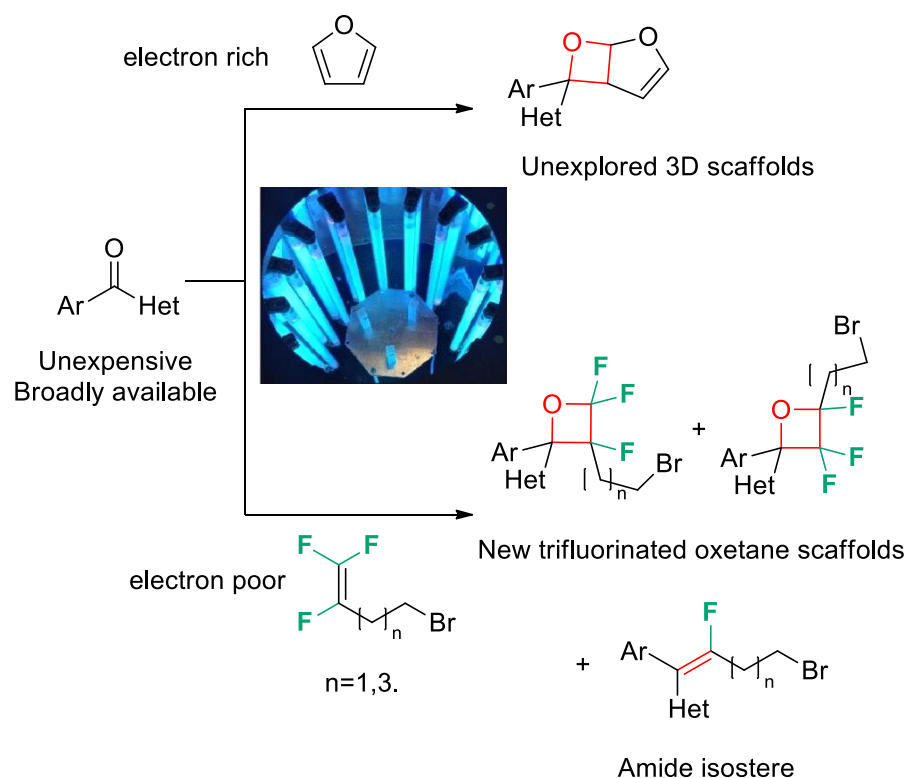
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Abstract: In the context of new scaffolds obtained by photochemical reactions, Paternò-Büchi reactions between heteroaromatic, trifluoromethylphenyl ketone and electron rich alkenes to give oxetanes are described. A comprehensive study has then been carried out on the reaction of aromatic ketones with fluorinated alkenes. Depending on the substitution pattern at the oxetane ring, a metathesis reaction is described as a minor side process to give mono fluorinated alkenes. Overall, this last reaction corresponds to a photo-Wittig reactions and yield amid isosteres. In order to explain the uncommon regioselectivity of the Paternò-Büchi reaction with these alkenes, electrostatic-potential derived charges (ESP) have been determined. In a second computational study, the relative stabilities of the typical 1,4-diradical intermediates of the Paternò-Büchi reaction have been determined. The results well explain the regioselectivity. Further transformations of the oxetanes or previous functionalization of the fluoroalkenes open perspectives for oxetanes as core structures for biologically active compounds.

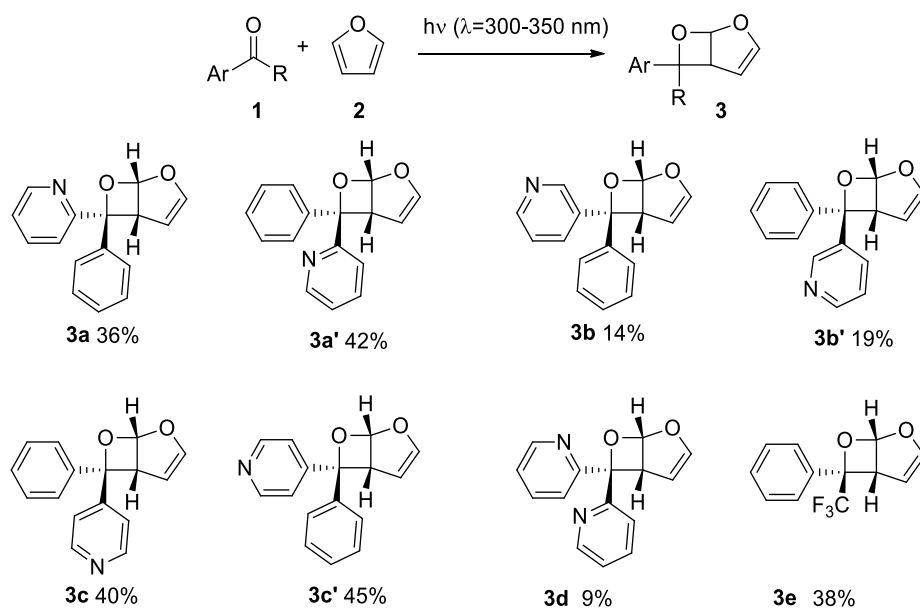


Introduction

Photochemical transformations are appreciated tools of organic synthesis.^[1, 2, 3] Electronic excitation dramatically modifies the configuration and thus the chemical reactivity compared to ground state reactions.^{4, 5} For example, many cycloaddition reactions preferentially occur under electronic excitation.^[6, 7] Such reactions particularly well fulfill requirements of sustainable chemistry since C-C bonds are created without chemical activation which reduces the formation of side products and waste.^[8] The Paternò-Büchi reaction is particularly useful in this regard.^[3, 9, 10, 11, 12, 13] The resulting oxetanes are valuable synthesis intermediates for the production of biologically active compounds.^[14] In the past, studies on this photochemical cycloaddition were mainly focused on reactivity and mechanistic aspects. Some applications to the total synthesis of natural products ^[2, 3, 13] and to the study of biochemical processes ^[15] have also been reported. Consequently, little efforts have been made to extent more systematically the scope to more relevant structures in connection to biological activity. In the present studies we therefore report particularly on reactions with carbonyl compounds possessing heterocyclic substituents, such as pyridine. Furthermore, we are interested in the synthesis of fluorine substituted oxetanes. Due to their particular chemical and physical properties, organofluorine compounds play an important role in biologically active molecules.^[16]

Results and Discussion

We started our investigation with the irradiation of various aromatic ketones **1** in furan **2** as solvent (Scheme 1). As heterocyclic compounds are particularly interesting, different pyridine-containing derivatives have been transformed and the corresponding oxetanes **3a-d** were obtained with medium to good yields. In the case of compounds **3a-c**, two stereoisomers were formed. Oxetane **3e** was isolated as single stereoisomer from the reaction of the trifluoromethylphenyl ketone (R=CF₃). As it has been previously reported for similar oxetanes obtained with furan (see for example ^[11, 17, 18]), the oxygen atom of $\pi\pi^*$ excited triplet ketone always attacks the furan ring in the 2 position so that only one regioisomer (head-to-head) was formed.



Scheme 1. Exploitation of Paternò-Büchi reaction using heteroaromatic ketones. Furan was used as solvent.

An interesting observation has been made for the reactions leading efficiently to oxetanes **3a,a'** and **3c,c'** on one hand and inefficiently to oxetanes **3b,b'** on the other. In ground state reactions, ortho and para substituents on the benzene ring affect the reactivity by mesomeric effects while meta substituents have much less influence. In contrast, in photochemical reactions, meta substituents have a major influence on the reactivity (meta effect).^[19] In the present case such a substitution pattern (**3b,b'**) modify the electronic structure of the excited state more significantly.

As previously mentioned, fluoroorganic compounds are of particular interest for the search of new scaffolds possessing biological activities. We therefore decided to perform the Paternò-Büchi reaction with alkenes carrying fluorine atoms. [2+2] Photocycloadditions with such alkenes have previously been performed to yield corresponding cyclobutanes.^[20] Some examples of the Paternò-Büchi reaction with fluorinated alkenes have also been reported.^[21]

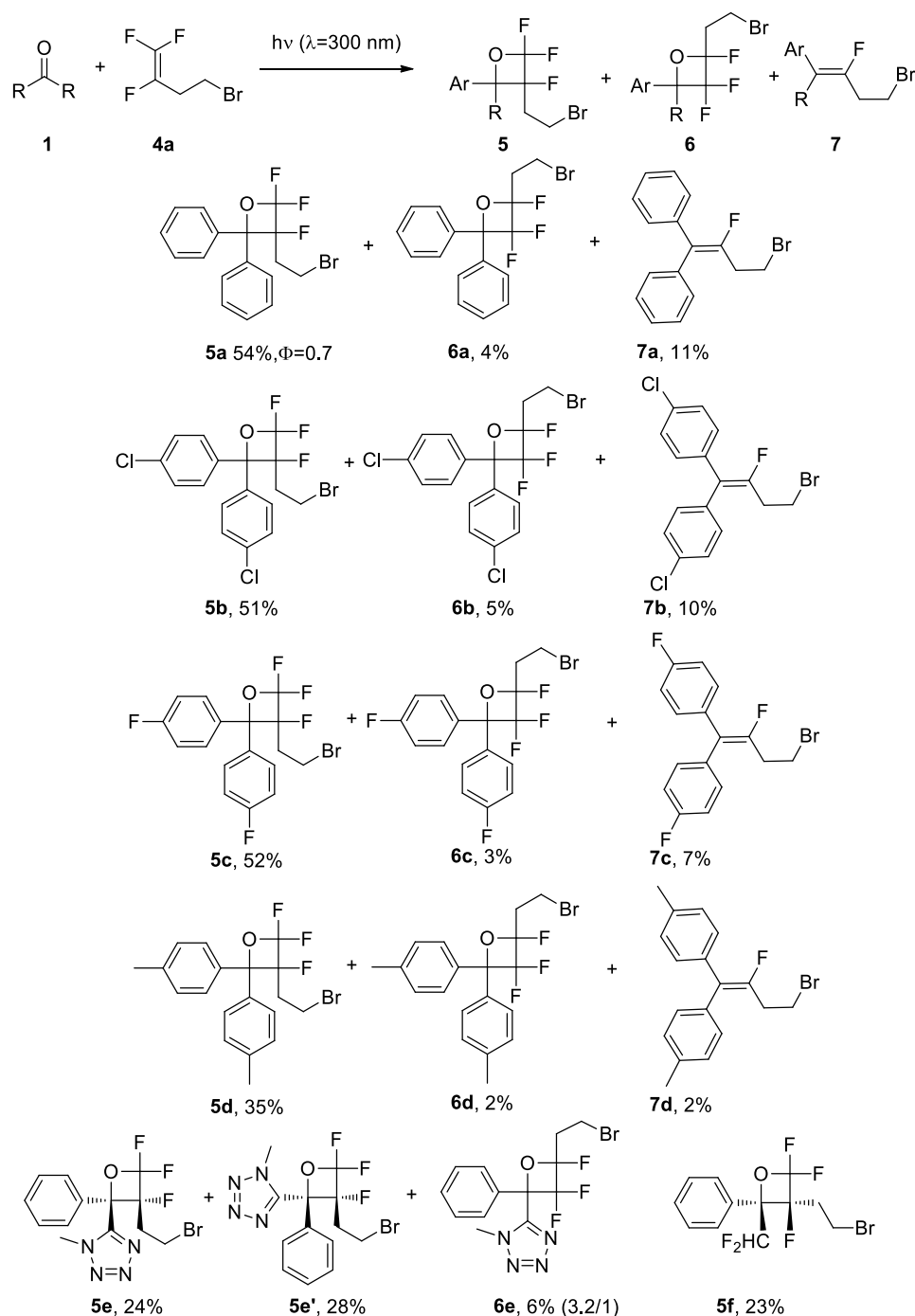
For the synthesis of fluorinated oxetanes, we started our investigations using benzophenone **1a** which was successfully transformed by irradiation at $\lambda=300$ nm in the presence of 3 equiv of the commercially available trifluoroolefin **4a** in α,α,α -trifluorotoluene as solvent to obtain oxetanes **5a** and **6a** in a 58% yield (Table 1, entry 1). The change of the solvent revealed that acetonitrile did not improve the yield (44%) compared to α,α,α -trifluorotoluene (58%) (Table 1, entry 2). The use of dichloromethane (CH_2Cl_2) as the solvent resulted in a 36% yield of **5a** and **6a** (Table 1, entry 3). When we used 2-propanol as the solvent we observed no formation of oxetanes **5a** and **6a** in this case the major product was the corresponding benzopinacol (Table 1, entry 4). Irradiation at 350 nm using acetonitrile resulted in a decreased yield of 38% for oxetanes **5a** and **6a** (Table 1, entry 5).

We have carried out the Paternò-Büchi reaction with a variety of aromatic ketones **1** and the trifluorinated alkene **4a** (Scheme 2). The main oxetane product is the regioisomer **5**. The transformation was quite efficient since a product quantum yield of 0.7 (in CF_3Ph) for the conversion of benzophenone **1a** was determined when using the Norrish type II reaction of valerophenone as actinometer.^[22]

Table 1. Optimization of reaction conditions for the formation of oxetanes starting from **1a**.

Entry ^[a]	λ (nm)	Solvent	Yield		
			5a	6a	7a
1 ^[b]	300	CF_3Ph	54%	4%	11%
2 ^[b]	300	MeCN	42%	2%	traces
3 ^[c]	300	CH_2Cl_2	33%	3%	traces
4 ^[d]	300	2-propanol		n.d.	
5 ^[c]	350	MeCN	36 %	2 %	-

[a] All reactions were conducted in deaerated solvent ($c=15.3$ mM). [b] Isolated yield, products were isolated as a mixture. [c] Yield calculated by ^{19}F NMR using 4,4'-difluorobenzophenone as standard. [d] Not detected, benzopinacol was isolated in a 57% yield.



Scheme 2. Paternò-Büchi reaction of aromatic ketones **1** using fluoroolefin **4a**. In all cases, the major obtained regioisomer is oxetane **5** (for reaction conditions see supporting information).

The transformation of unsymmetrical ketone **1e** yielded two diastereoisomers for each regioisomer. Oxetanes **5e** and **5e'** were the major products and they were separable. **5e** crystallized properly to perform an x-ray analysis which confirmed the structure of major products **5** (Figure 1).^[23]

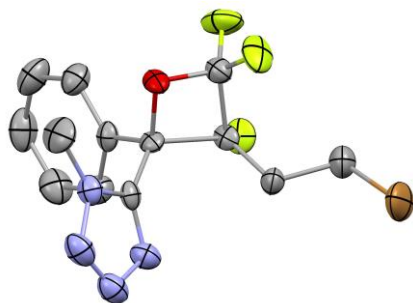


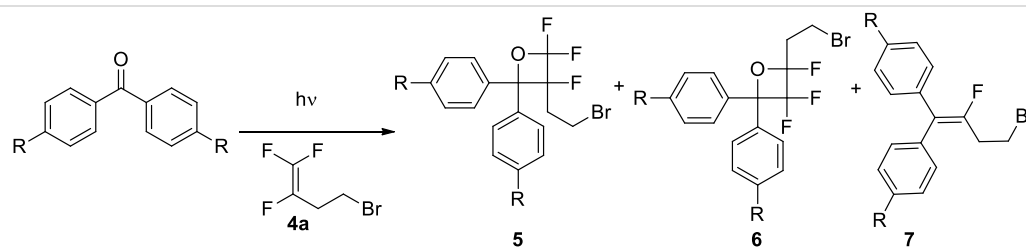
Figure 1. X-ray diffraction structure analysis of oxetane **5e** (CCDC deposition n° 2097493).

In most of the cases, olefin **7** was observed as a side product in the reaction mixture. The yield of this olefin varies from traces up to 11% (Scheme 2). The fact that the side product **7** could be obtained in moderate yield, combined with the fact that mono-fluorinated olefins are not easily available and are considered isosteres of amides [^{16a},²⁴] prompted us to explore the substitution in the 4,4'-positions of the benzophenone for this particular [2+2] cycloaddition to obtain products **7** (Table 2).

In all cases, conducting the reaction in α,α,α -trifluorotoluene slightly increases the yields in oxetane **5** and olefin **7** (Table 2, entries 1-6). Oxetane **5d** was obtained as a mixture with oxetane **6d** and olefin **7d**, in a ¹⁹F NMR ratio of 20:1.4:1 (Table 2, entry 4). Surprisingly, oxetane **5g** was not observed in the crude mixture: the only obtained product for the reaction of 4,4'-dimethoxybenzophenone with trifluoroolefin **4a** is olefin **7g** (Table 2, entry 9).

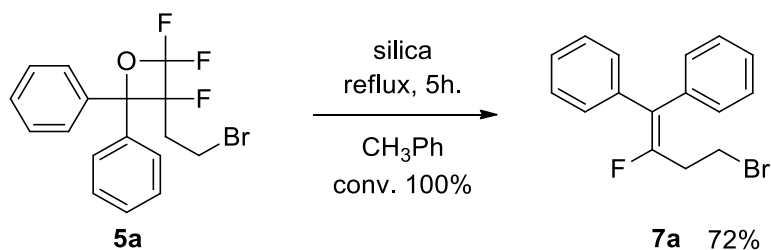
We continued the studies by testing the stability of oxetane **5a** to prove that it can be transformed to olefin **7a** (Scheme 3). Oxetane **5a** was heated for 5 hours in refluxing toluene. No transformation was detected showing its thermal stability. No transformation was observed when oxetane **5a** was treated at room temperature for 5 hours in acidic medium (HCl/MeOH). A slight conversion was observed when oxetane **5a** was heated to reflux (T=65°C) in acidic media (HCl/MeOH) (See supporting information). More importantly, heating of oxetanes **5a** in the presence of silica gel for 5h in refluxing toluene results in formation of olefin **7a** along with an unidentified product. Olefin **7a** was isolated in a 72% yield (Scheme 3) proving that oxetane **5a** leads under certain conditions to olefin **7a**. We also tested the stability of oxetane **5d**, which upon heating in CDCl₃ was transformed to olefin **7d** (See supporting information).

From these results we also conclude that the formation of an oxetane in the reaction of ketone **1g** with alkene **4a** (Table 2, entry 9) may take place. However the metathesis of the unstable oxetane occurs at lower temperature immediately after the photochemical cycloaddition.

Table 2. Formation of side product **7**.

Entry ^[a]	R	Solvent	Yield		
			5a	6a	7a
1 ^[b,c]	R=H	CH ₃ CN	42%	2%	n.d. ^[f]
2 ^[b,c]	R=H	CF ₃ Ph	54%	4%	11%
3 ^[d]	R=H	C ₆ H ₆	35%	2%	9%
			5d	6d	7d
4 ^[b,c]	R=Me	CH ₃ CN	35%	2%	2%
5 ^[d]	R=Me	CF ₃ Ph	39%	2%	7%
6 ^[d]	R=Me	C ₆ H ₆	30%	2%	7%
			5g ^[f]	6g ^[f]	7g
7	R=OMe	CH ₃ CN	n.d.	n.d.	Traces
8 ^[d]	R=OMe	CF ₃ Ph	n.d.	n.d.	1%
9 ^[b,e]	R=OMe	C ₆ H ₆	n.d.	n.d.	26%

[a] All reactions were conducted at 300 nm for 6 hours in deaerated solvent using 3 equiv of **4a**, ($c = 15.3$ mM). [b] Isolated yield. [c] The products were isolated as a mixture. [d] Yield calculated by ¹⁹F NMR using 4,4'-difluorobenzophenone as standard. [e] The reaction was conducted at 350 nm for 8.3 hours using 4.1 equiv of **4a** ($c = 15.6$ mM). At this wavelength optical density of the solution is comparable to those of ketones **1a** and **1d**. [f] not detected.

**Scheme 3.** Stability of oxetane **5a**. Oxetane **5a** can be transformed to olefin **7a**.

Based on these observations, we propose that formation of side product **7** can be explained as a two-step procedure similar to the Wittig reaction: photocycloaddition of the carbonyl group to the fluorinated olefin **4a** followed by a metathesis reaction. The formation of olefin **7** depends on the stability of the oxetane **5**. So far, we showed that oxetane **5a** is thermally stable. However, strong heating of oxetane **5a** in the presence of silica leads to obtention of product **7a** (Scheme 3). On the other hand, oxetane **5d** is less stable and will lead to olefin **7d** upon heating to 60°C in CDCl₃ (see supporting information). Some examples of such metathesis reactions with oxetanes have previously been described.^[12,25]

Computational studies

We observed that the formation of regioisomers **5** is favored. In order to get more information on this topic, we performed computational studies. The Paternò-Büchi reaction generally occurs with ³nπ* triplet excited carbonyl compounds, in particular when the reaction is carried out using aromatic ketones. The polarity of the carbonyl compound is reversed and the carbonyl oxygen gets an electrophilic character.^[5,10,11,12,13,26] Thus the oxygen atom preferentially attack the alkene at its most nucleophilic site. We have determined the polarization and quantum chemical properties of a family of fluorinated olefins **4** (Figure 2).

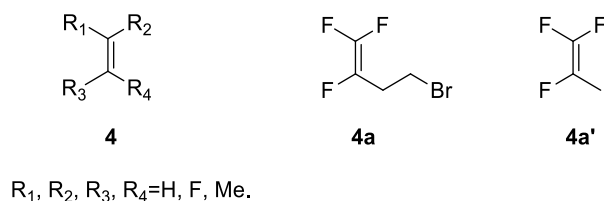


Figure 2. Family of fluorinated olefins that were studied by quantum-chemical calculations.

All possible 27 regio- and stereoisomers of alkene structures of the form **4** (Figure 2), were built in 3D and energy-optimized at MP2 level of theory (second-order Møller-Plesset) with def2-TZVPP basis set, gas phase (Turbomole). Structure of compounds **4a,4a'** was processed the same way.

From the resulting geometries, several quantum-chemical properties were calculated (single-point, SCF, def2-TZVPP basis set, gas phase): length of the C,C double bond, energies of the molecular orbitals HOMO, LUMO, HOMO-1, LUMO+1 and electrostatic-potential derived charges of the two sp² carbons. Compared to simple ethylene, the C=C double-bond length was mainly affected by the nature of the substituents; it increased with methyl and decreased with fluorine substitution. The energy of the HOMO was also very much affected by nature and number of substituents. A very good multivariate regression model ($r^2=0.987$) could be established, showing that energy of the HOMO increases with methylation and decreases (but to a lower extent) with fluorination:

$$E(\text{HOMO}) (\text{eV}) = -10.23 - 0.43 \text{ Me} - 0.16 \text{ F}$$

(Me and F are methyl group counts and fluorine atom counts respectively)

The model diagram is shown in Figure 3.

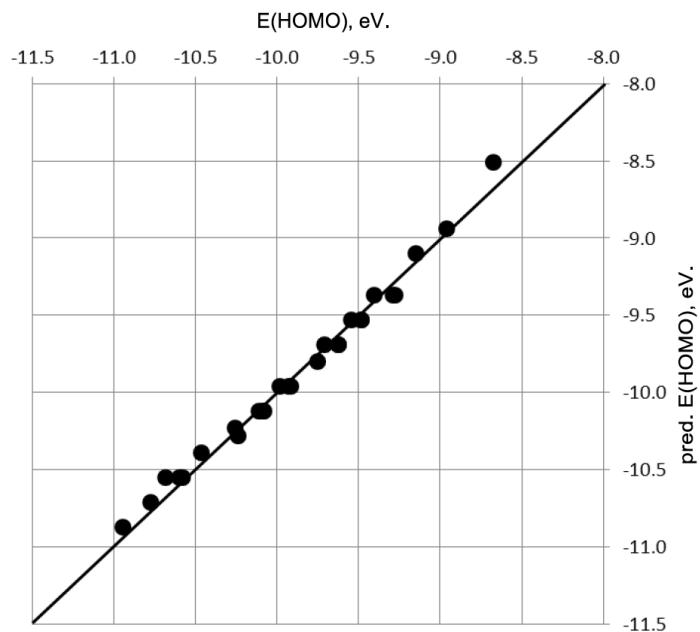


Figure 3. Plot of the predicted values of the HOMO energy from the model versus values issued from quantum chemical calculations. Model: $E(\text{HOMO}) (\text{eV}) = -10.23 - 0.43 \text{ Me} - 0.16 \text{ F}$ where Me and F are methyl group counts and fluorine atom counts ; Adj. $r^2 = 0.987$, Residual standard error 0.066 eV.

Interestingly, the energy of the HOMO orbital was not affected by the relative position of the substituents but only by substituent counts. The olefin **4a** showed rather similar values to its simpler methyl analogue 1,1,2-trifluoroprop-1-ene **4a'** (Figure 3, see supporting information). In contrast, the energy of the LUMO showed only a modest correlation to $E(\text{HOMO})$ ($r^2=0.48$) or to substituent content ($r^2=0.42$) (See supporting information). $E(\text{LUMO})$ was actually more affected by the relative positions of the substituents than by their counts.

Examination of the electrostatic-potential (ESP) derived charges on the two sp^2 carbons lead to the following result: The minimum of the two positive ESP charges was found with high-Me rich carbon atoms, whereas the maximum of the positive ESP charge was found with the carbon atoms that were fluorine-rich. This was in line with the expected idea of electron depletion on the neighboring carbon by fluorine atom, and its reverse effect with methyl groups. This fits also with the fact that nucleophilic alkene should react better than electron-poor ones in the Paternò-Büchi reaction. From the HOMO energy standpoint, reagent **4a'** should be more reactive than ethylene by one alkyl group equivalent, but also should be less reactive because of the three fluorine atoms which compensate the effect of the Me group. However, olefin **4a** reacted to form Paternò-Büchi products **5** and **6**, although its HOMO energy was not very different from that of ethylene.

Regarding the CF_2 -carbon in **4a**, the quantum calculations have shown that the CF_2 carbon is the most positive of all other possible ones (Figure 4), this do not explain the obtention of major regioisomer **5a** when an edge attack of the $\pi\pi^*$ excited carbonyl group is considered (Scheme 2).

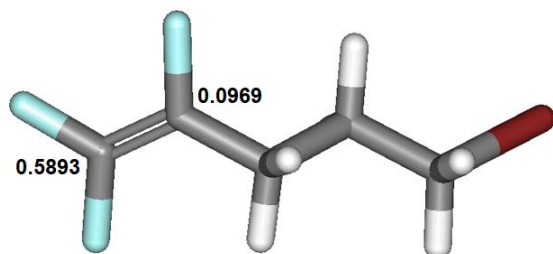
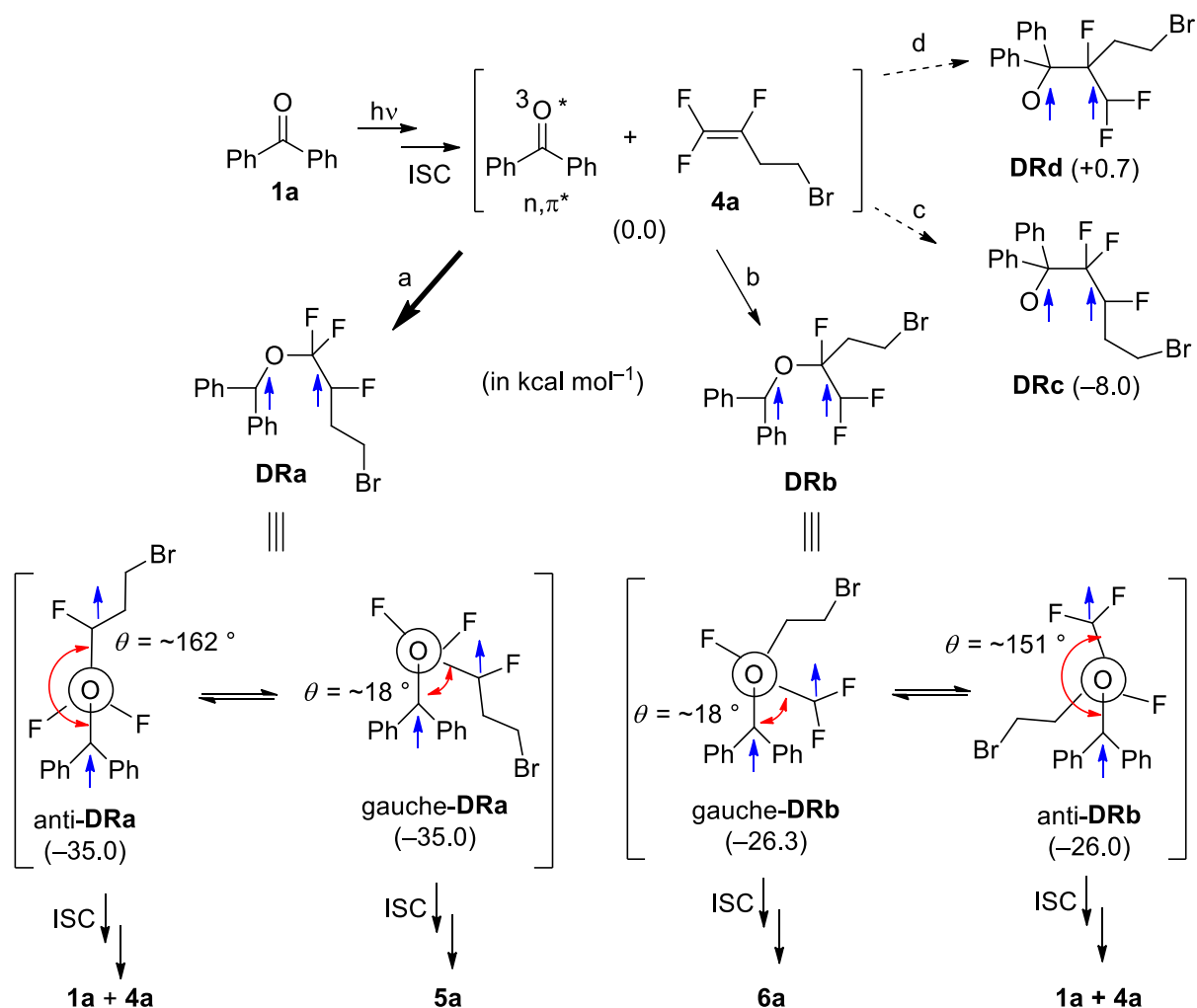


Figure 4. 3D structure of compound **4a**. Electrostatic-potential derived charges (ESP) indicated for the two olefinic carbon atoms.

In addition, E(HOMO-1) showed the same trend as E(HOMO), and E(LUMO-1) showed also the same trend as E(LUMO). The zero-point energy was also calculated but, as expected, was perfectly correlated to substituent content (for data see supporting information). Indeed, experimental reactivity and regioselectivity could not be rationalized solely on the basis of these ground-state quantum chemical endpoints.

The ground state polarization of alkenes such as **4a** should strongly favor the formation of regioisomers **6**. However, this is not observed. It has previously been reported that the 1,4-diradical intermediates play an important role for the stereo and regioselectivity of the Paternò-Büchi reaction.[10,11,12,13,17] These radicals are formed by attack of the electrophilic oxygen of the $^3n\pi^*$ triplet excited carbonyl compound to the alkene via an interaction of the n orbital of the carbonyl group and the π orbital of the alkene. In this case, a C-O bond is formed. Especially in the case of electron poor alkenes, a side approach of the two reaction partner *via* interaction of the π^* orbital of the carbonyl function and the π^* orbital of the alkene may also occur.[27] Thus various 1,4-diradical intermediates may be generated. We have calculated their stability.

To obtain more information on the regioselectivity observed in the photochemical reaction of benzophenone **1a** with **4a** (compare Scheme 2), the relative stability in energy was computed for the possible four triplet diradical intermediates **DRa-d** at the UB3LYP/6-31G(d) level of theory (Scheme 4). The triplet diradical **DRa**, which produces compound **5a** after the intersystem crossing (ISC) to the singlet state, was found to be the most stable in energy among the possible four triplet-diradicals. Other three isomers were calculated to be less stable in energy than **DRa** by ~ 10 kcal/mol. The processes to the diradicals **DRa** and **DRb** were found to be more energetically favored than those to **DRc** and **DRd** in the reaction of triplet benzophenone with **4a**, as judged by their reaction energies. The calculated energies are indicated in the parenthesis in Scheme 4.



Scheme 4. Relative stability of the possible four triplet 1,4-diradical intermediates in the Paternò-Büchi reaction of benzophenone **1a** with trifluoroolefin **4a**.

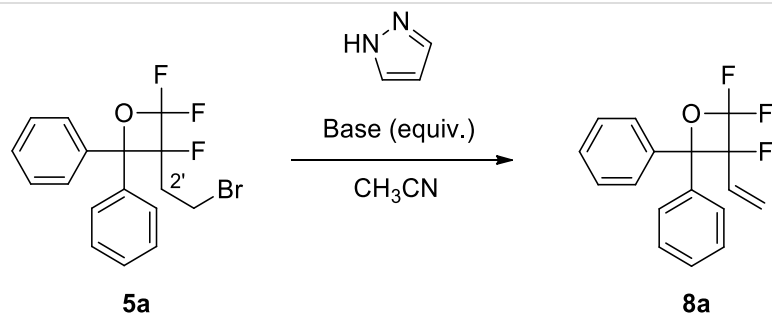
In **DRa**, two energy minima, anti-**DRa** ($\theta = \sim 162^\circ$) and gauche-**DRa** ($\theta = \sim 18^\circ$) were found at the same level of theory (Scheme 4). The anti-isomer returns to the starting compounds (**1a** + **4a**) after the intersystem crossing to the singlet state. The gauche conformer may go to the product **5a**. The energy barrier between two isomers was determined to be 3.0 kcal mol⁻¹. Similar to **DRa**, two energy minima were found for **DRb**, those are anti-**DRb** and gauche-**DRb**, which are connected with the energy barrier of 3.1 kcal mol⁻¹ (Scheme 3). These theoretical calculations show that the most stable 1,4-diradical **DRa** explains the favored formation of oxetanes **5**. This is in line with the experimental results.

Transformations of fluorinated oxetanes

Further reactions have been carried out in order to indicate strategies for the application of the Paternò-Büchi reaction to the synthesis of novel scaffolds with biological activity. The presence of a primary bromine function in compounds **5** should enable further functionalization. Using oxetane **5a**, we tried to attach heterocyclic substituents such as pyrazole via nucleophilic substitution (Table 3). However, under

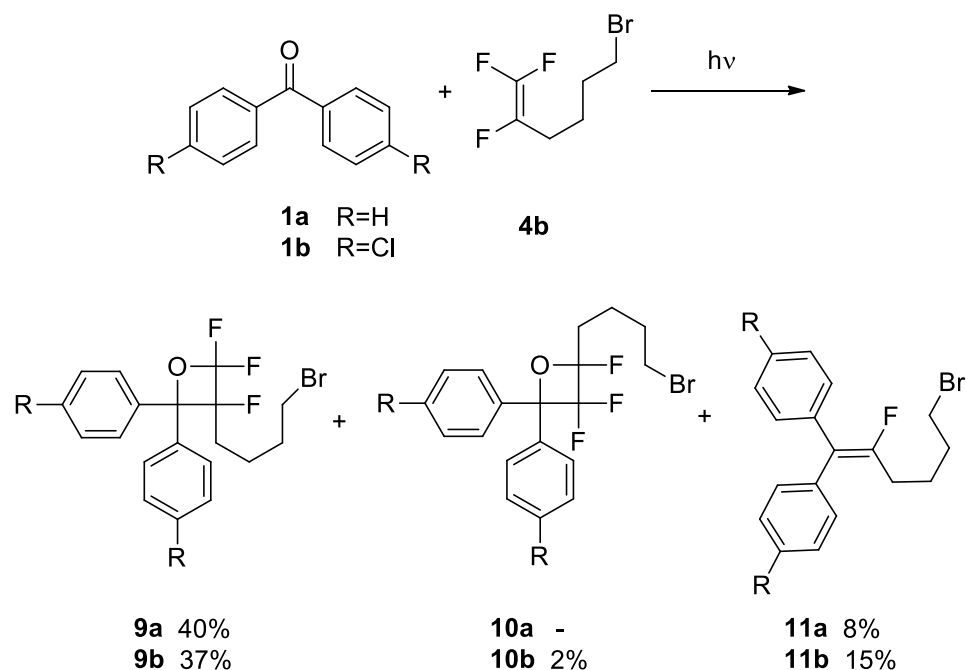
standard reaction conditions, we obtained the corresponding elimination product **8a** (Table 3, entries 1-3). This reaction may be explained by an increased C-H acidity in position 2' of compound **5a**. Further transformations of the vinyl group can be envisaged.

Table 3 : Reaction conditions for the nucleophilic substitution: only elimination product **8a** was obtained.

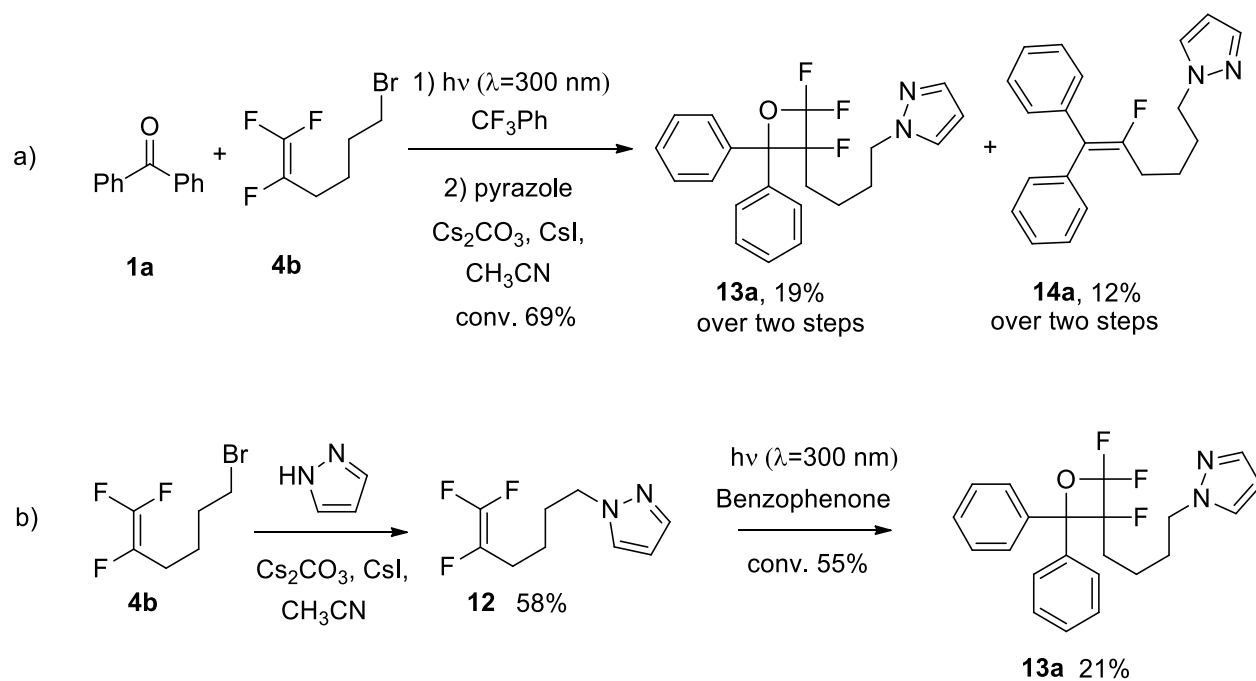


Entry	Pyrazole	Base	Temperature,	Time	Yield %
1	3.3 equiv	DBU (1.5 equiv)	70°C	6 h	62%
2	7.0 equiv	NaH (8.5 equiv)	r.t.	6 h	35%
3	4.0 equiv	Cs ₂ CO ₃ (3.4 equiv)	r.t.	48 h	46%

To prove that further transformations via nucleophilic substitution on the bromine moiety can be achieved, we synthesized oxetanes **9** and **10** starting from the corresponding ketones **1a,b** and trifluoroolefin **4b** under the same reaction conditions. For these two cases, we also observed the formation of olefin **11** as a side product (Scheme 5). Gratifyingly, the nucleophilic substitution proceeded in one pot under standard reaction conditions and we isolated the corresponding trifluorinated oxetane **13a** possessing heterocyclic substituents (Scheme 6). Side product **14a** from the “photo-Wittig” reaction was also obtained (Scheme 6a). The inverted strategy was also tested: first we performed the nucleophilic substitution using pyrazol, then we performed the Paternò-Büchi reaction with benzophenone (Scheme 6b). This allows the application of Paternò-Büchi reaction as a divergent oriented synthesis: trifluorinated olefin **4b** can be transformed with several nucleophiles and then be reacted with different ketones to obtain libraries of trifluorinated oxetanes. Thus, the fluorinated alkene **4b** was first transformed into the heterocyclic derivative **12** and then irradiated in the presence of benzophenone to obtain oxetane **13a** (Scheme 6b). This example also indicates that the Paternò-Büchi reaction with fluorinated alkenes is tolerant with respect to functional groups, especially heterocyclic groups. This strategy is also the preferred one when oxetanes should be synthesized which are less stable with respect to metathesis (photo-Wittig reaction).



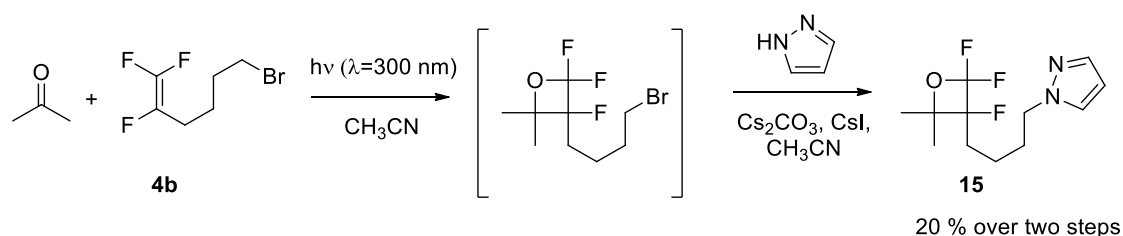
Scheme 5. Paternò-Büchi reaction of ketones **1a,b** and olefin **4b**. Side Photo-Wittig product **11a,b** was also obtained.



Scheme 6. Application of the Paternò-Büchi reaction to obtain original scaffolds possessing a trifluorinated oxetane and heterocyclic substituents.

Small heterocyclic substituents such as simple oxetanes can modulate physicochemical properties of biologically active scaffolds.^[28] We found that acetone undergoes easily [2+2] photocycloaddition with the fluorinated alkene **4b** (Scheme 7).

We successfully obtained oxetane **15** in one pot: first irradiation of acetone in the presence of alkene **4b** followed by nucleophilic substitution using pyrazole (Scheme 7). It should be pointed out that in this case, we didn't observe a metathesis reaction of the oxetane. This non-optimized strategy allows the convenient synthesis of libraries of simple trifluorinated oxetanes of the form **15** that could be used in drug discovery.



Scheme 7. Application of the Paternò-Büchi reaction to obtain simple trifluorinated oxetanes **15** as a pending motifs.

Conclusion

Heterocyclic and fluorinated compounds play a key role as scaffolds in many domains such as pharmaceutical or agro-chemistry. For example, oxetanes are interesting core structures. In this context, the Paternò-Büchi reaction has been carried out with heteroaromatic ketones, in particular benzoyl pyridine derivatives and trifluoro acetophenone.

A systematic investigation was performed on the Paternò-Büchi reaction with fluoroalkenes. Depending on the substitution pattern, more or less efficient metathesis (photo-Wittig reaction) has been observed as side reaction. An uncommon regioselectivity was observed and which cannot be explained by the polarities of the alkenes. A further computational study revealed that this phenomenon may be explained by different stabilities of the 1,4-diradical intermediate.

Experimental Section

Experimental Details are given in the electronic Supporting Information.

Acknowledgements

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Keywords: Cycloaddition • fluorinated scaffolds • heterocycles • photochemistry • reaction mechanisms

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